A systematic review of the neutrophil:lymphocyte and platelet:lymphocyte ratios in patients with lower extremity arterial disease

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Abstract

Background and Aims

Lower extremity arterial disease (LEAD) is caused by atherosclerotic plaque in the arterial supply to the lower limbs. The neutrophil:lymphocyte and platelet:lymphocyte ratios (NLR, PLR) are established markers of systemic inflammation which are related to inferior outcomes in multiple clinical conditions, though remain poorly described in patients with LEAD.

Methods

This review was carried out in accordance with PRISMA guidelines. The MEDLINE database was interrogated for relevant studies. Primary outcome was the prognostic effect of NLR and PLR on clinical outcomes following treatment, and secondary outcomes were the prognostic effect of NLR and PLR on disease severity and technical success following revascularisation.

Results

There were 34 studies included in the final review reporting outcomes on a total of 19870 patients. NLR was investigated in 21 studies, PLR was investigated in two studies, and both NLR & PLR were investigated in 11 studies. Relating to increased levels of systemic inflammation, 20 studies (100%) reported inferior clinical outcomes, 13 (92.9%) studies reported increased disease severity, and seven (87.5%) studies reported inferior technical results from revascularisation.

Conclusions

The studies included in this review support the role of elevated NLR and PLR as key components influencing the clinical outcomes, severity, and success of treatment in patients with LEAD. The use of these easily accessible, cost effective and routinely available markers is supported by the present review.

Key Words: NLR; PLR; LEAD; CLTI; inflammation; atherosclerosis

Introduction

Lower extremity arterial disease (LEAD) refers to chronic atherosclerotic disease of the lower limb arteries. It is a common disorder, with an estimated prevalence of 20% in individuals over the age of 50, though there is likely a significant amount of undiagnosed disease[1]. It is considered the limb manifestation of generalised atherosclerosis, and as such there is significant overlap with other atherosclerotic conditions such as cerebrovascular (CVD) and coronary artery disease (CAD)[2]. Atherosclerotic plaque buildup reduces blood flow to peripheral tissues, causing symptoms ranging from exertional ischaemic calf pain (intermittent claudication) to ischaemic rest pain and tissue breakdown/ulceration (chronic limb threatening ischaemia, CLTI). CLTI is considered the end-stage of LEAD and is associated with significant morbidity and mortality[3]. Scoring systems based on clinical presentation, such as the Rutherford[4] and Fontaine[5] scoring systems, allow classification of severity and can guide the need for intervention. Other scoring systems based on anatomic classification of lesions allow for planning of intervention based on the pattern of disease[6], for example the TASC-II system which is widely used in both clinical and research settings[7].

The management of LEAD is dictated by severity of symptoms and pattern of disease. Medical management consists of risk factor modification and administering appropriate secondary prevention agents[8]. Reconstruction options may be either open surgery or endovascular procedure (e.g. percutaneous transluminal angioplasty, PTA), with a variety of strategies available dependent on disease and patient factors[9].

Systemic inflammation is increasingly recognised as a key component in the pathogenesis of atherosclerosis, and is associated with increased progression of atherosclerosis in addition to itself being triggered by plaque deposition[10]. The systemic inflammatory response (SIR)

can be evaluated using several widely reported scoring systems. The absolute neutrophil, platelet, and lymphocyte counts of the differential white cell count can be used to derive the neutrophil:lymphocyte ratio and platelet:lymphocyte ratio (NLR, PLR). Both are markers of chronic systemic inflammation and have been associated with inferior prognosis in multiple conditions[11–13]. NLR is associated with generalised atherosclerosis and impaired outcome in CVD and CAD[14], though is less well described in LEAD. An additional systemic inflammation based prognostic score is the Modified Glasgow Prognostic Score (mGPS), which describes the acute phase protein response. mGPS is derived from albumin and C-reactive protein (CRP) levels, with higher scores conferring an increased level of systemic inflammation[15,16]. mGPS has been associated with inferior survival in several conditions, including patients with cancer and cardiovascular disease[17–19].

This review aimed to summarise the contemporary evidence base describing the prognostic value of NLR, PLR, and mGPS, in patients with LEAD.

Materials & Methods

This review and search strategy was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Both prospective and retrospective studies were included due to the lack of prospective data available. No ethical approval was required as individual patient data were not accessed. The review protocol was registered with the PROSPERO database (Registration Number: CRD42021292121).

Outcomes

The primary outcome of interest was the clinical outcome (measured as overall survival, or amputation-free survival, and rate of major adverse cardiovascular event; MACE or major adverse limb event; MALE) following diagnosis and management of LEAD (either medical, endovascular, surgical) in patients subgrouped by either NLR/PLR/mGPS measured as categorical or continuous variables. NLR, PLR and mGPS were chosen as markers of the SIR due to the body of evidence supporting their prognostic value in a range of conditions.

Secondary outcomes included severity of peripheral arterial disease (measured either as proportion of claudication vs. CLTI, or by objective scoring systems such as Fontaine, Rutherford classifications), and technical success rates in patients undergoing revascularisation (in-stent restenosis; ISR or target vessel revascularisation; TVR). Each secondary outcome was compared between the subgroups of inflammatory parameters.

Search Strategy

The MEDLINE database was accessed electronically using the PubMed (National Centre for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD, USA) search engine. The search was conducted on the 1st June 2022; any papers published after this date are not included in this review. The first studies reporting GPS (the precursor to mGPS),

NLR, and PLR were published in 2003, 2001, and 2010 respectively[16,20,21], therefore studies published before 2001 were excluded. Review articles, case reports, editorials/comments, animal studies, and studies unavailable in English as a full text version were excluded.

Due to the significant overlap between patients suffering from peripheral arterial, cerebrovascular, and coronary artery diseases a broad initial search strategy was employed to ensure sufficient breadth of inclusion. Therefore, the following search string was used:

"((NLR) OR (neutrophil lymphocyte ratio) OR (PLR) OR (platelet lymphocyte ratio) OR (mGPS) OR (modified glasgow prognostic score) OR (GPS) OR (glasgow prognostic score)) AND ((CLI) OR (critical limb ischaemia) OR (CLTI) OR (chronic limb threatening ischaemia) OR (atherosclerosis) OR (coronary artery disease) OR (LEAD) or (lower extremity arterial disease) OR (LEAD) OR (peripheral arterial disease) OR (cerebrovascular disease) OR (CVA) OR (stroke) OR (STEMI) OR (NSTEMI) OR (myocardial infarction) OR (angina) OR (ischaemic heart disease) OR (revascularisation) OR (bypass) OR (angioplasty))"

This search term was applied to study title, key words, and Medical Subject Heading (MeSH) terms. Duplicate results were screened by identifying their PubMed Identifier (PMID), an integer value unique to each record. Relevant review articles underwent bibliography screening to identify additional relevant papers. Abstract screening was performed on the initial results to generate a list of studies to undergo full paper screening for final inclusion. Following initial abstract screening it was determined that there were no relevant studies investigating mGPS as the independent variable, therefore mGPS was not included in the subsequent final review.

Data Extraction

Data extracted from study documents include:

- Study design (centres, follow-up, prospective/retrospective) and study information (journal, authors, year).
- Baseline clinical and demographic data of patients.
- Classification of "inflamed" vs. "non-inflamed" i.e. cutoff of NLR/PLR (whether using data derived cut-offs or absolute values), or whether analysed as a continuous variable.
- Disease severity based on clinical assessment and using objective scoring systems detailed above.
- Technical success rate of revascularisation (in-stent restenosis, ISR, and target vessel revascularisation, TVR).
- Survival data for overall survival and amputation-free survival, where hazard ratio and 95% confidence intervals are reported these will be extracted.
- Rate of post-procedure major adverse cardiovascular event (MACE) and major adverse limb event (MALE), where hazard ratio and 95% confidence intervals are reported these will be extracted.

The risk of bias in each study was assessed using the Cochrane Quality in Prognostic Studies (QUIPS) tool to systematically assess and record bias. Preliminary literature review showed that due to significant heterogeneity between outcome measures reported and patient selection across all studies meaningful meta-analysis was impossible. Therefore, studies were grouped based on their reporting of each of the outcomes of this review and qualitative analysis performed.

Results

The study selection process is summarised in the PRISMA diagram (figure 1). There were 35 studies included in the final review reporting outcomes on a total of 20396 patients. NLR was investigated in 21 studies, PLR was investigated in two studies, and both NLR & PLR were investigated in 12 studies. There were no studies investigating mGPS. Where reported outcomes qualified for both primary and secondary outcome analysis studies were included in multiple outcome categories. The characteristics of each study and main outcomes are studied in tables 1, 2, and 3.

Studies Investigating Clinical Outcomes in LEAD (Table 1)

20 studies reported clinical outcomes in 10826 patients. Study design was prospective in one study, retrospective in 19 studies, and observational in all studies. Seven of these studies reported outcomes in pooled patients without subgrouping based on management strategy, one study reported outcomes following surgical revascularisation, Six studies reported outcomes following endovascular revascularisation, two studies reported outcomes following amputation, and four studies reported outcomes following conservative / medical management.

Studies Reporting Outcomes Following All Revascularisation Techniques

Erturk et al[22] used an NLR > 3.0 as a cutoff in 508 patients with symptomatic LEAD (77.8% claudication, 22.2% CLTI) with >50% angiographic stenosis who underwent medical (52.2%), surgical (15.0%), or endovascular (32.8%) management strategies. Median follow-up was 20 months. Multivariate analysis showed that NLR > 3.0 predicted cardiovascular mortality (HR 2.04, 1.26 – 3.30, $p = 0.004$), however the high NLR cohort had significantly more patients with CLTI than the low NLR cohort (28% vs. 19%, $p = 0.019$).

Spark et al[23] reported a patient cohort of 149 patients admitted with CLTI undergoing endovascular (22.1%) or open (28.9%) revascularisation, or amputation (21.5%), or conservative management (33.6%). ROC analysis was used to determine an NLR cutoff of ≥5.25, which was associated with increased risk of mortality at a median follow-up of 8.7 months (HR 2.3, 1.2 – 4.2, $p = 0.007$).

González-Fajardo et al[24] reported outcomes on 561 patients with CLTI admitted for elective open or endovascular infrainguinal revascularisation, with a median follow-up of 31 months. High NLR was defined as NLR >5.0. The high NLR cohort had a higher rate of coronary artery disease and congestive cardiac failure. There was a higher proportion of severe disease (Rutherford Category 5) in the High NLR cohort. Amputation-free survival was lower in the high NLR cohort on multivariate analysis (HR 2.325, 1.732 – 3.121).

Sanz et al[25] included 672 patients with CLTI who underwent revascularisation (both surgical and endovascular), though excluded cases with early (<24 hours) post-operative deaths. At 12-month followup, AFS was inferior in patients with NLR >5 (HR 2.325, 1.732 – 3.121, $p < 0.001$) on multivariate analysis. NLR was subsequently used as part of a larger risk prediction model in a validation cohort of patients.

Uzun et al[26] included 602 patients with a clinical diagnosis of LEAD (18.3% CLTI, 81.7% claudication), subsequently diagnosed with >50% angiographic stenosis, who then underwent surgical (16.8%), endovascular (34.4%), or medical (48.8%) management. They compared outcomes between patients with a PLR cutoff of 142 based on previously published results. PLR > 142 was associated with long-term cardiovascular mortality (HR 1.03, 1.01 – 1.04, $p = 0.001$).

