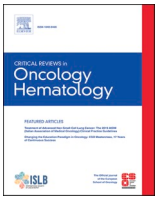
Critical Reviews in Oncology / Hematology 199 (2024) 104378

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc



The relationship between LDH and GLIM criteria for cancer cachexia: Systematic review and meta-analysis

Joshua J. Thompson [a,*], Josh McGovern [a], Campbell S.D. Roxburgh [a], Joanne Edwards [b], Ross D. Dolan [a], Donald C. McMillan [a]

[a] Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK
[b] Wolfson Wohl Cancer Research Centre, School of Cancer Sciences, University of Glasgow, Glasgow, UK

ARTICLE INFO

Keywords:
Lactate Dehydrogenase (LDH)
Cancer Cachexia
Global Initiative on Malnutrition (GLIM)
Systemic Inflammatory Response (SIR)
CRP
Modified Glasgow Prognostic Score (mGPS)
Neutrophil Lymphocyte Ratio (NLR)
Cancer

ABSTRACT

Introduction: Cancer cachexia is a clinical condition characterized by recognizable "sickness behaviors" accompanied by loss of lean body tissue. The Global Leadership on Malnutrition (GLIM) has proposed phenotypic (unintentional weight loss, low body mass index and low muscle mass) and aetiologic (reduced food intake and inflammation or disease burden) diagnostic criteria. Recent work has suggested serum lactate dehydrogenase (LDH) might represent a 3rd aetiologic criteria. Little is known of its relationship with GLIM. A systematic review and meta-analysis of their comparative prognostic value and association was performed.

Methods: A search of electronic databases (PubMed, Medline, Ovid, Cochrane) up to February 2023 was used to identify studies that compared the prognostic value of LDH and components of the GLIM criteria in cancer. An analysis of the relationship between LDH and the components of GLIM was undertaken where this data was available. RevMan 5.4.1 was used to perform a meta-analysis for each diagnostic criteria that had 3 or more studies which reported hazard ratios with a 95 per cent confidence interval for overall survival (OS).

Results: A total of 119 studies were reviewed. Advanced lung cancer was the most studied population. Included in the meta-analysis were 6 studies (n=2165) on LDH and weight loss, 17 studies (n=7540) on LDH and low BMI, 5 studies (n=758) on LDH and low muscle mass, 0 studies on LDH and food intake and 93 studies (n=32,190) on LDH and inflammation. There was a significant association between elevated serum LDH and each of low BMI (OR 1.39, 1.09 – 1.77; p=0.008), elevated NLR (OR 2.04, 1.57 – 2.65; p<0.00001) and elevated CRP (OR 2.58, 1.81 – 3.67; p<0.00001). There was no association between elevated serum LDH and low muscle mass. Only one study presented data on the association between LDH and unintentional weight loss. Elevated LDH showed a comparative OS (HR 1.86, 1.57 – 2.07; p<0.00001) to unintentional weight loss (HR 1.57, 1.23 – 1.99; p=0.0002) and had a similar OS (HR 2.00, 1.70 – 2.34; p<0.00001) to low BMI (HR 1.57, 1.29–2.90; p<0.0001). LDH also showed an OS (HR 2.25, 1.76 – 2.87; p<0.00001) congruous with low muscle mass (HR 1.93, 1.14 – 3.27; p=0.01) and again, LDH conferred as poor an OS (HR 1.77, 1.64–1.90; p<0.00001) as elevated NLR (HR 1.61, 1.48 – 1.77; p<0.00001) or CRP (HR 1.55, 1.43 – 1.69; p<0.00001).

Conclusion: Current literature suggests elevated serum LDH is associated with inflammation in cancer (an aetiologic GLIM criterion), however more work is required to establish the relationship between LDH and the phenotypic components of GLIM. Additionally, elevated serum LDH appears to be a comparative prognosticator of overall survival in cancer when compared to the GLIM criteria.

1. Introduction

Cachexia is a broad term used to describe recognisable "sickness behaviours" or symptoms associated with loss of lean body tissue (Baracos et al., 2018). Frequently present in advanced malignancy, the definition of cancer cachexia has steadily evolved over time. It is generally thought of as disease related malnutrition with increasing importance placed upon systemic inflammation (McGovern et al., 2022). Recently, the Global Leadership Initiative on Malnutrition (GLIM) have developed standardised diagnostic criteria for malnutrition

* Correspondence to: Clinical Research Fellow, Academic Unit of Surgery, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, Glasgow G4 0SF, UK.
E-mail address: joshua.thompson@glasgow.ac.uk (J.J. Thompson).

https://doi.org/10.1016/j.critrevonc.2024.104378
Received 12 October 2023; Received in revised form 2 April 2024; Accepted 30 April 2024
Available online 14 May 2024

(Cederholm et al., 2019). This consists of three phenotypic criteria (involuntary weight loss, low BMI, reduced muscle mass) and two aetiologic criteria (reduced food intake and inflammation or disease burden). Cachexia is diagnosed by the presence of one criterion from each category.

Recent work by McGovern et al. (2023) has examined the relationship between lactate dehydrogenase (LDH) and the GLIM criteria in a prospective cohort of palliative cancer patients. They found that LDH was independently associated with 3-month survival independent of weight loss, BMI, skeletal muscle mass, metastatic disease or systemic inflammation. They concluded that LDH might represent an additional aetiologic criterion within the GLIM framework.