Pourafkari et al[27] retrospectively analysed 1228 patients with LEAD (67.2% CLTI, 22.8% claudication) undergoing both surgical and endovascular revascularisation. ROC analysis for

each outcome was performed to determine a cutoff of NLR. High NLR cohort predicted MALE (HR 1.094, 1.071 – 1.118, $p < 0.001$) and 10-year mortality (HR 1.096, 1.072 – 1.120, $p < 0.001$).

Bath et al[28] used retrospective registry interrogation to identify 3687 patients undergoing revascularisation (59% PTA, 41% surgical bypass) for LEAD (53.4% intermittent claudication, 14.5% rest pain, 32.1% tissue loss). High NLR (pre-operative) was defined as ≥ 3.65 based on ROC analysis. Pre-operative high NLR was associated with in hospital death (HR 5.359, 1.682 – 17.074, $p = 0.004$) and MACE (HR 2.907, 1.565 – 5.400, $p = 0.0007$) on multivariate analyses.

Studies Reporting Outcomes Following Surgical Revascularisation

González-Hernandez et al[29] included 150 patients undergoing surgical bypass to the below knee vessels for LEAD (93% CLTI) who were followed-up for 24 months. High NLR was defined by the 4th quartile. On multivariate analyses, the high NLR cohort was associated with inferior AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$).

Studies Reporting Outcomes Following Endovascular Revascularisation

Chan et al[30] included 83 patients undergoing infrapopliteal PTA for CLTI, and defined high NLR as ≥ 5.25 based on previously published results. High NLR was associated with increased mortality at final followup of 12 months (HR 1.97, 1.08 – 3.62, $p = 0.03$).

Chen et al[31] reported outcomes in a cohort of patients with LEAD (87.2% CLTI) who also had a diagnosis of chronic kidney disease (defined as CrCl ≤30mL/min/1.73m^2) admitted for PTA. Multivariate analysis showed that NLR ≥ 3.76 (based on previously published data) was associated with increased risk of death or major amputation (HR 2.07, 1.00 – 4.35, p <0.05).

Huang et al[32] reported amputation rates in 736 patients undergoing PTA for CLTI. NLR and PLR at baseline were higher in patients who subsequently underwent amputation following initial revascularisation.

Jhang et al[33] included 232 octogenerians with LEAD (83% CLTI) undergoing PTA. Baseline NLR and PLR were higher in patients who died at 24-month followup compared with those who were alive. NLR > 3.89 was associated with increased hazard of 24-month mortality (HR 2.679, 1.312 – 5.470, $p = 0.007$).

Lee et al[34] observed no difference baseline NLR and PLR between patients who suffered MACE (n=7) and those who did not (n=88) at 24-month prospective follow-up following PTA and stent placement for intermittent claudication.

Su et al[35] reported outcomes on 195 patients with CLTI (defined as ≥ 4 on the Rutherford Classification) undergoing PTA, subgrouped into high (≥ 8) and low NLR based on receiver operating characteristics (ROC) analysis. The high NLR group had inferior one-year all-cause mortality, cardiac related mortality, MACE, and MALE. These associations were reproduced on multivariate analyses for all-cause mortality (HR 3.599, 1.818 – 7.123, $p < 0.001$) and cardiac-related mortality (HR 5.286, 2.075 – 13.47, $p < 0.001$), however MACE and MALE were not significant.

Studies Reporting Outcomes Following Amputation

Wang et al[36] subgrouped patients with CLTI who underwent amputation into "poor prognosis" (MI, CVA. 30-day mortality) and control cohorts and reported high pre-operative NLR and PLR in the former. ROC analysis defined cutoffs of NLR and PLR. NLR ≥ 8.08 (OR 26.228, 5.801 – 118.583, $p <0.001$), and PLR ≥ 237.14 (3.464, 1.289 – 9.308, $p = 0.014$) predicted "poor-prognosis" outcomes.

Pierre-Louis et al[37] included 410 patients undergoing major (above- and below- knee) amputations for CLTI. Patients who went on to require revision of their amputation had a higher post-operative NLR at their initial amputation. Both pre- and post-operative NLR were higher in patients who suffered 30-day mortality, the association in post-operative NLR was reproduced on multivariate analysis.

Studies Reporting Outcomes Following Conservative Management

Taşoğlu et al[38] reported outcomes on a cohort of 104 patients with non-operable CLTI (due to technically impossible revascularisation, patient fitness, or patient declining intervention). NLR ≥ 3.2 and PLR ≥ 160 were determined as cutoffs using ROC analysis. High NLR (OR 5.6, 2.2 – 14.2, p <0.001) and high PLR (OR 3.4, 1.4 – 8.2, p = 0.005) were associated with increased risk of amputation. When a composite measure of "high risk" status, defined as high NLR and high PLR was investigated, it was associated with amputation (OR 4.7, 1.7 – 12.6, p = 0.002).

Luo et al[39] reported outcomes on 172 patients with CLTI without tissue loss who underwent conservative management alone (due to technically impossible revascularisation, patient fitness, or patient declining intervention). NLR ≥ 3.8 was selected as a cutoff based on ROC analysis. High NLR predicted need for amputation on multivariate analysis (HR 1.140, 1.086 – 1.197, p < 0.001). 3-year AFS was 43.2% vs. 82.7% in the high vs. Low NLR groups (p <0.001).

Amrock et al[40] evaluated 556 participants who were part of a multicentre research registry, and diagnosed LEAD through measuring ankle:brachial pressure index (ABPI) with a cutoff of ≤ 0.9. These patients did not present with symptoms of LEAD as their means of entering into this study. At a median followup of 97.2 months, NLR (HR 1.20, 1.04 – 1.39, p = 0.012) predicted all-cause mortality.

Erdoğan et al[41] reported outcomes on 268 patients with CLTI who were unable to undergo revascularisation and therefore receieved optimal medical therapy. Clinical progression of disease was used to define ”non-response” as the primary outcome. ROC analysis determined cutoffs for NLR and PLR. Multivariate analyses showed that NLR ≥ 4.63 (HR 3.983, 1.973 – 8.042, $p < 0.001$) and PLR ≥ 151.24 (HR 2.254, 1.163 – 4.371, $p = 0.016$) were associated with non-response to medical therapy.

Studies Investigating Severity of LEAD (Table 2)

14 studies reported the severity of LEAD in 13632 patients (Table 2). Study design was prospective in one study, retrospective in 13 studies, and observational in all studies. Nine of these studies reported clinical measures of disease severity assessment; in the remaining five studies angiographic measures of disease severity assessment were reported.

Studies Reporting Clinical Assessment of Severity

Bath et al[28] used retrospective registry interrogation to identify 3687 patients undergoing revascularisation (59% PTA, 41% surgical bypass) for LEAD (53.4% intermittent claudication, 14.5% rest pain, 32.1% tissue loss). High NLR (pre-operative) was defined as ≥ 3.65 based on ROC analysis. There was a higher rate of more severe disease (tissue loss 56.47% vs. 27.33%, $p < 0.001$) in the high NLR vs. low NLR groups.

Velioglu et al[42] compared 75 patients with symptomatic LEAD (diagnosed by clinical assessment and ABPI) seen at outpatient clinics with 75 healthy controls. NLR was found to be higher in the LEAD cohort, however NLR did not predict LEAD on multivariate analysis.

Demirdal et al[43] recruited 280 patients who were admitted to hospital for management of diabetic foot sepsis. LEAD was diagnosed following review by vascular surgeon and

imaging. NLR was higher in the LEAD group ($p = 0.007$), and PLR demonstrated a non-significant trend towards being higher in the LEAD group.

Belaj et al[44] calculated the "derived NLR" (dNLR) by dividing the neutrophil count by the difference between the leucocyte count and the neutrophil count. This was performed on 1995 patients who were managed for LEAD by any management strategy. ROC analysis was used to determine a cutoff of dNLR to predict CLTI. dNLR > 2.5 was associated with CLTI (OR 1.6, 1.3 – 2.0, $p < 0.01$).

Demirtas et al[45] prospectively recruited 82 consecutive patients undergoing investigation and management for LEAD. Disease severity was classified according to Fontaine's stages, with baseline NLR similar between different stages.

Gary et al[46] retrospectively analysed 2121 patients treated for LEAD (32.1% CLTI, 67.9% claudication). PLR > 150 was determined as a cutoff based on ROC analysis. There was a higher proportion of patients with CLTI and tissue loss in the high PLR cohort. PLR > 150 was associated with CLTI on multivariate analysis (OR 1.9, 1.7 – 2.1, $p <0.001$). The same patient population was subsequently analysed in terms of NLR[47]. NLR > 3.95 was determined as a cutoff based on ROC analysis. There was a higher proportion of patients with CLTI in the high NLR cohort. NLR > 3.95 was associated with CLTI on multivariate analysis (OR 2.5, 2.3 – 2.7, $p <0.001$).

Erturk et al[22] used an NLR > 3.0 as a cutoff in 508 patients with symptomatic LEAD (77.8% claudication, 22.2% CLTI, defined by Fontaine classification). The high NLR cohort had significantly more patients with CLTI than the low NLR cohort (28% vs. 19%, $p = 0.019$).

Pourafkari et al[27] retrospectively analysed 1228 patients with LEAD (67.2% CLTI, 22.8% claudication) undergoing both surgical and endovascular revascularisation. In the high NLR tertile there was a significantly higher proportion of patients with CLTI.

Studies Reporting Angiographic Assessment of Severity

Celebi et al[48] reported outcomes in 280 patients referred for invasive angiography to confirm LEAD based on clinical suspicion. The pattern of disease as per TASC-II criteria was used to diagnose disease severity; TASC A/B were considered mild-moderate, TASC C/D were considered advanced. Patients without significant disease on angiography had lower baseline NLR. NLR was higher in TASC C/D patients compared to TASC A/B, and NLR predicted advanced disease on multivariate analysis (HR 0.896, 0.845 – 0.950, $p <$ 0.001).

Teperman et al[49] retrospectively analysed 733 patients who had been referred for invasive angiography due to symptoms of LEAD (85.4% claudication, 14.6% CLTI). Patients were subgrouped based on tertiles of NLR. There was a higher proportion of CLTI in the high NLR tertile. Severe multilevel disease (defined as >70% stenosis in both supra- and infra-popliteal segments) was associated with high NLR tertile on univariate analysis (OR 1.11, 1.03 – 1.19, $p = 0.007$), however this was not reproduced on multivariate analysis (OR 1.07, 1.00 – 1.15, $p = 0.056$).

Hamur et al[50] reported outcomes on 211 patients with symptomatic LEAD (67.8% claudication, 32.1% CLTI) who were referred for invasive angiography with a primary outcome of angiographic chronic total occlusion (CTO). Baseline NLR was higher in patients with angiographic CTO, however this was not reproduced on multivariate analysis (OR 0.620, 0.220 – 1.745, $p = 0.365$).

Aykan et al[51] retrospectively reported outcomes on 343 patients undergoing invasive angiography who were grouped based on TASC-II criteria of their disease. Patients with TASC A/B disease had significantly lower baseline NLR than those with TASC C/D disease. ROC analysis resulted in a cutoff of NLR > 3.05 to predict TASC C/D disease, which showed significant association on multivariate analysis (OR 1.914, 1.515 – 2.418, $p < 0.001$).

Studies Investigating Technical Success of Revascularisation (Table 3)

Eight studies reported technical success of revascularisation in 1587 patients (Table 3). Study design was prospective in one study, retrospective in seven studies, and observational in all studies. Seven of these studies reported outcomes in patients undergoing endovascular management, in the one remaining study patients underwent surgical management.