LDH is a constituent intracellular enzyme from the oxidoreductase class which catalyses the conversion of pyruvate to lactate with the reduction of NAD^+ to NADH and vice versa (Farhana and Lappin, 2023). Cells in anaerobic or hypoxic environments cannot generate adenosine triphosphate (ATP) by oxidative phosphorylation. An upregulation of LDH facilitates an alternate yet inefficient pathway for energy production. As such, it is integral to anaerobic metabolism. Cancer cells demonstrate an affinity for the anaerobic metabolism of glucose, with the generation of large amounts of lactate, often despite the presence of oxygen (Warburg, 1956; Walenta and Mueller-Klieser, 2004; Claps et al., 2022). The reason for this observation, termed the "Warburg Effect", remains unclear. Some have theorized that this diverts bioactive glycolytic substrates for use by rapidly dividing cancer cells, or that this outpaces the relatively slow mitochondrial electron transfer chain. The chaotic and precocious nature of tumor vasculature also creates regions of hypoxia and tumor necrosis which will result in further anaerobic production of lactate. Excreted by tumor and host cells, lactate will reduce the pH of the surrounding tumor microenvironment (TME) before it is ultimately converted back to pyruvate by the "Cori cycle" in the liver. This results in amplified gluconeogenesis with a reactive hyperinsulinemia which ultimately leads to insulin resistance, a contributing factor to the phenotype of cachexia (Masi and Patel, 2021). Much work has focused on the importance of the tumor-host interaction (McAllister and Weinberg, 2014; Roxburgh and McMillan, 2014, 2012) and lactate as an orchestrator of metabolic reprogramming within the TME is one such example (Ippolito et al., 2019). Work has shown that lactate is pro-tumorigenic promoting angiogenesis, metastasis and tumor resistance with additional roles in immunosuppression and tumor evasion (Claps et al., 2022; Certo et al., 2021). Thus, LDH may play an important role in the tumor-host interaction that results in the dysregulated metabolism and systemic inflammation which drives cancer cachexia.

Elevated serum lactate dehydrogenase (LDH) is recognized to be a predictor of disease progression and poorer survival in cancer. However, the biological mechanisms underlying this observation, how this relates to tumor burden or if this represents a therapeutic target remains unclear. To date there has been little work on the relationship between LDH and the GLIM criteria and their relative prognostic value. This systematic review and meta-analysis aimed to compare the prognostic value of LDH and GLIM on overall survival (OS) in patients with cancer and examine the association between LDH and GLIM where possible.

2. Methodology

The following systematic review and meta-analysis was performed according to a pre-defined protocol described in the updated 2020 PRISMA-P statement. A search of the electronic databases PubMed, MEDLINE and Embase (Excerpta Medica Database) up to 31st January 2023 was performed. This utilized a combination of Medical Subject Heading (MeSH) terms and keywords to include all cancer, lactate dehydrogenase and the GLIM criteria. The full search syntax has been included in the supplementary material. The terms searched were: "lactate dehydrogenase", "LDH", "Global Leadership Initiative on Malnutrition", "GLIM", "weight loss", "body mass index", "BMI", "body weights and measures", "muscle mass", "sarcopenia", "food intake", "modified Glasgow Prognostic Score", "mGPS", "C-reactive protein", "CRP", "neutrophil-lymphocyte ratio", "NLR", "neoplasm" and "cancer".

Structuring the search as outlined above produced 1575 results (Fig. 1). Titles and abstracts were screened for relevance and any duplicates removed (n=140). Articles were excluded if there was no full text (n=151), they were not published in English (n=103), they were a review (n=24) or survival was not the primary outcome (n=977). A full text review of the remaining 180 papers was performed. Included studies investigated a measurable prognostic outcome (overall survival (OS), time to death (TTD), cancer specific survival (CSS) or disease free survival (DFS)) in patients with cancer for both serum LDH and a component of the GLIM criteria (weight loss, low BMI, reduced muscle mass, inflammation, food intake). Until recently, the GLIM consensus did not objectively define inflammation. Therefore, as previous reviews have highlighted both the prevalent use and prognostic value of the modified Glasgow prognostic score (mGPS) and neutrophil lymphocyte ratio (NLR) these were chosen to represent systemic inflammation (Dolan et al., 2018, 2017a, 2017b; Shimoyama et al., 2024). Additionally, they reflect the hepatic and myeloid components respectively of the systemic inflammatory response. Additional studies were excluded if they had less than 80 subjects (n=43), did not present survival as hazard ratios with 95% confidence intervals (n=20) or were publications on data from the same cohort (n=4). Where two papers by the same author appeared to investigate the same cohort, the larger cohort with more substantial follow up was included. Overall survival was the only outcome used in the meta-analysis due to the inconsistency in TTD, CSS and DFS outcomes reported amongst the papers. Lastly, the references of included studies were examined to identify additional relevant papers (n=6). Two senior authors agreed on strict inclusion and exclusion criteria. The first author performed the search and review of abstracts, and a second senior author was consulted where advice was required concerning inclusion. The STROBE checklist (Vandenbroucke et al., 2007) was used to evaluate the quality of eligible studies. Extracted data was stored electronically and included author, country, trial design, sample size, cancer type, intervention (if any), number of events/deaths, length of follow up, timing of measurements and values chosen, multivariable and univariable survival analysis and a brief description of the population studied (Supplementary Table). Results are presented in a descriptive fashion for each different component of the GLIM criteria. A meta-analysis was undertaken for each individual component of the GLIM criteria where at least 3 studies presented hazard ratios (HR) with a 95 per cent confidence interval using the same outcome measure.

2.1. Statistics

The hazard ratios and 95% CIs for overall survival were taken directly from each article. Whenever both estimates were presented, the multivariable analysis was taken over the univariable analysis. There were a minority of studies which only presented univariable analysis (see Supplementary Table). Hazard ratios were log transformed prior to pooling. All meta-analysis was undertaken using Review Manager (RevMan)[Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, using the random effects (DerSimonian-Laird) model. Heterogeneity between studies was evaluated by both Tau^2 and I^2. All p-values were 2-sided and $p<0.05$ were considered statistically significant. Visual analysis of funnel plots was performed to assess publication bias (see Supplementary Material)."

3. Results

After final review of the full texts, 119 papers were suitable for systematic review (Fig. 1 – PRISMA diagram). Separating the papers into those examining both LDH and the different components of the GLIM criteria produced: 39 studies on weight loss and/or low BMI (Abdel-Rahman, 2018, 2019; Aben, 2011; Banna, 2022; Bremnes, 2003;

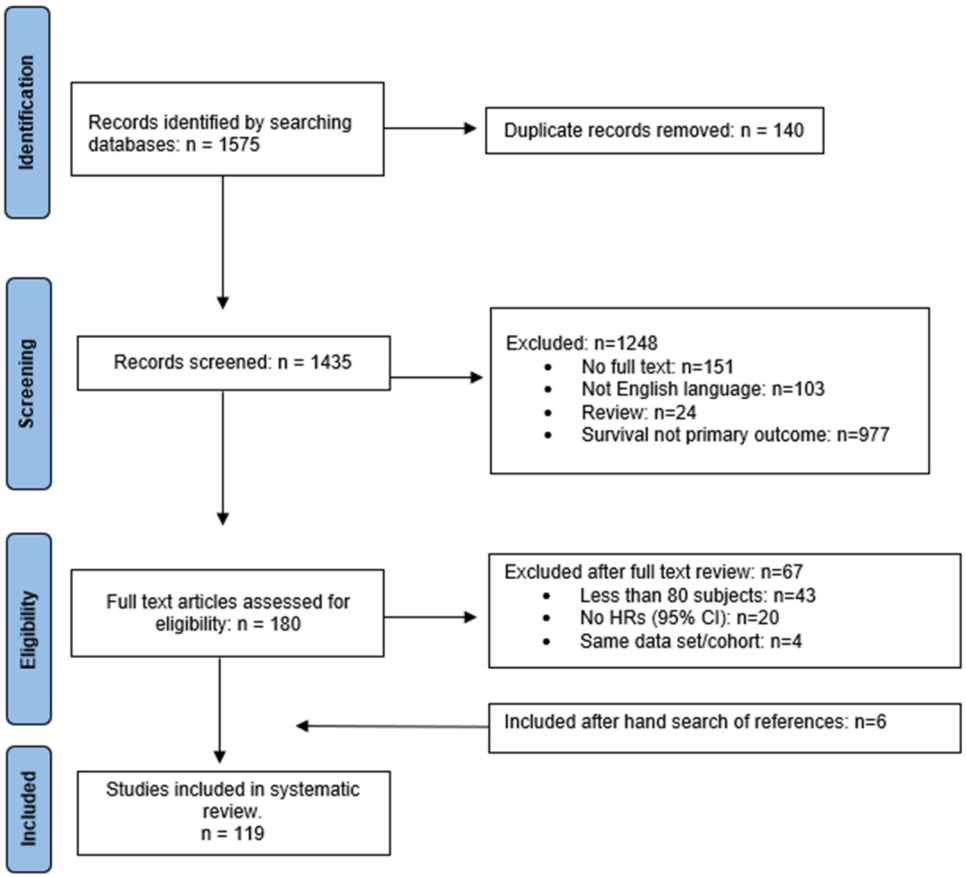


Fig. 1. PRISMA-P diagram showing selection of studies for review.

Fukushima, 2015; Gravis, 2015; Hoang, 2012; Huang, 2015; Hwang, 2015; Jung, 2014; Kanemasa, 2018; Kim, 2015, 2018; Knetki-Wroblewska, 2021; Lara, 2015; Li, 2017; Liu, 2016; Lu, 2013; Okamoto, 2019; Rutkowski, 2020; Shah, 2015; Shibuki, 2022; Simmons, 2019b; Smith, 2011; Song, 2016; Sougioultzis, 2011; Suzuki, 2019, 2020; Takemura, 2019; Tang, 2016; Tanrikulu, 2010; Tanriverdi, 2014; Tsai, 2021; Viganó, 2000; Wang, 2018a, 2019, Zeng, 2016a,b), 6 studies on skeletal muscle mass (Burkart, 2019; Fukushima, 2015; Go, 2016; Kim, 2015; Park, 2016; Veasey Rodrigues, 2013), 0 studies on food intake and 106 studies on systemic inflammation (Shibuki et al., 2022; Tang et al., 2016; Banna et al., 2022; Suzuki et al., 2020; Fukushima et al., 2015; Takemura et al., 2019; Berghoff et al., 2017; Stangl-Kremser et al., 2020; Vogl et al., 2006; Chan et al., 2021; Jimenez-Zepeda et al., 2016; Ksienski et al., 2022; Mercier and Voutsadakis, 2019; Nicholas et al., 2018; Templeton et al., 2014; Pinto et al., 2018; Cao et al., 2017; Chen et al., 2022, 2018; Cui et al., 2018; Deng et al., 2017; Guo et al., 2018; He et al., 2021, 2015; Hong et al., 2015; Hu et al., 2020; Jiang et al., 2020; Li et al., 2015, 2013a, 2013b; Liu et al., 2017; Ma et al., 2022a, 2022b; Peng et al., 2020; Pu et al., 2021; Wang et al., 2014a, 2018b, 2014b; Xie et al., 2021; Yang et al., 2017; Yu et al., 2017; Zhang et al., 2022, 2015; Zhao et al., 2022, 2021; Zhou et al., 2015a, 2015b; Drpa et al., 2020; Olgun and Diker, 2023; Jorgensen et al., 2017; Bigot et al., 2017; Chasseuil et al., 2018; Di Blasi et al., 2022; Atzpodien et al., 2003; Boegemann et al., 2017; Desch et al., 2017; Haas et al., 2013; Hartrampf et al., 2022; Heppt et al., 2017; Klumper et al., 2022; Kripp et al., 2014; Reinert et al., 2020; Bersanelli et al., 2020; Buttigliero et al., 2017; Capone et al., 2018; Casamassima et al., 2005; Cocorocchio et al., 2020; Del Prete et al., 2015; Loupakis et al., 2019; Marcheselli et al., 2020; Pisano et al., 2021; Hashimoto et al., 2009; Ishioka et al., 2012; Ito et al., 2019; Kamba et al., 2014; Kanemasa et al., 2016; Nakagawa et al., 2013; Nakai et al., 2010; Nakamura et al., 2016; Namikawa et al., 2019; Takada et al., 2020; Takemura et al., 2020; Tamura et al., 2021; Tanizaki et al., 2018; Tatsugami et al., 2015; Uehara et al., 2021; Xue et al., 2014; Yamada et al., 2020; Yamazaki et al., 2021; Kang et al., 2014; Suh and Ahn, 2007; Suh et al., 2010; Maas et al., 2019; Strijker et al., 2021; Aamdal et al., 2022a, 2022b; Baicus et al., 2014; Teterycz et al., 2018; Ng et al., 2021; Mirili et al., 2019; Giri et al., 2022; Peyton et al., 2020; Sonpavde et al., 2014; Li et al., 2018; Nakagawa et al., 2017; Artac et al., 2017; Saito et al., 2009). For conciseness, results of individual studies can be found in the supplementary material. From the 119 studies included in the meta-analysis, only 10 failed to provide multivariable survival analysis (8%).