Studies Reporting Success of Endovascular Management

Lee et al[34] reported TVR (>80% stenosis on colour-coded duplex sonography) on 95 patients undergoing PTA and stent placement for intermittent claudication with 24-month prospective follow-up. The absolute values of NLR and PLR were higher in patients who developed TVR than those who did not. ROC-derived cutoffs to predict TVR were NLR ≥ 2.75 and PLR ≥ 91. On multivariate analysis high NLR (HR 3.1, 1.3 – 7.7, $p = 0.01$) and high PLR (HR 3.0, 1.1 – 8.5, $p = 0.04$) were associated with TVR < 24 months.

Zhen et al[52] reported 6 month primary patency rates in 70 patients who underwent femoro-popliteal PTA with drug coated balloons for LEAD (42.9% CLTI and 57.1% claudication), with restenosis defined on colour-coded duplex sonography. In the group with primary patency < 6 months there was lower baseline PLR and a non-significant trend towards lower baseline PLR. Baseline PLR was associated with inferior 6-month primary patency on multivariate analysis (OR 1.008, 1.001 – 1.016, $p = 0.031$).

Zhen et al[53] also reported 6-month primary patency rates on a cohort of patients with LEAD (45.1% CLTI, 54.9% claudication) undergoing femoro-popliteal PTA with drug coated (n = 44) and uncoated (n = 62) balloons. Post-procedure NLR predicted 6-month primary patency on multivariate analysis, with a lower NLR conferring a superior result (OR 1.589, 1.078 – 2.343, $p = 0.019$).

Chang et al[54] reported rates of ISR (< 12 months, early, and >12 months, late) in patients undergoing PTA and stent insertion for femoropopliteal CTO. 180 patients with CTO were included (60 claudication, 120 CLTI), with ROC analysis producing a cutoff of NLR ≥ 3.62. Multivariate analysis showed that high NLR predicted early ISR (OR 1.703, 1.521 – 2.063, $p = 0.002$).

Nakazawa et al[55] retrospectively assessed 479 patients with LEAD undergoing first-time stenting of the femoral-above knee popliteal arteries, with a primary outcome of ISR within 12 months on either colour-coded duplex sonography or angiography. NLR was similar between ISR and no-ISR groups, and multivariate analysis did not demonstrate NLR as a significant covariate.

Teperman et al[49] retrospectively analysed 733 patients who had been referred for invasive angiography due to symptoms of LEAD (85.4% claudication, 14.6% CLTI). Of these, 424 underwent intervention (PTA) and had followup data available. Patients were subgrouped based on tertiles of NLR. At a median followup of 10.4 months there was no difference in TVR between NLR tertiles.

Chan et al[30] included 83 patients undergoing infrapopliteal PTA for CLTI, and defined high NLR as ≥ 5.25 based on previously published results. High NLR cohort was not associated with 12-month primary patency (HR 1.03, 0.74 – 1.43, $p = 0.87$).

Studies Reporting Success of Surgical Management

González-Hernandez et al[29] included 150 patients undergoing surgical bypass to the below knee vessels for LEAD (93% CLTI) who were followed-up for 24 months. High NLR was defined as the 4th quartile. On multivariate analyses, the high NLR cohort was associated with inferior primary patency (HR 1.77, 1.01 – 3.10, $p = 0.04$), with a non-significant association with primary assisted patency (HR 1.70, 0.89 – 3.24, $p = 0.10$).

Risk of Bias Assessment (Table 4)

The risk of bias assessment using the QUIPS tool is shown in supplemental appendix 1, with a summary of the assessment outcomes in the included studies in table 4. High risk of bias was judged in 17 of 204 (8%) domains, moderate risk in 119 of 204 (59%) domains, and low risk in 68 of 204 (33%) domains.

Discussion

The present systematic review identified 20 studies that reported clinical outcomes in relation to NLR and PLR; all reported inferior clinical outcomes in patients with increased inflammatory parameters. Increased NLR and PLR were also associated with more severe LEAD in 13 of 14 studies (93%), and with inferior revascularisation outcomes in seven of eight studies (88%).

The precise mechanism by which elevated NLR or PLR confer inferior clinical outcomes is incompletely understood. Inflammatory cytokines such as interleukin-6 (IL-6) are known to have on the rate of cardiovascular events[56]. Elevated IL-6 has been associated with increased levels of fatigue and poor quality of life, though this is not specifically described in LEAD patients[57]. IL-6 is expressed by vascular endothelial cells in response to oxidative stress, which is a potential mechanism by which atherosclerotic disease may lead to increase morbidity and mortality[58].

It appears that in patients with established atherosclerotic disease, the use of immunomodulation can reduce the future risk of cardiovascular events as well as lower the NLR. The CANTOS trial described promising results in patients with IHD undergoing IL-1β blockade[59], however these results have not yet been reproduced in patients with LEAD. Follow-up studies with alternative immunomodulatory agents are eagerly awaited[60], and the results may prove transferable to patients with LEAD. Glucocorticoids have been used to suppress periprocedural inflammation in patients undergoing intervention for abdominal aortic aneurysm[61], however remain underreported in patients with LEAD.

The association between LEAD severity and NLR or PLR highlights the important role of inflammation as a key aetiopathological component of atherosclerosis[10]. The rate of atherosclerotic progression appears to be related to levels of pro-inflammatory cytokines,

though this has largely been demonstrated in pre-clinical studies[62]. Due to the established progression of LEAD, early identification of patients with increased NLR and PLR when presenting with less severe disease may allow for modulation of their chronic inflammation and resultant prevention of disease progression. Prospective evaluation of this relationship in LEAD patients with clinically meaningful outcomes such as AFS and MACE is lacking.

Treatment success rate following revascularisation is complex and multifactorial. Neointimal hyperplasia is a key component of ISR[63], which is modulated by the use of drug-coated technology, however this is the subject of some current controversy[64]. Pre-clinical models of vein graft failure highlight a complex inflammatory insult to vascular endothelium resulting in accelerated atherosclerotic plaque deposition and a propensity to thrombosis[65]. Thrombus itself is known to promote inflammation due to a large pro-inflammatory cytokine content, in particular IL-6[66], and additionally thrombosis is an established consequence of inflammation[67,68]. Current secondary prevention measures focus on modulation of the coagulation cascade, with recent evidence supporting the concomitant use of both anti-coagulant and anti-platelet agents[69]. Identification of patients with increased levels of NLR and PLR may allow for tailored secondary prevention strategies which focus on suppressing the inflammatory environment rather than platelet aggregation.

Historically studies reporting technical success of revascularisation have been criticised for reporting rates of graft or vessel patency whilst neglecting clinically meaningful outcomes such as limb salvage rates, quality of life, and functional performance. Whilst some of the studies in this review report patency rates alone, there are also seven studies included which report either MALE, AFS, or rate of amputations (the inverse of limb salvage rate). This strengthens the clinical application of their conclusions and supports the use of NLR and PLR as a meaningful clinical risk assessment tool. Furthermore, NLR and PLR are attractive

options for use as prognostic markers as they are easily obtained through investigations which are already typically part of routine clinical practice.

The present review initially attempted to describe the effect that mGPS has on LEAD, however, the lack of any relevant studies made this impossible. We recently reported associations between systemic inflammation, skeletal muscle loss, frailty, and outcomes in patients with abdominal aortic aneurysm and with CLTI[70–72], using the novel systemic inflammatory grade (SIG). SIG describes both the differential white cell and acute phase inflammatory responses (NLR and mGPS), and therefore may offer a more comprehensive assessment of systemic inflammation, however further evaluation of this parameter is required.

Limitations

The majority of studies in this review employed a retrospective study design and as such the inherent limitations of retrospective studies apply to their findings.

A proportion of the studies included in this review include patients with intermittent claudication in their reporting of outcomes. Worldwide there is significant heterogeneity in management of claudication, with advocates for both conservative and more aggressive strategies. The inclusion of claudication by some authors limits the generalisability of these results.

A major limitation which affects all studies in this review is the lack of consensus definition on a cut-off for high/low NLR and PLR. Methods used include ROC analysis, data-derived cut-offs (e.g., tertiles), or absolute values based on previous studies. Each of these methods limits the generalisability of the results beyond the population studied.

Performing meaningful quantitative analysis is impossible given the significant heterogeneity in interventions, populations, and outcomes reported by the studies in this review.

Any inflammatory parameter measured in LEAD patients will be confounded by tissue loss with secondary infection. Whilst some studies specifically excluded these patients, this was not universal and so may impact upon the reliability of their results. Universal application of the Society for Vascular Surgery Wound, Ischaemia, and Foot Infection Score (SVS WIFI)[73] was not performed; this would enable more accurate assessment of heterogeneity between studies.

Conclusions

The studies included in this review support the role of elevated NLR and PLR as key components influencing the clinical outcomes, severity, and success of treatment in patients with LEAD. The use of these easily accessible, cost effective and routinely available markers is supported by the present review.

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Disclosures

The authors declare that there is no conflict of interest.

Author Contributions

Study Conceptualisation: CSDR, DCM, GJKG

Data Collection: NAB

Data Analysis: NAB

Manuscript Preparation: NAB, GJKG

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Table 1: Studies investigating the association between clinical outcomes and NLR or PLR in patients with PAD following (A) all methods of management (B) surgical revascularisation (C) endovascular revascularisation (D) amputation (E) conservative management

Author	PMID	Population	*n*	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
(A).										
Erturk et al (2014)	24685686	Symptomatic PAD (77.8% IC, 22.2% CLTI) with >50% angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	High NLR associated with MACE on multivariate analysis (HR 2.04, 1.26 – 3.30, $p = 0.004$)
Spark et al (2010)	20573475	All CLTI admissions	149	Retrospective	Single	All-cause mortality	NLR	Tertiles, ROC (5.25)	8.7 months	Inferior OS in high NLR group, NLR > 5.25 associated with increased mortality on multivariate analysis (HR 2.3, 1.2 – 4.2, $p = 0.007$)
González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	AFS	NLR	Absolute value (5.0)	31 months	Inferior 5 year OS and AFS in high NLR group, high NLR associated with inferior 5-year AFS on multivariate analysis (HR 2.325, 1.732 – 3.121)

Sanz et al (2016)	26602223	All CLTI (Rutherford > 4) patients undergoing open or endo revascularisation (excluded deaths <24hrs)	672	Retrospective	Single	AFS 12 months post-procedure	NLR	NLR > 5 (data derived)	12 months	NLR > 5 predicted increased risk of amputation or death at 12 months on multivariate analysis (HR 2.325, 1.732 – 3.121, $p < 0.001$)
Uzun et al (2017)	28344615	PAD with >50% angiographic stenosis (18.3% CLTI, 81.7% IC) undergoing open (16.8%), endo (34.4%), or medical (48.8%) management	602	Retrospective	Single	MACE	PLR	Absolute value of PLR	33.8 months	Rate of MACE higher in High PLR group, PLR > 142 associated with MACE on multivariate analysis (HR 1.03, 1.01 – 1.04, $p = 0.001$)
Pourafkari et al (2018)	29848209	All patients with PAD (67.2% CLTI) undergoing PTA / bypass	1228	Retrospective	Multi	MALE, MACE, all-cause mortality	NLR	Tertiles, ROC	NR	High NLR tertile associated with CLTI, increased risk of MALE in high NLR tertile (HR 1.094, 1.071 – 1.118, $p <0.001$), increased risk of 10-year mortality in high NLR tertile (HR 1.096, 1.072 – 1.120, $p <0.001$)
Bath et al (2020)	31882318	Elective PTA (59%) / bypass (41%) for PAD (53.4% IC, 14.5% rest pain,	3687	Retrospective	Multicentre (registry interrogation)	Association between NLR and severity, in hospital	NLR	ROC	NR	Higher NLR in more severe disease (TL vs. rest pain vs. IC), Baseline raised NLR associated with in hospital death (HR 5.359, 1.682 –

		32.1% tissue loss)				death/cardiac event				17.074, $p = 0.004$) and cardiac event (HR 2.907, 1.565 – 5.400, $p = 0.0007$)

(B).