3.1. *The relationship between elevated LDH and weight loss*

Six studies (n=2165) examined the prognostic value of both unintentional weight loss and elevated LDH. There were 3 papers on advanced lung cancer (Bremnes et al., 2003; Lara et al., 2015; Tanriverdi et al., 2014), 2 on all palliative cancer (Simmons et al., 2019a; Viganó et al., 2000) and 1 on advanced gastric cancer (Sougioultzis et al., 2011). Patients received palliative chemoradiotherapy or supportive treatment only. One randomized control trial of chemotherapy regimes in small cell lung cancer did include both early and advanced disease (Bremnes et al., 2003). All measurements were taken at baseline and no study recorded serial measurements of either weight or LDH. Only two studies were prospective (Supplementary Tables). Five studies used multivariable and one used univariable survival analysis (Supplementary Tables).

The prevalence of weight loss amongst all studies was 38% whereas 48% of patients had an elevated serum LDH. There was not sufficient data to analyze the prevalence between early and advanced disease or different cancer types. Only one study examining weight loss explicitly presented data on the association with elevated LDH (Lara et al., 2015).

Lara *et al.* retrospectively analyzed data on 329 patients from trials of platinum-based chemotherapy in advanced small cell lung cancer. Of 89 patients losing >5% body weight 30 had an elevated LDH (30/89, 34%) compared to 86 out of 240 weight stable patients (86/240, 36%).

The largest of the remaining studies on weight loss was a prospective observational cohort investigating prognostic factors in advanced cancer patients over an 18-year period (Simmons et al., 2019a). Of 478 subjects, 462 experienced weight loss however only 190 (190/478, 41%) had experienced weight loss >2.5% of their body weight in the previous 3 months. In comparison, 375 (375/478, 75%) subjects had an elevated LDH (>250 U/L). Although this suggests that elevated LDH is more prevalent than weight loss in advanced cancer, the study did not break down the number of patients with elevated LDH within each weight loss category. Bremnes et al. performed a retrospective analysis of prognostic factors in a randomized control trial of chemotherapy regimes in limited versus extensive small cell lung cancer (Bremnes et al., 2003). They found that amongst patients with early-stage disease 26% (55/210) had an elevated LDH and 15% (32/211) had lost more than 10% of their bodyweight whereas in advanced disease this changed to 52% (110/212) and 35% (77/220) respectively. Again, they did not present data on the prevalence of elevated LDH amongst the patients with weight loss and this was a common observation amongst included studies.

3.2. The prognostic value of elevated LDH compared to weight loss

Of the six studies (n=2165) that investigated weight loss, four (n=1659) used a percentage loss (>5%, 2.5–10.0) (Bremnes et al., 2003; Lara et al., 2015; Simmons et al., 2019a; Sougioultzis et al., 2011) whilst the remaining two (n=506) used fixed amounts over time (10 kg and 8.1 kg) (Tanriverdi et al., 2014; Viganó et al., 2000). There were three studies (n=40) with incomplete data on weight loss (Bremnes et al., 2003; Simmons et al., 2019a; Sougioultzis et al., 2011). There were 1836 deaths. Meta-analysis (Fig. 2) resulted in a pooled HR for OS with unintentional weight loss of 1.57 (1.23 – 1.99, p=0.0002). The median value used for elevated LDH was 395 U/L (225 – 618 U/L) and was unclear in 2 papers (n=713) (Lara et al., 2015; Tanriverdi et al., 2014). 3 papers (n=430) declared incomplete data on serum LDH in their cohort (Bremnes et al., 2003; Simmons et al., 2019a; Tanriverdi et al., 2014). Meta-analysis (Fig. 2) showed a pooled HR for OS with elevated LDH of 1.81 (1.57 – 2.07, p<0.00001).

Table 1
Pooled hazard ratios (HR) for overall survival (OS) in papers examining the effect of both lactate dehydrogenase (LDH) and a Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria (weight loss, low body mass index (BMI), low muscle mass and systemic inflammation) in cancer. NLR=neutrophil lymphocyte ratio.

Marker	N	Pooled HR for OS (95% CI)	Heterogeneity
The prognostic value of LDH compared to weight loss			
LDH	2165	1.81 (1.57 – 2.07) p<0.00001	I^2=0% p=0.50
Weight Loss	2165	1.57 (1.23 – 1.99) p=0.0002	I^2=72% p=0.003
The prognostic value of LDH compared to low BMI			
LDH	6978	2.00 (1.70 – 2.34) p<0.00001	I^2=41% p=0.04
Low BMI	6978	1.57 (1.29 – 2.90) p<0.0001	I^2=88% p<0.00001
The prognostic value of LDH compared to low muscle mass			
LDH	818	2.25 (1.76 – 2.87) p<0.00001	I^2=37%, p=0.17
Low Muscle Mass	818	1.93 (1.14 – 3.27) p=0.01	I^2=88%, p<0.00001
The prognostic value of LDH compared to systemic inflammation			
LDH	37,185	1.77 (1.64 – 1.90) p<0.00001	I^2=90% p<0.00001
NLR	19,344	1.61 (1.48 – 1.77) p<0.00001	I^2=66% p<0.00001
CRP	22,885	1.55 (1.43 – 1.69) p<0.00001	I^2=83% p<0.00001

3.3. The relationship between elevated LDH and low BMI

Seventeen papers (n=7540) examined the prognostic value of both low BMI and elevated serum LDH in cancer (Shibuki et al., 2022; Tsai et al., 2021; Hoang et al., 2012; Kim et al., 2015, 2018; Li et al., 2017; Liu et al., 2016; Lu et al., 2013; Zeng et al., 2016a; Huang et al., 2015; Suzuki et al., 2020; Zeng et al., 2016b; Wang et al., 2019; Fukushima et al., 2015; Takemura et al., 2019; Jung et al., 2014; Hwang et al., 2015). Studies included eight different cancer types (lung=3, nasopharyngeal=3, urothelial cell cancer=3, lymphoma=3, myeloma=2, gastric=1, pancreatic=1, hepatocellular=1). All but 2 papers included advanced, metastatic or unresectable cancer. No study recorded serial measurements of either BMI or serum LDH, with both measured at baseline or diagnosis. Only two studies were prospective (Supplementary Table). Fifteen studies used multivariable and two studies used univariable survival analysis (Supplementary Table).