González-Hernandez et al (2021)	33496158	PAD (93% CLTI, 7% claudicants) undergoing infragenicular vein bypass	150	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE), graft patency, AFS	NLR	Quartiles (Q4 = high, Q1-3 = low)	24 months	High NLR associated with worse AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$), patency loss (HR 1.77, 1.01 – 3.10, $p = 0.04$)

(C).

Chan et al (2014)	24816510	All patients undergoing infrapopliteal PTA for CLTI	83	Retrospective	Single	Technical success (<50% residual stenosis, restored perfusion), OS, 12-month primary patency, AFS	NLR	Absolute value (5.25)	12 months	High NLR associated with increased 1-year mortality (HR 1.97, 1.08 – 3.62, $p = 0.03$). NS values for primary patency and AFS
Chen et al (2016)	27713601	PAD patients with CKD (CrCl ≤30mL/min/1.73 m^2) admitted for PTA (12.8% IC, 87.2% CLTI)	148	Retrospective	Single	AFS	NLR, PLR	Absolute value	8.6 months	High NLR cohort associated with increased risk AFS (HR 2.23, 1.03 – 4.82, $p = 0.04$)
Huang et al (2019)	31415395	CLTI undergoing PTA	736	Retrospective	Single	Amputation rate	NLR, PLR	-	NR	Higher NLR & PLR at baseline in patients who required amputation, PLR

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Jhang et al (2020)	33177036	PAD (83% CLTI) undergoing lower limb PTA	232	Retrospective	Single	2-year "longevity"	NLR, PLR	ROC (NLR > 3.89)	24 months	High NLR cohort associated with increased 2 year mortality (HR 2.679, 1.312 – 5.470, $p = 0.007$)
Lee et al (2020)	32503291	IC patients undergoing SFA stent	95	Prospective	Single	Target Vessel Restenosis (TVR) on duplex within 2 years, MACE	NLR, PLR	ROC	24 months	NLR associated with TVR (HR 3.1, 1.3 – 7.7, $p = 0.01$), PLR associated with TVR (HR 3.0, 1.1 – 8.5, $p = 0.04$)
Su et al (2021)	34043672	CLTI undergoing PTA	195	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE)	NLR	ROC (NLR ≥8)	NR	High NLR associated with increased 1-year mortality, MALE, MACE ($p < 0.05$). Reproduced on multivariate analysis.
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Wang et al (2017)	28042626	ALI (28.5%) and CLTI (71.5%, Rutherford V/VI) undergoing minor (11.1%) and major (88.9%) amputation	270	Retrospective	Single	"poor prognosis" group	NLR, PLR	ROC	NR	Higher NLR and PLR in "poor prognosis" group, reproduced on multivariate
Pierre-Louis et al (2019)	30339899	Patients undergoing major amputation	410	Retrospective	Multicentre	30-day mortality, need for revision	NLR	-	NR	Post-op NLR higher in patients requiring revision, Pre- and Post-op NLR higher in patients who died

										within 30-days, post-op NLR associated with 30-day mortality on multivariate analysis

(E).

Taşoğlu et al (2014)	23393289	CLTI patients with non-operable disease (due to non-reconstructable, fitness, declined)	104	Retrospective	Single	Amputation, overall survival	NLR, PLR	ROC, patients group into "low/medium/ high risk" based on 0/1/2 being elevated	NR	Composite outcome of "High risk" (High NLR & High PLR) predicted amputation (OR 4.7, 1.7 – 12.6, $p = 0.002$)
Luo et al (2015)	26017794	CLTI patients without tissue loss undergoing medical management	172	Retrospective	Single	AFS at 36 months	NLR	ROC	36 months	Higher rate of total amputations, BKA, Toe amp in High NLR group, inferior survival in high NLR group, NLR predicted amputation on multivariate (HR 1.140, 1.086 – 1.197, $p < 0.001$)
Amrock et al (2016)	26762418	Patients with PAD diagnosed by ABPI (<0.9)	556	Retrospective	Multicentre (registry interrogation)	All cause mortality and cardiovascular mortality	NLR	NR	97.2 months	NLR predicted all cause mortality (HR 1.20, 1.04 – 1.39, $p = 0.012$)
Erdoğan et al (2021)	33427105	CLTI with no revasc option, medical management	268	Retrospective	Single	Response to medical treatment (less pain, ulcer healing)	NLR, PLR	ROC (NLR ≥ 4.63, PLR ≥ 151.24)	NR	High NLR associated with no response (HR 3.983, 1.973 – 8.042, $p < 0.001$), high PLR associated with no response (HR 2.254, 1.163 – 4.371, $p = 0.016$)

Table 2: Studies investigating the association between disease severity and NLR or PLR in patients with PAD based on A) clinical assessment and B) angiographic assessment

Author	PMID	Population	*n*	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
(A).										
Bath et al (2020)	31882318	Elective PTA (59%) / bypass (41%) for PAD (53.4% IC, 14.5% rest pain, 32.1% tissue loss)	3687	Retrospective	Multicentre (registry interrogation)	Association between NLR and severity, in hospital death/cardiac event	NLR	ROC	NR	Higher NLR in more severe disease (TL vs. rest pain vs. IC), Baseline raised NLR associated with in hospital death (HR 5.359, 1.682 – 17.074, $p = 0.004$) and cardiac event (HR 2.907, 1.565 – 5.400, $p = 0.0007$)
Velioglu et al (2019)	30924393	OP clinic PAD patients (CLTI vs. IC NR) and controls	75	Retrospective	Single	Difference in NLR/PLR in PAD vs. control	NLR, PLR	Cases vs. controls	NR	NLR higher in PAD patients ($p = 0.034$), NLR & PLR not significant at predicting PAD on multivariate analysis
Demirdal et al (2018)	30176260	All patients hospitalised with foot sepsis and known diabetes	280	Retrospective	Single	Role of NLR/PLR in predicting PAD	NLR, PLR	ROC		NLR significantly higher in patients with PAD ($p = 0.007$)
Belaj et al (2015)	26058674	All patients treated for PAD (27.6% CLTI)	1995	Retrospective	Single	Association of dNLR with CLTI	dNLR (derived NLR)	dNLR > 2.5 (ROC analysis)	NR	Higher rate of CLTI in patients with dNLR >2.5, dNLR >2.5 predicted CLTI on multivariate analysis

										(OR 1.6, 1.3 – 2.0, $p <$ 0.01)
González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	Association of NLR with Rutherford Category	NLR	Absolute value (5.0)	31 months	Higher proportion of Rutherford 5 disease in the NLR > 5.0 cohort (54.8% vs 71.4%, $p = 0.002$)
Demirtas et al (2014)	24522438	Consecutive PAD patients without tissue loss (Fontaine I 36%, Fontaine II 28%, Fontaine III 36%)	50	Prospective	NR	Association between NLR and disease severity (Fontaine stage)	NLR	Fontaine stage	NR	No difference in NLR in different Fontaine stages (I-III)
Gary et al (2013)	23457609	PAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between NLR and rate of CLTI	NLR	Tertiles, ROC	NR	Rate of CLTI higher in High NLR Tertile, NLR > 3.95 (ROC) associated with increased risk of CLTI in multivariate model (OR 2.5 2.3 – 2.7, $p < 0.001$)
Gary et al (2013)	23844064	PAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between PLR and rate of CLTI	PLR	Tertiles, ROC	NR	Rate of CLTI higher in High PLR Tertile, PLR > 150 (ROC) associated with increased risk of CLTI in multivariate model (OR 1.9, 1.7 – 2.1, $p < 0.001$)
Erturk et al (2014)	24685686	Symptomatic PAD (77.8% IC, 22.2% CLTI) with >50%	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	Higher proportion CLTI in high NLR cohort

		angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)								
Pourafkari et al (2018)	29848209	All patients with PAD (67.2% CLTI) undergoing PTA / bypass	1228	Retrospective	Multi	Rate of CLTI	NLR	Tertiles	NR	Rate of CLTI 86.8% in high NLR tertile vs. 64.9% and 49.9% in mid and low tertiles ($p < 0.001$)
(B).										
Celebi et al (2020)	32445291	Patients referred for angiography to diagnose PAD (TASC II definition)	280	Retrospective	Single	Presence of TASC II PAD	NLR	-	NR	NLR predicted "advanced" (TASC C/D) PAD (OR 0.896. 0.845 – 0.950, $p <$ 0.001), NLR higher in TASC C/D vs. TASC A/B. NLR higher in PAD vs. no PAD.
Teperman et al (2016)	27865186	Symptomatic PAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	733	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	Higher proportion of CLTI in high NLR tertile, higher proportion of multilevel disease in high NLR tertile, no difference in rates of target vessel revascularisation in NLR tertiles

Hamur et al (2016)	27059289	Symptomatic PAD (67.8% IC, 32.1% CLTI) referred for angiography with ipsilateral lesion >50% stenosis	211	Retrospective	Single	Determinants of angiographic CTO	NLR	CTO yes or no	NR	Higher baseline NLR in CTO group, not reproduced on multivariate
Aykan et al (2016)	27004700	Patients undergoing angiography with suspected PAD	343	Retrospective	Single	Complexity of disease (TASC-II classification)	NLR	TASC-A/B/C/D	NR	Higher baseline NLR in TASC-C&D vs. TASC-A&B, NLR predicted TASC-C&D category on multivariate (HR1.914, 1.515 – 2.418, p <0.001)

Table 3: Studies investigating the association between the technical success of revascularisation strategies and NLR or PLR in patients with PAD in patients undergoing A) endovascular treatment and B) surgical treatment

Author	PMID	Population	*n*	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
(A).										
Lee et al (2020)	32503291	IC patients undergoing SFA stent	95	Prospective	Single	Target Vessel Restenosis (TVR) on duplex within 2 years, MACE	NLR, PLR	ROC	24 months	NLR associated with TVR (HR 3.1, 1.3 – 7.7, p = 0.01*)*, PLR associated with TVR (HR 3.0, 1.1 – 8.5, p = 0.04*)*
Zhen et al (2020)	31918662	Patients undergoing drug-coated balloon PTA for fem-pop disease	70	Retrospective	Single	Primary patency (duplex) at 6 months	NLR, PLR	-	6 months	Higher baseline PLR in TVR group, similar baseline NLR in TVR group. Baseline PLR predicted 6-month primary patency (OR 1.008, 1.001-1.016, p = 0.031)
Zhen et al (2019)	30221973	Fem-pop PTA (CLTI vs. IC NR), 41.5% DCB, 58.5% UCB	106	Retrospective	Single	6-month primary patency	NLR	ROC	6 months	Post-op NLR higher in DCB group (p = 0.004), primary patency higher in DCB (p = 0.011), low post-op NLR predicted superior primary patency (OR 1.589, 1.078 – 2.343, p = 0.019)

Chang et al (2018)	28635304	Patients undergoing stent for fem-pop CTO	180	Retrospective	Single	Early ISR (<12 months)	NLR	ROC, early ISR vs. no early ISR	NR	Baseline NLR higher in early ISR group (p = 0.04), high NLR associated with increased risk early ISR on multivariate analysis
Nakazawa et al (2017)	28259571	First time fem-AK pop segment stent (76.0% CLTI, 24.0% IC)	479	Retrospective	Single	ISR within 24 months (>50% narrowing / 2.5 x PSV)	NLR, PLR	ISR in 24 months vs. not	24 months	Absolute values of neutrophils and platelets higher in ISR-yes group but NLR and PLR similar. Reproduced on multivariate analyses.
Teperman et al (2016)	27865186	Symptomatic PAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	424	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	No difference in rates of target vessel revascularisation in NLR tertiles
Chan et al (2014)	24816510	All patients undergoing infrapopliteal PTA for CLTI	83	Retrospective	Single	Technical success (<50% residual stenosis, restored perfusion), OS, 12-month primary patency, AFS	NLR	Absolute value (5.25)	12 months	High NLR associated with increased 1-year mortality (HR 1.97, 1.08 – 3.62, p = 0.03). NS values for primary patency and AFS

(B).