Only two studies included patients with early disease. Zeng and colleagues (Zeng et al., 2016a) retrospectively analyzed 1593 patients with non-metastatic nasopharyngeal carcinoma (20% T1, 44% T2 or 8% Stage 1 and 41% Stage II), where the mainstay of treatment is radiotherapy in early disease or concurrent chemoradiotherapy in locally advanced disease while Wang et al. retrospectively analyzed 419 hepatocellular carcinoma patients treated by curative resection (Wang et al., 2019).

Amongst included studies the prevalence of elevated serum LDH was 33% whereas only 23% of patients had a low BMI. There was not sufficient data to analyze the prevalence between early and advanced disease or different cancer types. Five studies (n=2109) presented data on the relationship between low BMI and an elevated serum LDH (Tsai et al., 2021; Li et al., 2017; Liu et al., 2016; Jung et al., 2014; Hwang et al., 2015) (supplementary material). A retrospective analysis of 742 patients with extranodal natural killer/T-cell lymphoma was the largest of these studies (Li et al., 2017). The authors observed an elevated serum LDH in 32% (82/254) of patients with a low BMI compared to 26% (129/488) of patients with a BMI>20. Meta-analysis (Fig. 3.) showed an OR of 1.39 (1.09 – 1.77, p = 0.008) for elevated serum LDH amongst patients with a low BMI.

3.4. Prognostic value of elevated LDH compared to low BMI

Seventeen papers (n=7540) examined the prognostic value of both low BMI and elevated serum LDH in cancer (Shibuki et al., 2022; Tsai et al., 2021; Hoang et al., 2012; Kim et al., 2015, 2018; Li et al., 2017; Liu et al., 2016; Lu et al., 2013; Zeng et al., 2016a; Huang et al., 2015; Suzuki et al., 2020; Zeng et al., 2016b; Wang et al., 2019; Fukushima et al., 2015; Takemura et al., 2019; Jung et al., 2014; Hwang et al., 2015). There were 3244 deaths. The median value used for low BMI was <20 (18 – 25). Three studies (n=20) reported incomplete data on BMI in their cohort (Lu et al., 2013; Zeng et al., 2016b; Wang et al., 2019; Takemura et al., 2019) and three studies (n=398) did not present what proportion of their cohort had a low BMI (Suzuki et al., 2020; Fukushima et al., 2015; Takemura et al., 2019). Meta-analysis (Fig. 4.) showed a pooled HR for OS with low BMI of 1.57 (1.29 – 1.90, p<0.0001).

Eleven papers (n= 5296) declared the cut off value used for elevated LDH with a median value of 246 U/L (168.5 – 486 U/L) (Shibuki et al., 2022; Tsai et al., 2021; Kim et al., 2015, 2018; Li et al., 2017; Zeng et al., 2016a; Huang et al., 2015; Suzuki et al., 2020; Zeng et al., 2016b; Wang et al., 2019; Takemura et al., 2019). Of these, 2 (n=310) papers did not present the proportion of patients in the normal and elevated LDH groups (Suzuki et al., 2020; Takemura et al., 2019), and 2 papers (n=282) declared incomplete data on LDH (Tsai et al., 2021; Zeng et al., 2016b). Five papers (n=2156) used the “upper limit of normal” without declaring the value (Hoang et al., 2012; Liu et al., 2016; Lu et al., 2013; Jung et al., 2014; Hwang et al., 2015) and one of these papers declared

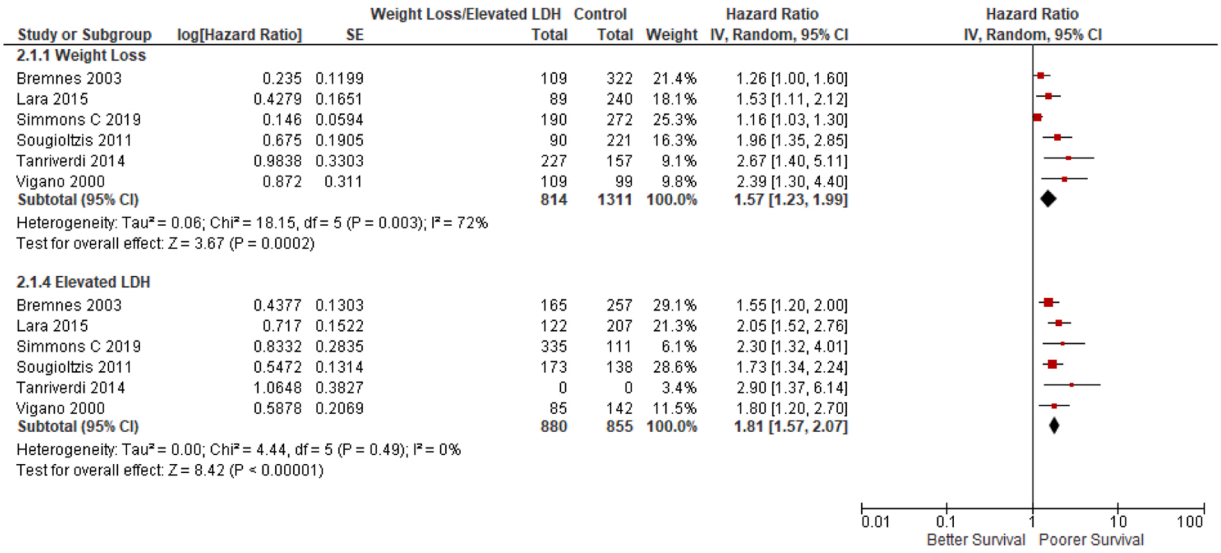


Fig. 2. Forest Plot showing pooled hazards ratios (HR)for overall survival (OS) from studies which reported the prognostic value of both lactate dehydrogenase (LDH) and weight loss (a phenotypic GLIM criterion) in cancer.

Table 2
Odds ratios (OR) for the association between an elevated serum lactate dehydrogenase (LDH) and any of the Global Leadership Initiative on Malnutrition (GLIM) criteria for cancer cachexia. There was insufficient data to estimate OR for weight loss or food intake. BMI= body mass index. NLR=neutrophil lymphocyte ratio.