González-Hernandez et al (2021)	33496158	PAD (93% CLTI, 7% claudicants) undergoing infragenicular vein bypass	150	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE), graft patency, AFS	NLR	Quartiles (Q4 = high, Q1-3 = low)	24 months	High NLR associated with worse AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$), patency loss (HR 1.77, 1.01 – 3.10, $p = 0.04$)

Table 4: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Erturk et al (2014)						
Spark et al (2010)						
González-Fajardo et al (2014)						
Sanz et al (2016)						
Uzun et al (2017)						
Pourafkari et al (2018)						
Bath et al (2020)						
González-Hernandez et al (2021)						
Chan et al (2014)						

Chen et al (2016)						
Huang et al (2019)						
Jhang et al (2020)						
Lee et al (2020)						
Su et al (2021)						
Wang et al (2017)						
Pierre-Louis et al (2019)						
Taşoğlu et al (2014)						
Luo et al (2015)						
Amrock et al (2016)						
Erdoğan et al (2021)						
Velioglu et al (2019)						
Demirdal et al (2018)						

Belaj et al (2015)						
Demirtas et al (2014)						
Gary et al (2013)						
Gary et al (2013) (2)						
Celebi et al (2020)						
Teperman et al (2016)						
Hamur et al (2016)						
Aykan et al (2016)						
Zhen et al (2020)						
Zhen et al (2019)						
Chang et al (2018)						
Nakazawa et al (2017)						

Green – low risk of bias. Amber – moderate risk of bias. Red – high risk of bias.

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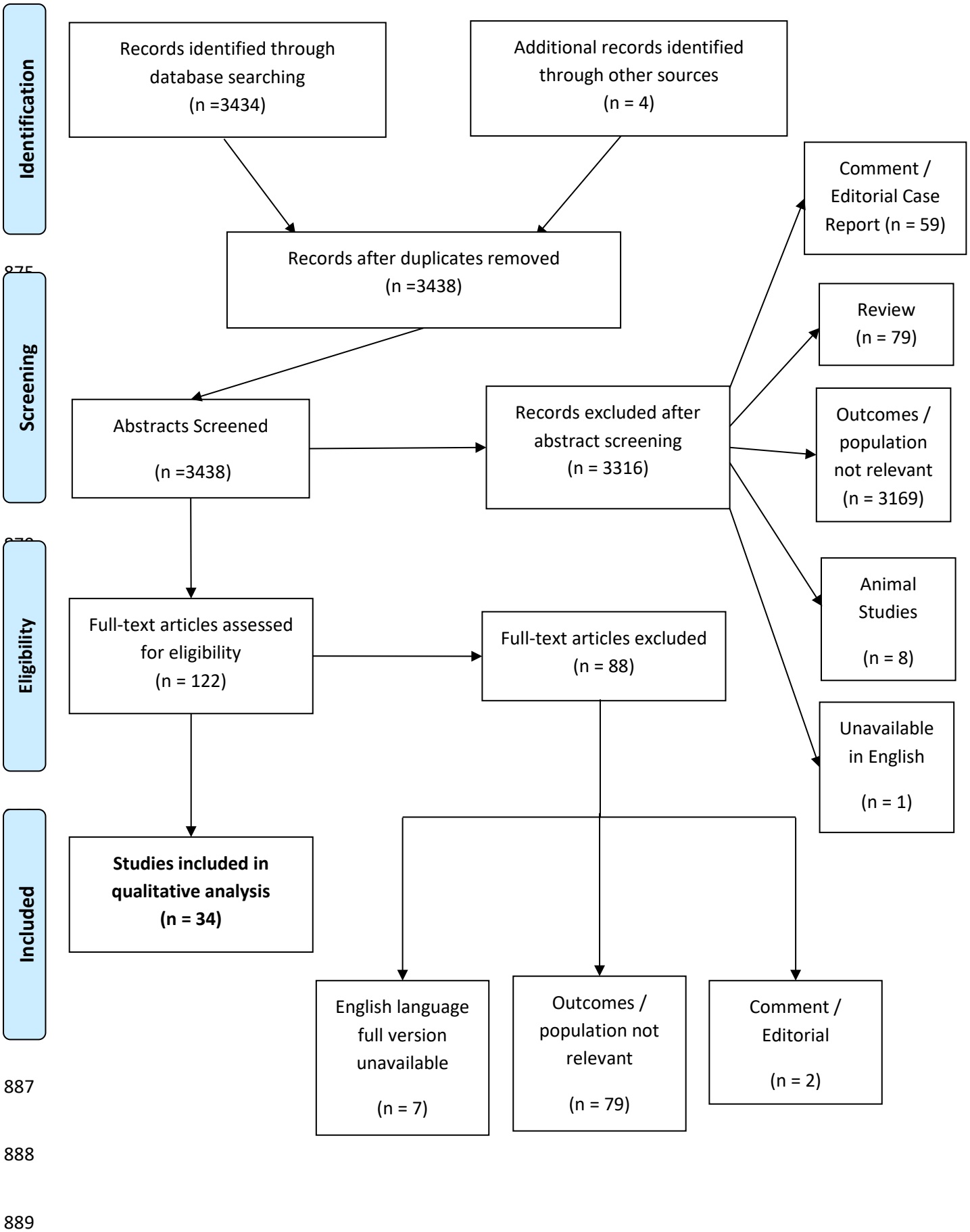

Figure 1: *PRISMA diagram showing study inclusion*

Figure Legends

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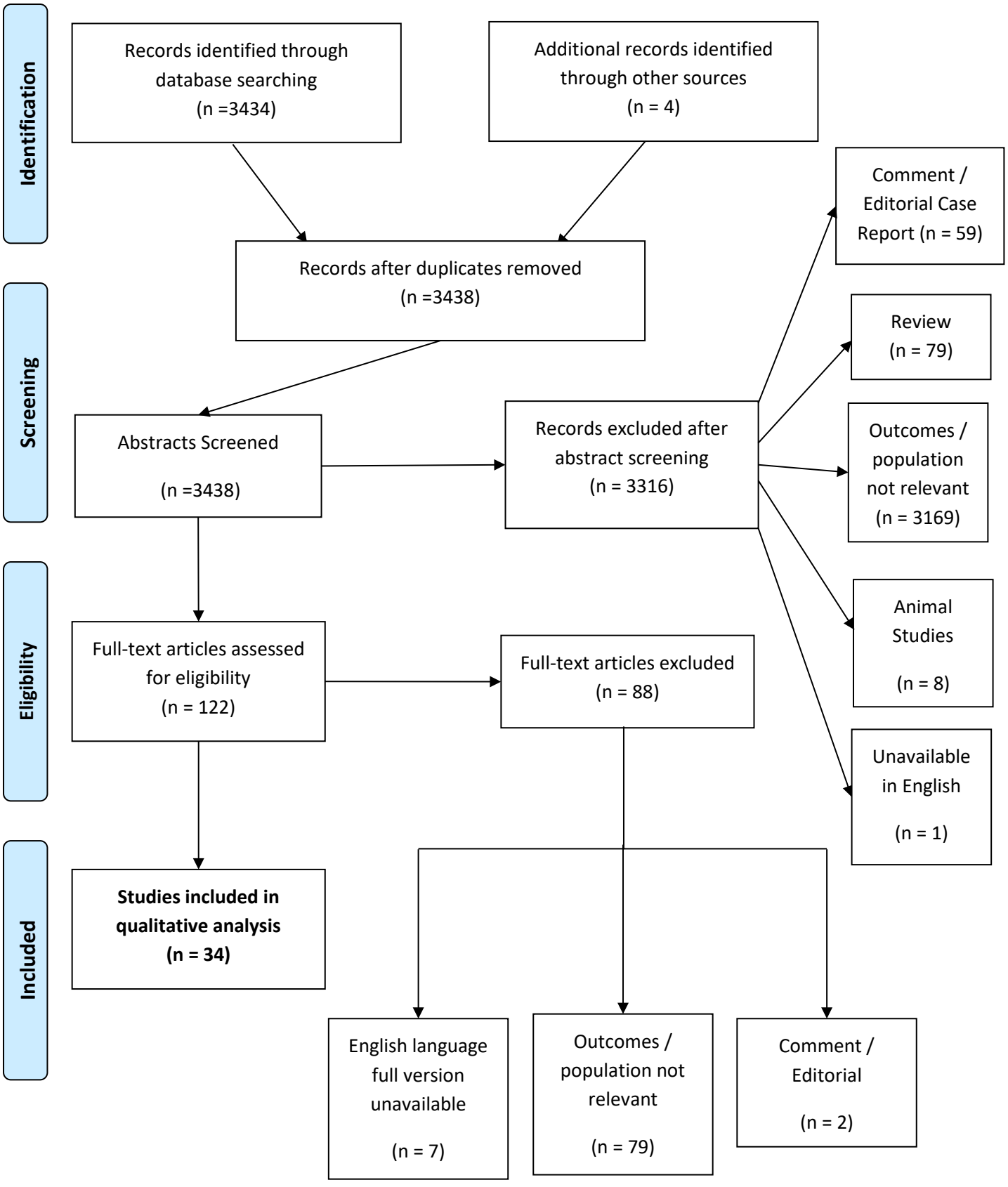

Figure 1: *PRISMA diagram showing study inclusion*

Table 1: Studies investigating the association between clinical outcomes and NLR or PLR in patients with PAD following A) all methods of management B) surgical revascularisation C) endovascular revascularisation D) amputation E) conservative management

Author	PMID	Population	*n*	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
A).										
Erturk et al (2014)	24685686	Symptomatic PAD (77.8% IC, 22.2% CLTI) with >50% angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	High NLR associated with MACE on multivariate analysis (HR 2.04, 1.26 – 3.30, $p = 0.004$)
Spark et al (2010)	20573475	All CLTI admissions	149	Retrospective	Single	All-cause mortality	NLR	Tertiles, ROC (5.25)	8.7 months	Inferior OS in high NLR group, NLR > 5.25 associated with increased mortality on multivariate analysis (HR 2.3, 1.2 – 4.2, $p = 0.007$)
González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	AFS	NLR	Absolute value (5.0)	31 months	Inferior 5 year OS and AFS in high NLR group, high NLR associated with inferior 5-year AFS on multivariate analysis (HR 2.325, 1.732 – 3.121)
Sanz et al (2016)	26602223	All CLTI (Rutherford > 4) patients undergoing open or endo revascularisation (excluded deaths <24hrs)	672	Retrospective	Single	AFS 12 months post-procedure	NLR	NLR > 5 (data derived)	12 months	NLR > 5 predicted increased risk of amputation or death at 12 months on multivariate analysis (HR 2.325, 1.732 – 3.121, $p < 0.001$)
Uzun et al (2017)	28344615	PAD with >50% angiographic	602	Retrospective	Single	MACE	PLR	Absolute value of PLR	33.8 months	Rate of MACE higher in High PLR group, PLR >

		stenosis (18.3% CLTI, 81.7% IC) undergoing open (16.8%), endo (34.4%), or medical (48.8%) management								142 associated with MACE on multivariate analysis (HR 1.03, 1.01 – 1.04, p = 0.001)
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Belaj et al (2015)	26058674	All patients treated for PAD (27.6% CLTI)	1995	Retrospective	Single	Association of dNLR with CLTI	dNLR (derived NLR)	dNLR > 2.5 (ROC analysis)	NR	Higher rate of CLTI in patients with dNLR >2.5, dNLR >2.5 predicted CLTI on multivariate analysis (OR 1.6, 1.3 – 2.0, $p < 0.01$)
González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	Association of NLR with Rutherford Category	NLR	Absolute value (5.0)	31 months	Higher proportion of Rutherford 5 disease in the NLR > 5.0 cohort (54.8% vs 71.4%, $p = 0.002$)
Demirtas et al (2014)	24522438	Consecutive PAD patients without tissue loss (Fontaine I 36%,	50	Prospective	NR	Association between NLR and disease severity (Fontaine stage)	NLR	Fontaine stage	NR	No difference in NLR in different Fontaine stages (I-III)

		Fontaine II 28%, Fontaine III 36%)								
Gary et al (2013)	23457609	PAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between NLR and rate of CLTI	NLR	Tertiles, ROC	NR	Rate of CLTI higher in High NLR Tertile, NLR > 3.95 (ROC) associated with increased risk of CLTI in multivariate model (OR 2.5 2.3 – 2.7, $p < 0.001$)
Gary et al (2013)	23844064	PAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between PLR and rate of CLTI	PLR	Tertiles, ROC	NR	Rate of CLTI higher in High PLR Tertile, PLR > 150 (ROC) associated with increased risk of CLTI in multivariate model (OR 1.9, 1.7 – 2.1, $p < 0.001$)
Erturk et al (2014)	24685686	Symptomatic PAD (77.8% IC, 22.2% CLTI) with >50% angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	Higher proportion CLTI in high NLR cohort
Pourafkari et al (2018)	29848209	All patients with PAD (67.2% CLTI) undergoing PTA / bypass	1228	Retrospective	Multi	Rate of CLTI	NLR	Tertiles	NR	Rate of CLTI 86.8% in high NLR tertile vs. 64.9% and 49.9% in mid and low tertiles ($p < 0.001$)
B).										
Celebi et al (2020)	32445291	Patients referred for angiography to diagnose PAD (TASC II definition)	280	Retrospective	Single	Presence of TASC II PAD	NLR	-	NR	NLR predicted “advanced” (TASC C/D) PAD (OR 0.896. 0.845 – 0.950, $p < 0.001$), NLR higher in TASC C/D vs. TASC A/B. NLR higher in PAD vs. no PAD.

Teperman et al (2016)	27865186	Symptomatic PAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	733	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	Higher proportion of CLTI in high NLR tertile, higher proportion of multilevel disease in high NLR tertile, no difference in rates of target vessel revascularisation in NLR tertiles
Hamur et al (2016)	27059289	Symptomatic PAD (67.8% IC, 32.1% CLTI) referred for angiography with ipsilateral lesion >50% stenosis	211	Retrospective	Single	Determinants of angiographic CTO	NLR	CTO yes or no	NR	Higher baseline NLR in CTO group, not reproduced on multivariate
Aykan et al (2016)	27004700	Patients undergoing angiography with suspected PAD	343	Retrospective	Single	Complexity of disease (TASC-II classification)	NLR	TASC-A/B/C/D	NR	Higher baseline NLR in TASC-C&D vs. TASC-A&B, NLR predicted TASC-C&D category on multivariate (HR1.914, 1.515 – 2.418, p <0.001)

Table 3: Studies investigating the association between the technical success of revascularisation strategies and NLR or PLR in patients with PAD in patients undergoing A) endovascular treatment and B) surgical treatment

Author	PMID	Population	*n*	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
A).										
Lee et al (2020)	32503291	IC patients undergoing SFA stent	95	Prospective	Single	Target Vessel Restenosis (TVR) on duplex within 2 years, MACE	NLR, PLR	ROC	24 months	NLR associated with TVR (HR 3.1, 1.3 – 7.7, p = 0.01*)*, PLR associated with TVR (HR 3.0, 1.1 – 8.5, p = 0.04*)*
Zhen et al (2020)	31918662	Patients undergoing drug-coated balloon PTA for fem-pop disease	70	Retrospective	Single	Primary patency (duplex) at 6 months	NLR, PLR	-	6 months	Higher baseline PLR in TVR group, similar baseline NLR in TVR group. Baseline PLR predicted 6-month primary patency (OR 1.008, 1.001-1.016, p = 0.031)
Zhen et al (2019)	30221973	Fem-pop PTA (CLTI vs. IC NR), 41.5% DCB, 58.5% UCB	106	Retrospective	Single	6-month primary patency	NLR	ROC	6 months	Post-op NLR higher in DCB group (p = 0.004), primary patency higher in DCB (p = 0.011), low post-op NLR predicted superior primary patency (OR 1.589, 1.078 – 2.343, p = 0.019)
Chang et al (2018)	28635304	Patients undergoing stent for fem-pop CTO	180	Retrospective	Single	Early ISR (<12 months)	NLR	ROC, early ISR vs. no early ISR	NR	Baseline NLR higher in early ISR group (p = 0.04), high NLR associated with increased risk early ISR on multivariate analysis
Nakazawa et al (2017)	28259571	First time fem-AK pop segment stent (76.0% CLTI, 24.0% IC)	479	Retrospective	Single	ISR within 24 months (>50% narrowing / 2.5 x PSV)	NLR, PLR	ISR in 24 months vs. not	24 months	Absolute values of neutrophils and platelets higher in ISR-yes group but NLR and PLR similar. Reproduced on multivariate analyses.

Teperman et al (2016)	27865186	Symptomatic PAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	424	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	No difference in rates of target vessel revascularisation in NLR tertiles
Chan et al (2014)	24816510	All patients undergoing infrapopliteal PTA for CLTI	83	Retrospective	Single	Technical success (<50% residual stenosis, restored perfusion), OS, 12-month primary patency, AFS	NLR	Absolute value (5.25)	12 months	High NLR associated with increased 1-year mortality (HR 1.97, 1.08 – 3.62, p = 0.03). NS values for primary patency and AFS
B).										
González-Hernandez et al (2021)	33496158	PAD (93% CLTI, 7% claudicants) undergoing infragenicular vein bypass	150	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE), graft patency, AFS	NLR	Quartiles (Q4 = high, Q1-3 = low)	24 months	High NLR associated with worse AFS (HR 2.10, 1.06 – 4.14, p = 0.03), MALE (HR 2.04, 1.03 – 4.04, p = 0.04), patency loss (HR 1.77, 1.01 – 3.10, p = 0.04)

Table 4: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Erturk et al (2014)						
Spark et al (2010)						
González-Fajardo et al (2014)						
Sanz et al (2016)						
Uzun et al (2017)						
Pourafkari et al (2018)						
Bath et al (2020)						
González-Hernandez et al (2021)						
Chan et al (2014)						
Chen et al (2016)						
Huang et al (2019)						
Jhang et al (2020)						
Lee et al (2020)						
Su et al (2021)						

Wang et al (2017)						
Pierre-Louis et al (2019)						
Taşoğlu et al (2014)						
Luo et al (2015)						
Amrock et al (2016)						
Erdoğan et al (2021)						
Velioglu et al (2019)						
Demirdal et al (2018)						
Belaj et al (2015)						
Demirtas et al (2014)						
Gary et al (2013)						
Gary et al (2013) (2)						
Celebi et al (2020)						
Teperman et al (2016)						
Hamur et al (2016)						
Aykan et al (2016)						
Zhen et al (2020)						
Zhen et al (2019)						
Chang et al (2018)						

Nakazawa et al (2017)						
Green – low risk of bias. Amber – moderate risk of bias. Red – high risk of bias.						