GLIM Criterion		N	OR for elevated LDH (95% CI)	P value
Phenotypic				
Weight Loss		-	-	-
Low BMI		2109	1.39 (1.09 – 1.77)	p=0.008
Low Muscle Mass		660	1.31 (0.82 – 2.11)	p=0.26
Aetiologic				
Inflammation	CRP	652	2.58 (1.81 – 3.67)	p<0.00001
	NLR	3664	2.04 (1.57 – 2.65)	p<0.00001
Reduced Food Intake		-	-	-

incomplete data on LDH (n=39) (Lu et al., 2013). Additionally, 1 paper used the log of LDH (n=88) (Fukushima et al., 2015). Meta-analysis (Fig. 4.) showed a pooled HR for OS with elevated LDH of 2.00 (1.70 – 2.34, p<0.00001).

3.4.1. *The relationship between elevated LDH and reduced muscle mass*

There were five studies (n=818) which reported the presence of both elevated serum LDH and reduced muscle mass amongst their subjects (lung =1, lymphoma=1, pancreatic=1, urothelial cell=1,various=1) (Kim et al., 2015; Fukushima et al., 2015; Park et al., 2016; Veasey Rodrigues et al., 2013; Go et al., 2016). All cohorts included advanced, palliative or unresectable cancers. There were no prospective studies and muscle mass and serum LDH were assessed at baseline or the time of diagnosis (Supplementary Table). All five studies performed multivariable survival analysis (Supplementary Table).

Across all studies the prevalence of elevated LDH was 48% whereas 70% of patients had reduced muscle mass. Four studies (n=533) presented data on the relationship between elevated LDH and reduced muscle mass in their cohort (Kim et al., 2015; Park et al., 2016; Go et al., 2016; Burkart et al., 2019). There was not sufficient data to analyze the prevalence between early and advanced disease or different cancer types. The largest of these studies was a retrospective analysis of 187 patients receiving R-CHOP chemotherapy for diffuse large B-cell lymphoma. They found that LDH was elevated in 61% (28/46) of patients with sarcopenia compared to 57% (81/141) in those without (Go et al., 2016). Although a smaller sample size, it was another study of lymphoma patients that showed the only significant association between LDH and reduced muscle mass (p=0.047) (Burkart et al., 2019). Meta-analysis of these four studies did not produce a significant association with an OR of 1.31 (0.82 – 2.11, p = 0.26) for elevated serum LDH amongst patients with sarcopenia (Fig. 5).

3.4.2. *Prognostic value of elevated LDH compared to reduced muscle mass*

Amongst the five studies reporting the prognostic value of both elevated LDH and reduced muscle mass the median cut off for low SMI was 53.7 cm^2/m^2 (43 – 55 cm^2/m^2) in men and 40 cm^2/m^2 (38.5 – 55 cm^2/m^2) in women. The median value for raised LDH was 486 U/L (225 – 618 U/L). One study (n=88) used the log of serum LDH (Fukushima et al., 2015) and one study (n=88) did not state the value used for raised LDH (Park et al., 2016). One paper (n=306) did not make

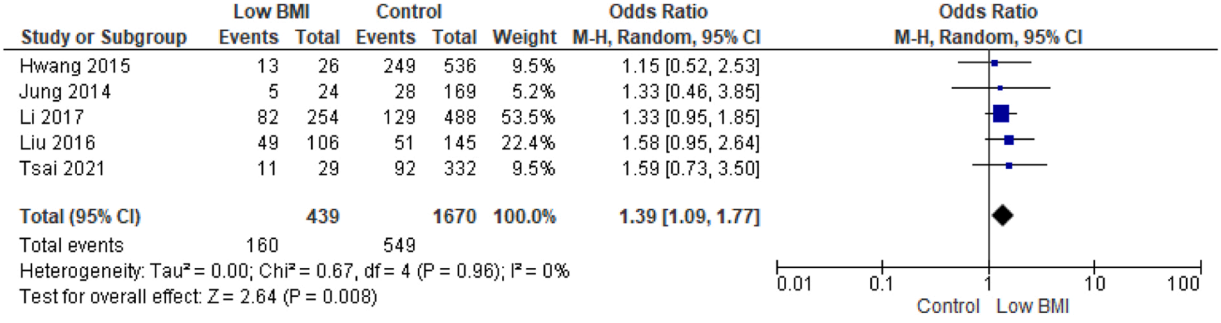


Fig. 3. Forest plot showing Odds Ratio (OR) for association between an elevated serum lactate dehydrogenase (LDH) and a low body mass index (BMI).

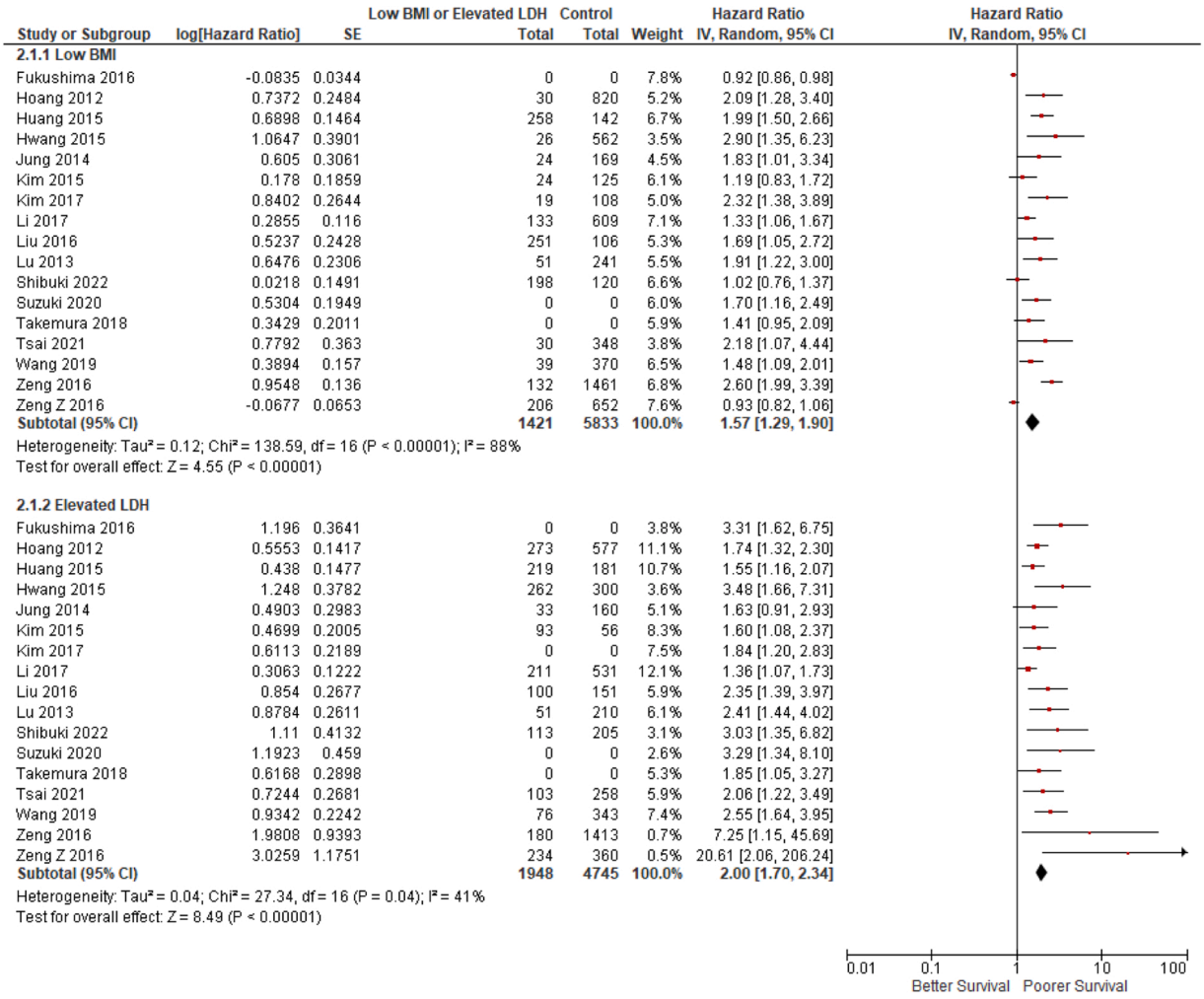


Fig. 4. Forest plot showing pooled hazard ratios (HR) for overall survival (OS) from studies which reported the prognostic value of both elevated serum lactate dehydrogenase (LDH) and low body mass index (BMI)(a phenotypic GLIM criteria) in cancer.

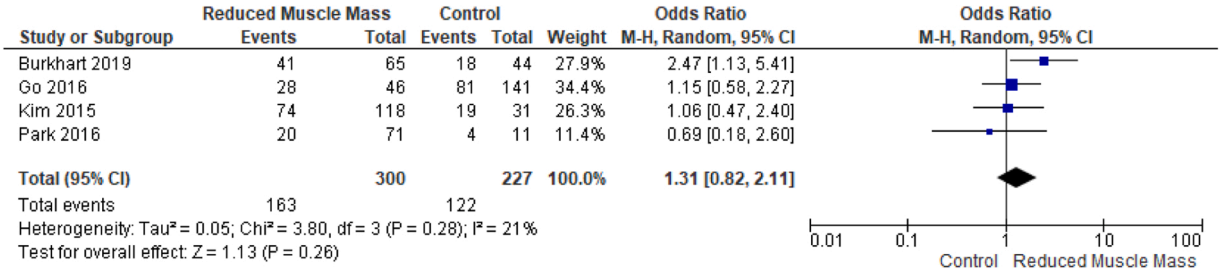


Fig. 5. Forest plot showing odds ratio (OR) for the association between an elevated serum lactate dehydrogenase (LDH) and reduced muscle mass (a phenotypic GLIM criterion) in cancer.

clear how many subjects fell into the raised LDH group (Veasey Rodrigues et al., 2013). Across all studies there were 413 deaths.

Meta-analysis (Fig. 6.) on the effect of reduced muscle mass on OS showed a pooled HR of 1.93 (95 per cent ci,1.14–3.27, p=0.01).

Meta-analysis (Fig. 6.) on the effect of elevated LDH on OS showed a pooled HR of 2.25 (95 per cent ci,1.76–2.87, p<0.00001).

3.4.3. *The relationship between elevated LDH and systemic inflammation*

One hundred and six studies (n=35,427) investigated the prognostic effect of serum LDH and markers of systemic inflammation on OS. Of these, sixty-four studies used NLR and fifty-nine studies used CRP. There were seventeen studies which reported the prognostic value of both NLR and CRP (Supplementary Table).

3.4.4. *LDH and NLR*

Included in the meta-analysis were fifty seven studies (n=18,664) which reported the presence of both elevated serum LDH and NLR amongst their subjects (lung=18, melanoma=7, prostate=5, colorectal=5, head and neck=4, renal=3, gastric=2, various=2, glioblastoma=2, lymphoma=2, pancreatic=1, penile=1, ovarian=1, urothelial=1, gallbladder=1, uveal=1, myeloma=1). Thirty seven included cohorts with only advanced, recurrent or metastatic cancer (n=10288).The remaining 20 papers included populations with both early and advanced disease (n=8376). There were no studies of early cancer