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Author and year of publication	Erturk et al (2014)			
Study identifier	24685686			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*In this retrospective study, 593 consecutive patients who had been admitted to an inpatient ward of the vascular department of a large tertiary training and research hospital with diagnosis of symptomatic PAOD between May 2009 and September 2012 were included.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility, justified	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Ineligible patients excluded and justified	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Clearly stated including number at risk	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	reported clearly	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	reported clearly	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	no	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	no	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly stated	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements conducted similarly	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	not justified	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	The same for all participants	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Specific endpoint stated	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as "clinical records" however unclear if death registries used	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	The same for all participants	yes	**Low**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given universally	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Sourced from clinical records	yes	**Low**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Adequately described	yes	**Low**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Multivariate analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Appropriate survival analysis allows for the primary outcome to be assessed independently of the variables which were different in the baseline cohorts	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate modelling is used	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate modelling is used	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Spark et al (2010)			
Study identifier	20573475			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*All patients admitted with CLI at a single university teaching hospital were entered into this prospective study over a 2-year period*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	"all patients", However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	Not stated	No	**High**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Ineligible patients stated	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	not described	No	**High**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Ineligible patients stated due to missing data	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	no	**high**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Ineligible patients stated due to missing data	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	no	**high**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	no	**high**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**High**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Stated "admission" but not defined	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Measurement not stated	No	**High**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Data-dependent cutoff used however use of internal validation	No	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Not stated	No	**High**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequate	partial	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Not stated	No	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Endpoints stated and defined	No	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source reported	No	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Baseline variables not stated apart from in survival analysis	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**High**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated where the source of confounding variables was	no	**High**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**High**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Multivariate analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Multivariate analysis accounted for confounders	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**High**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	Baseline study characteristics not reported overall, just by subgroup	partial	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate modelling is used	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate modelling is used	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	González-Fajardo et al (2014)			
Study identifier	24559786			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*All patients with CLI undergoing elective infrainguinal vascular surgery (open or endovascular) at a single university teaching hospital between January 2005 and December 2009 were retrospectively identified from a prospectively maintained database.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Prospectively maintained database	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Adequately described	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Not reported	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Exclusions not reported	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly stated	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Cutoff used based on previous data	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	The same for all participants	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Well described endpoint, justified	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data reported	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	No clear definitions of comorbidities	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated where the source of confounding variables was, assumed the same	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Survival model included multivariater analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Appropriate survival analysis allows for the primary outcome to be assessed independently of the variables which were different in the baseline cohorts	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate modelling is used	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate modelling is used	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Sanz et al (2016)			
Study identifier	26602223			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*All revascularized patients diagnosed with critical ischaemia (Rutherford stages 4, 5, or 6) between January 1, 2005, and June 30, 2010, were included (conventional or endovascular treatment)*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	"all patients" stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Ineligible patients not stated or justified	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Not stated	Partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not stated - as above	Partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not stated - as above	Partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not stated - as above	Partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not stated - as above	Partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	not stated	partial	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Absolute value, not justified	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	All measurements implied to be conducted similarly but not specifically stated.	partial	**High**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	not stated	partial	**High**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	not stated	partial	**High**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	AFS not clearly defined	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as "medical records" however unclear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	no	**High**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not stated, implied	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Multivariate analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	MV model accounts	partial	**Moderate**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Multivariable model generation robust, appropriate justification	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Adequate	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Uzun et al (2017)			
Study identifier	28344615			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Six hundred two consecutive patients, who were admitted to inpatient clinic of the vascular department of a large tertiary training and research hospital with diagnosis of symptomatic PAOD between May 2009 and September 2013, were included in this retrospective study.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Clearly described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Clearly described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described forprocedural and patients factors.	Clearly described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Clearly stated	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Clearly stated	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Clearly stated	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Partial	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Partial	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	"admission" but no speciifc times.	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated	partial	**High**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Data-dependent cutoff used, not justified, based on survival analyses	partial	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Assumed similar but not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequate	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Not performed	partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	clearly stated	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Sources stated	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	Assumed similar but not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables, clearly defined	yes	**Low**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities given	yes	**Low**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Implied from clinical records	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Implied from clinical records	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Multivariate analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Appropriate survival analysis allows for the primary outcome to be assessed independently of the variables which were different in the baseline cohorts	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate modelling is used, however absolute cutoff of PLR based on data dependent survival data therefore bias	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate modelling is used	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Pourafkari et al (2018)			
Study identifier	29848209			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*This is a retrospective cohort study including all patients with a diagnosis of lower-limb PAD who had undergone revascularization (stenting/bypass graft) from May 2001 to December 2015 at the Veterans Affairs Western New York Healthcare System*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	"all patients" stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	stated	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	Adequately described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Clearly stated, adequate, flow diagram	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not stated	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Adequately described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not stated	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not stated	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	no speciifc times.	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Adequately described	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Data-dependent cutoff used, tertile	partial	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied though not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequately described	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Adequately described	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Specific endpoint stated, clear definitions for primary. Source stated	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as "clinical records" however unclear if death registries used	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given universally	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Medical records	yes	**Low**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Implied	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Modelling corrects for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Mvmodel	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate model building	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate, adequate model	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Bath et al (2020)			
Study identifier	31882318			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*registry data*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Adequately described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Ineligible patients not stated	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Ineligible patients not stated	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Registry therefore unclear	partial	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**High**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Data-dependent cutoff used (ROC)	partial	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	All measurements implied to be conducted similarly but not specifically stated, registry therefore bias	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	endpoints stated, not defined, data source registry	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Not stated	no	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given in all cases, coded registry data used	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Assumed yet not stated	no	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Multivariate analysis accounted for confounders	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Appropriate survival analysis allows for the primary outcome to be assessed independently of the variables which were different in the baseline cohorts	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate modelling is used	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate modelling is used	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	González-Hernandez et al (2021)			
Study identifier	33496158			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*clear* *a 10-year period were identified from a single vascular surgeons prospectively maintained database."*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Clear	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	No missing	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	No missing	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	No missing	yes	**Low**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	No missing	yes	**Low**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly state pre-op, day before	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Specifically stated	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Data dependent, quartiles	no	**high**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clearly defined	Yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Not stated	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	no	**High**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Nil missing	yes	**low**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not matched	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted in analysis	yes	**low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**high**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Appropriate	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Appropriate	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Chan et al (2014)			
Study identifier	24816510			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*All patients who underwent infrapopliteal angioplasty for the treatment of CLI between August 2001 and January 2010 were identified from the Department of Vascular Surgery prospectively collected patient information system.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, prospectively collected patient information system	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Implied that all contribute data	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	All contributed	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	All contributed	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	All contributed	yes	**Low**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	All contributed	yes	**Low**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	variable, depends on scheduled vs unscheduled, biased	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Previous literature used	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	clearly defined	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	method of outcome measurement not stated, source not stated	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was, implied that it is patient records	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	no missing confounder data	yes	**Low**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Accounted for through statistics	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Multivariable	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Adequate	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Adequate	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Chen et al (2016)			
Study identifier	27713601			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Eligible PAD patients without acute limb ischemia, who were hospitalized for PTA from January, 2011 to June, 2014 were consecutively enrolled in this single-center retrospective study from a prospective registry.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, indicated from prospective registry	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	ESRD not clearly defined	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Implied to be 100% based on selection	partial	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Implied to be 100% based on selection	partial	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Implied to be 100% based on selection	partial	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Implied to be 100% based on selection	partial	**Low**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Implied to be 100% based on selection	partial	**Low**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	"at the time of admission", defined, not justified whether exclusions (i..e sepsis)	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Previous literature used	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clear definiton and justification	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Speciifc report of outcome data	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is implied to be the case however not stated	partial	**Low**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	No missing condounder data	yes	**Low**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design, no matching, however MV analysis	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Accounted for in MV analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design but in analysis	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Accounted for in MV analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Huang et al (2019)			
Study identifier	31415395			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Single centre registray (TRENDPAD)*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Adequately described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	Adequately described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Adequately described	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Implied	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Implied as above, not stated	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Implied as above, not stated	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Implied as above, not stated	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Implied as above, not stated	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Bias, within 2 months pre procedure	no	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Adequately described, specific definition	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	no	**High**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Implied no missing data	yes	**Low**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Accounted for in decision tree	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Accounted for in decision tree	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	unclear if confounders accounted for in analysis - univariate to develop model	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	unclear if confounders accounted for in analysis - univariate to develop model	partial	**Moderate**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Jhang et al (2020)			
Study identifier	33177036			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Data were extracted from the Tzuchi Registry of Endovascular Intervention for Peripheral Artery Disease, which is a single-center observational registry of patients who have undergone EVT for LEAD starting from July 2005.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Adequately described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequately described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Adequately described	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Adequately described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	timing unclear	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous and ROC	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	adequate	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	adequate	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Specific definition	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	clearly stated, sources defined	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined, source not stated	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	no	**High**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Account in model design	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Accounted in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Model building rationale not clear	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Accounted in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**low**

Author and year of publication	Lee et al (2020)			
Study identifier	32503291			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We included 95 patients who underwent successful infrainguinal angioplasty with stent implantation at the Division of Vascular Medicine of the Medical University of Vienna.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	no indication of how cases were identified.	no	**High**
Recruitment period	Period of recruitment is adequately described	Not stated	no	**High**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Adequately described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	not specifically stated, implied	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not specifically stated, implied	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not specifically stated, implied	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not stated	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not stated	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly state pre-op, day before	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Previous literature used	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Specifically defined	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Method of assessment clearly stated	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Low**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design, but are in analysis	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Su et al (2021)			
Study identifier	34043672			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We retrospectively and continuously enrolled patients with CLI undergoing percutaneous transluminal angioplasty at our hospital between 2013/1/1 and 2018/12/31.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not stated	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequate, exclusions not stated	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Exclusions not stated	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Exclusions not stated	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Exclusions not stated	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Exclusions not stated	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Not stated	No	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not stated	No	**High**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC, data depdendent, also continuous	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequate	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	not performed	partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Defined	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data not stated	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	source from medical records	yes	**Low**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design, however, analysis does	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in MV analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Wang et al (2017)			
Study identifier	28042626			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Two-hundred and seventy patients complying with the previously mentioned criteria were retrospectively recruited from January 2010-December 2014 in The First Hospital of Jilin University, Changchun, China.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	not defined	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	not stated	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	performed before amputation but no definition, no time points "last routine data" non specific	no	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	no	**High**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC data depdendent	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	not stated or defined	no	**High**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	unclear what survival outcome reported	no	**High**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was, report from software system however unclear	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported. - unclear if any missing	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Not accounted for in MV analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	subgroups mismatched, numbers unequal	no	**High**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Pierre-Louis et al (2019)			
Study identifier	30339899			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Retrospective review of all patients who had undergone below-knee amputation (BKA) or above-knee amputation (AKA) between 2004 and 2014 at all 3 institutions was performed and captured in a database.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	locations stated	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequate	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Explained	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	stated	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Described specifically	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data not entirely clear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not all given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	accounted for in analysis	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders accounted for in design	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Taşoğlu et al (2014)			
Study identifier	23393289			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*A total of 112 patients presented with CLI to our hospital between February 2007 and June 2012 who could not have radiological (percutaneous transluminal angioplasty) or surgical revascularization and had medical treatment are included in our study.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Adequately described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for CLTI procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequate	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	stated	partial	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	not clearly stated	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	absolute cutoff used but not defined or justified	no	**high**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequate	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Adequate	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	defined, source of data and time point not stated	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	not clear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified or defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	using combination of NLR and PLR to generate "risk" not clearly justified	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	adequate design, MV model	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Luo et al (2015)			
Study identifier	26017794			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	The patients included in this study were recruited from the Vascular Department of West China Hospital, Sichuan University, between January 2009 and January 2011.	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear criteria	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequately described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Adequately described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly state on admission and post procedure times	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	tertiles, data dependent	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	stated but not clearly defined	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	source as followup but data source not reported	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	N/A	yes	**Low**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design but in analysis	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis, but data dependent cutoffs	partial	**Moderate**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Amrock et al (2016)			
Study identifier	26762418			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*NHANES, a repeated, cross-sectional, stratified, multistage survey of the non-institutionalized US population, has been previously described.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	defined	yes	**Low**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	as above, survey performed	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequately described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not applicable to study design	yes	**Low**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not applicable to study design	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not applicable to study design	yes	**Low**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not applicable to study design	yes	**Low**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	timing unclear	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	reliable	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	use multimarker model, continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	specifically defined, and source defined	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities given	yes	**Low**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	accounted through model generation	yes	**Low**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted through model generation	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	model generation unclear	partial	**Moderate**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	accounted through model generation	yes	**Low**
	The selected statistical model is adequate for the design of the study.	accounted through model generation	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Erdoğan et al (2021)			
Study identifier	33427105			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Patients in a single tertiary cardiovascular center with critical limb ischemia unsuitable for surgical or interventional revascularization between January 2014 and June 2018 were retrospectively identified.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment implied, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	not clear	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	not clear	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Stated	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	stated	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	time of admission	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC, data dependent	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	defined groups as non-responders vs responders	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	definition clearly defined	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design but in analysis	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Not accounted for in design but in analysis	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Velioglu et al (2019)			
Study identifier	30924393			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	Adequately described	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	no clear description of how identified	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	defined	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	implied, not stated	partial	**Moderate**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not stated	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	minimal confoundders reported	partial	**Moderate**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	not stated, implied 100%	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not stated, unclear	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not stated, unclear	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not stated, unclear	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not stated, unclear	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	unclear when taken	no	**high**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	described, defined well	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	stated, described	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	non exhaustive list	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in MV analysis	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Demirdal et al (2018)			
Study identifier	30176260			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*A total of 280 consecutive patients who were hospitalized in our Infectious Disease Clinic were analyzed retrospectively from February 2010 through March 2016 at the Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Clearly described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	Clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Not reported	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not reported	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not reported	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not reported	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not reported	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	clearly defined	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	implied thatAll patients in the sample contributed PF data	partial	**Moderate**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	implied thatAll patients in the sample contributed PF data	partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clear definitions	Yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data not clear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	yes	**Low**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	not performed	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	not performed	partial	**Moderate**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in model	no	**High**
	The selected statistical model is adequate for the design of the study.	Confounders not accounted for in analysis	no	**High**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**High**

Author and year of publication	Belaj et al (2015)			
Study identifier	26058674			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We performed a retrospective data analysis including 1995 patients with PAD who were treated at our department in the years 2005 to 2010.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Unclear cse ID, unclear if consecutive	no	**high**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	not reported	no	**high**
Adequate study participation	There is adequate participation in the study by eligible individuals	Adequately described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequately described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	state at OPD but timing unclear	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	data dependent	no	**high**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	No description or data source reported	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data unclear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified, source not identified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	no	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	implied	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for entirely	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Not entirely accounted for in analysis (BLR)	partial	**Moderate**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders not accounted for in analysis - not all confounders in multivariate model, use of data dependent cutoffs	no	**High**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Demirtas et al (2014)			
Study identifier	24522438			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*In this cross-sectional study, 82 consecutive PAD patients were examined prospectively*	partial	**Moderate**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment not stated, no indication of how cases were identified.	no	**high**
Recruitment period	Period of recruitment is adequately described	inadequate	partial	**Moderate**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	inadequate	partial	**Moderate**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	clear exclusion	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	not reporrted	no	**high**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not reporrted	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not reporrted	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not reporrted	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	don't state time, state technique	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuus	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	defined, data source unclear	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	unclear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	do not account for clearly important confounders	no	**high**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	no	**high**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Not accounted for in analysis	no	**High**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**high**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Not accounted for in design	no	**High**
	The selected statistical model is adequate for the design of the study.	Not accounted for in analysis	no	**High**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Gary et al (2013)			
Study identifier	23457609			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We included 2121 consecutive PAOD patients treated at our department from 2005 to 2010 in our retrospective data analysis*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Adequately described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	Adequately described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Adequately described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility, limited exclusion	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	adequate	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	vague, unclear when taken	no	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Definition of PAOD, CLI, clear	yes	**low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	implied, not clear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given , source not stated	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	unclear given univariate OR not reported	no	**High**
	The selected statistical model is adequate for the design of the study.	Confounders ?partially accounted for in analysis	no	**High**
Reporting of results	There is no selective reporting of results.	univariate OR not reported - unclear whether adjustment appropriate	no	**High**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**High**

Author and year of publication	Gary et al (2013)			
Study identifier	23457609			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We included 2121 consecutive PAOD patients treated at our department from 2005 to 2010 in our retrospective data analysis*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Adequately described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	Adequately described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Adequately described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility, limited exclusion	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	adequate	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	not performed	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	vague, unclear when taken	no	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Definition of PAOD, CLI, clear	yes	**low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	implied, not clear	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given , source not stated	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analysis	yes	**low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	unclear given univariate OR not reported	no	**High**
	The selected statistical model is adequate for the design of the study.	Confounders ?partially accounted for in analysis	no	**High**
Reporting of results	There is no selective reporting of results.	univariate OR not reported - unclear whether adjustment appropriate	no	**High**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**High**

Author and year of publication	Celebi et al (2020)			
Study identifier	32445291			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*From March 2014 to December 2018, 168 patients who underwent peripheral angiography at our clinics because of suspected LEAD after physical examination, history, and non-invasive tests were screened, and 152 patients were enrolled in our cross-sectional retrospective study.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Adequately described	yes	**Low**
Recruitment period	Period of recruitment is adequately described	Adequately described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Adequately described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Adequately described	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Adequately described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Adequately described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not stated	partial	**Low**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not stated	partial	**moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Low**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Adequately described	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Adequately described	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Adequately described	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Implied as above, not stated	partial	**moderate**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Implied as above, not stated	partial	**moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	TASC defined, LEAD not	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	source implied from records	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	implied	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities given	yes	**Low**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	implied	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	implied	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	partially accounted for	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	partially accounted for	partial	**Moderate**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders partially accounted for in model	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Teperman et al (2016)			
Study identifier	27865186			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*This retrospective observational study identified 928 consecutive patients referred for peripheral angiography with possible endovascular intervention for symptomatic PAD at a tertiary care center between December 2012 and June 2015*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	not stated how cases identified	no	**High**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Not stated	no	**High**
Adequate study participation	There is adequate participation in the study by eligible individuals	reported	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	reported	Yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	no	**High**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	reported though limited	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not reported	no	**High**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not reported	no	**High**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**High**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	reported, though range of dates, heterogenous	Partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Clearly defined	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	tertiles	Partial	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	Partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Implied as above, not stated	Partial	**Moderate**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	not performed	Partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	no standard definitions of severity, observer subjectivity	No	**High**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Angiographic assessment defined	No	**High**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**High**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured, not justified, not defined	No	**High**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	as above	No	**High**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	poor definition	No	**High**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for	No	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Not accounted for	No	**High**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**High**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Not accounted for	No	**High**
	The selected statistical model is adequate for the design of the study.	Not accounted for	No	**High**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**High**

Author and year of publication	Hamur et al (2016)			
Study identifier	27059289			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*The study included a total of 211 nonanemic patients with PAD who were admitted to the Erzincan Mengu¨cek Gazi Training and Research Hospital and Gaziantep Dr Ersin Uysal State Hospital who underwent lower limb peripheral angiography between January 2014 and October 2015*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	not stated whether allcomers included, case identified	no	**High**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	Not stated	no	**High**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Not reported	no	**High**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	no	**High**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not reported	no	**High**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not reported	no	**High**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not reported	no	**High**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**High**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly defined	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Clearly defined	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	Continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	Partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Implied as above, not stated	Partial	**Moderate**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Not required	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clearly defined CTO	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Angiographic assessment defined	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured	yes	**Low**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	defined	yes	**Low**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	comorbidity data seems to be defined however relies on patient recall	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Accounted partially	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Accounted partially	partial	**Moderate**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Accounted partially	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Accounted partially	partial	**Moderate**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**

Author and year of publication	Aykan et al (2016)			
Study identifier	27004700			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*This cross-sectional retrospective study enrolled 343 patients with PAD who underwent peripheral angiography at Ahi Evren Chest Cardiovascular Surgery Education and Research Hospital cardiology inpatient clinic due to suspected PAD in noninvasive tests between June 2011 and October 2013.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	not reported how cases identified	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	As above, clearly described	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, implied	partial	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	As above, clearly described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	As above, clearly described	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not reported	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	As above, clearly described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not reported	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not reported	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Not clearly defined when samples taken	No	**High**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC and continuous	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Moderate**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clearly defined TASC using appropriate established criteria	yes	**low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Unclear where source is, implied	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	Clearly defined	Yes	**Low**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in dsign	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	multivariate modelling accounts for confounders	Yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in modelling	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	multivariate modelling accounts for confounders	Yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Zhen et al (2019)			
Study identifier	30221973			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*Seventy patients who underwent DCB for FPD in our institution were contained in our analysis.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, no justifcation of numbers	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Not specifically stated, no exclusions reported	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not specifically stated, no exclusions reported	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not specifically stated, no exclusions reported	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not specifically stated, no exclusions reported	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not specifically stated, no exclusions reported	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly state definition and time	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	valid, implied to be similar	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous and ROC	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	No description or data source reported	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as "prospectively maintained database"	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was "the clinical data"	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design but in analysis	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in MV analysis	yes	**low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	appropriate	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Zhen et al (2019)			
Study identifier	30221973			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*106 consecutive patients were successfully treated with DCB (n ¼ 44) or UCB (n ¼ 62) from July 2016 to August 2017*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	Consecutive recruitment stated, However no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated however specific location inferred from author affiliations	partial	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	not specifically stated, no justifcation of numbers	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Low**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Not specifically stated, no exclusions reported	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not specifically stated, no exclusions reported	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Not specifically stated, no exclusions reported	partial	**Moderate**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not specifically stated, no exclusions reported	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not specifically stated, no exclusions reported	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	Clearly state definition and time	yes	**Low**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	valid, implied to be similar	partial	**Moderate**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous and ROC	partial	**Moderate**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	All patients in the sample contributed PF data	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	All patients in the sample contributed PF data	yes	**Low**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	No description or data source reported	partial	**Moderate**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as "prospectively maintained database"	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was "the clinical data"	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design but in analysis	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in MV analysis	yes	**low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	appropriate	yes	**Low**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Chang et al (2018)			
Study identifier	28635304			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*A total of 258 consecutive patients with femoropopliteal CTO lesions were screened between January 2012 and December 2014.*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	However no indication of how cases were identified.	no	**High**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	not stated	partial	**Moderate**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	not described	partial	**Moderate**
Adequate study participation	There is adequate participation in the study by eligible individuals	dropouts explained, adequate participation	yes	**Low**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	adequate	yes	**Low**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Adequately described	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	1 to 3 days before, defined, though large range	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	All measurements implied to be conducted similarly but not specifically stated.	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	ROC, data dependent	no	**High**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied, not stated	yes	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	yes	yes	**Low**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	not performed	partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	ISR defined and timepoint stated	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Source of outcome data recorded as followup US, however protocol not explained	partial	**Moderate**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified nor defined	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	definitions of comorbidities not given	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Not specifically stated where the source of confounding variables was	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	partial	**Moderate**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	MV analysis accounts	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design, but are in analysis	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Low**

Author and year of publication	Nakazawa et al (2017)			
Study identifier	28259571			
Reviewer	NAB			
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for single centre, retrospective.	*We conducted a retrospective assessment of clinical and angiographic records from January 2005 to October 2014 of all patients who underwent first-time stenting of femoral or above-the-knee popliteal arterial occlusive disease at the Mount Sinai Hospital (New York).*	yes	**Low**
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	no indication of how cases were identified.	partial	**Moderate**
Recruitment period	Period of recruitment is adequately described	As above, clearly described	yes	**Low**
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	Single centre stated	yes	**Low**
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	Clear inclusion criteria and eligibility	yes	**Low**
Adequate study participation	There is adequate participation in the study by eligible individuals	only 138/479 available	partial	**Moderate**
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for AAA, procedural and patients factors.	Adequately described	yes	**Low**
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**			**Moderate**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	only 138/479 available	partial	**Moderate**
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	Not performed	partial	**Moderate**
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	Stated	yes	**Low**
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	Not performed	partial	**Moderate**
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	Not performed	partial	**Moderate**
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**			**Moderate**

3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	variable, within 30 days pre-op in some cases	partial	**Moderate**
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	Adequately described	yes	**Low**
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	continuous	yes	**Low**
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	Implied as above, not stated	partial	**Low**
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	only 138/479 available	partial	**Moderate**
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	only 138/479 available, no impution used	partial	**Moderate**
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**			**Moderate**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	Clear definition and time point	yes	**Low**
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	Defined, valid, timepoints stated	yes	**Low**
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	This is assumed to be the case however not stated	partial	**Moderate**
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**			**Low**
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Appropriately selected baseline variables measured however not justified, defined from"charts"	partial	**Moderate**
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	defined from"charts"	partial	**Moderate**
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	implied from medical charts	partial	**Moderate**
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	Not specifically stated, assumed	partial	**Moderate**
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Missing confounder data not reported.	partial	**Moderate**
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	Not accounted for in design	no	**High**
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	accounted for in analyses	yes	**Low**
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**			**Moderate**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	The data allows for assessment of analysis	yes	**Low**
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Confounders not accounted for in design, but in analysis	partial	**Moderate**
	The selected statistical model is adequate for the design of the study.	Confounders accounted for in analysis	yes	**Low**
Reporting of results	There is no selective reporting of results.	All results are reported	yes	**Low**
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**			**Moderate**