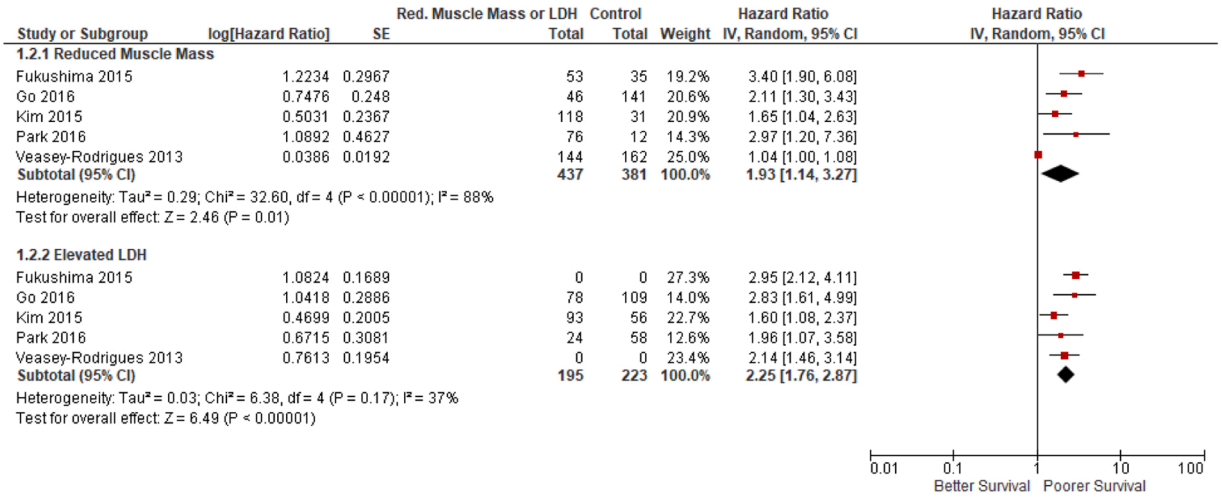


Fig. 6. Forest plot of pooled hazard ratios (HR) for overall survival (OS) in studies which reported the prognostic vale of both elevated serum lactate dehydrogenase (LDH) and reduced muscles mass (a phenotypic GLIM criterion) in cancer.

alone. Only three studies (n=386) were prospective (Pinto et al., 2018; Klumper et al., 2022; Aamdal et al., 2022b) and only one study performed serial measurements (Klumper et al., 2022), the remainder recording NLR and LDH at baseline or time of diagnosis (Supplementary Table). Fifty-two studies performed multivariable and five studies univariable survival analysis (Supplementary Table).

The median value used for raised NLR was 3.42 (range 0.38 – 6.1). This data was not available in 4 studies; 1 papers (n=132) gave no indication of the chosen cut off used for raised NLR (Nicholas et al., 2018), 1 paper (n=196) used the median as a cut off but did not state the value (Yamada et al., 2020), 1 paper(n=848) analyzed NLR on the logarithmic scale (Sonpavde et al., 2014) and 1 paper (n=1729) analyzed patients by quartiles (Giri et al., 2022).

Sixteen studies (n=6644) did not declare the proportion of subjects who fell into the raised NLR category (Aamdal, 2022b; Bersanelli, 2020; Chan, 2021; Giri, 2022; He, 2021; Li, 2018; Mercier and Voutsadakis, 2019; Namikawa, 2019; Ng, 2021; Peng, 2020; Pinto, 2018; Takada, 2020; Takemura, 2019, 2020; Tamura, 2021; Yamada, 2020). Seven studies declared incomplete data on NLR in their cohort. There were 10, 170 deaths across all papers that looked at raised LDH and NLR. Three studies did not report the number of deaths in their cohort.

3.4.5. The association between elevated NLR and elevated LDH

Across all studies utilizing NLR, the prevalence of elevated LDH was 41% whereas 45% of subjects had a raised NLR. Nine studies (n=3664) presented data on the relationship between an elevated NLR and serum LDH (Wang et al., 2018a; Mercier and Voutsadakis, 2019; Cao et al., 2017; Deng et al., 2017; Boegemann et al., 2017; Buttigliero et al., 2017; Kang et al., 2014; Giri et al., 2022; Shao and Cai, 2015). One large study of 1729 myeloma patients examined the prognostic value of pre-treatment biomarkers. They found that 16% (71/432) of patients whose NLR value fell in the 4th quartile (3.32 – 16.49) had an elevated LDH, compared to 8% (35/433) of patients in the lowest quartile (0.17–1.43) (Giri et al., 2022). Another retrospective review looked at prognostic factors in those receiving etoposide and platinum based chemotherapy regimes for small cell lung cancer. Similarily, they found that 35% (86/245) of patients with raised NLR (>3.18) also had an elevated LDH, whereas this fell to 23% (106/462) in patients with a low NLR (<3.18) (Cao et al., 2017).

Meta-analysis (Fig. 7.) showed an OR for elevated serum LDH in the presence of elevated NLR of 2.04 (95 per cent ci, 1.57 – 2.65, p<0.00001).

3.4.6. The prognostic value of elevated NLR

Meta-analysis (Fig. 8.) of the effect of raised NLR on OS gave a HR of 1.61 (95 per cent ci, 1.48 – 1.77, p<0.00001).

3.4.7. LDH and CRP

There were forty seven studies (n=17,924) which reported the presence of both elevated serum LDH and CRP amongst their cohorts

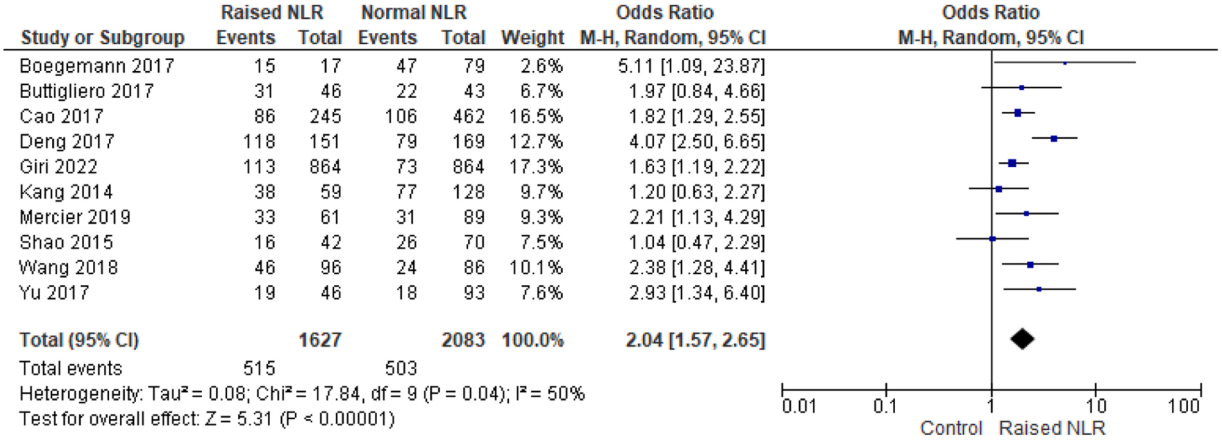


Fig. 7. Forest plot showing odds ratios (OR) for the association between elevated serum lactate dehydrogenase (LDH) and elevated neutrophil lymphocyte ratio (NLR) (an aetiologic GLIM criterion) in cancer.

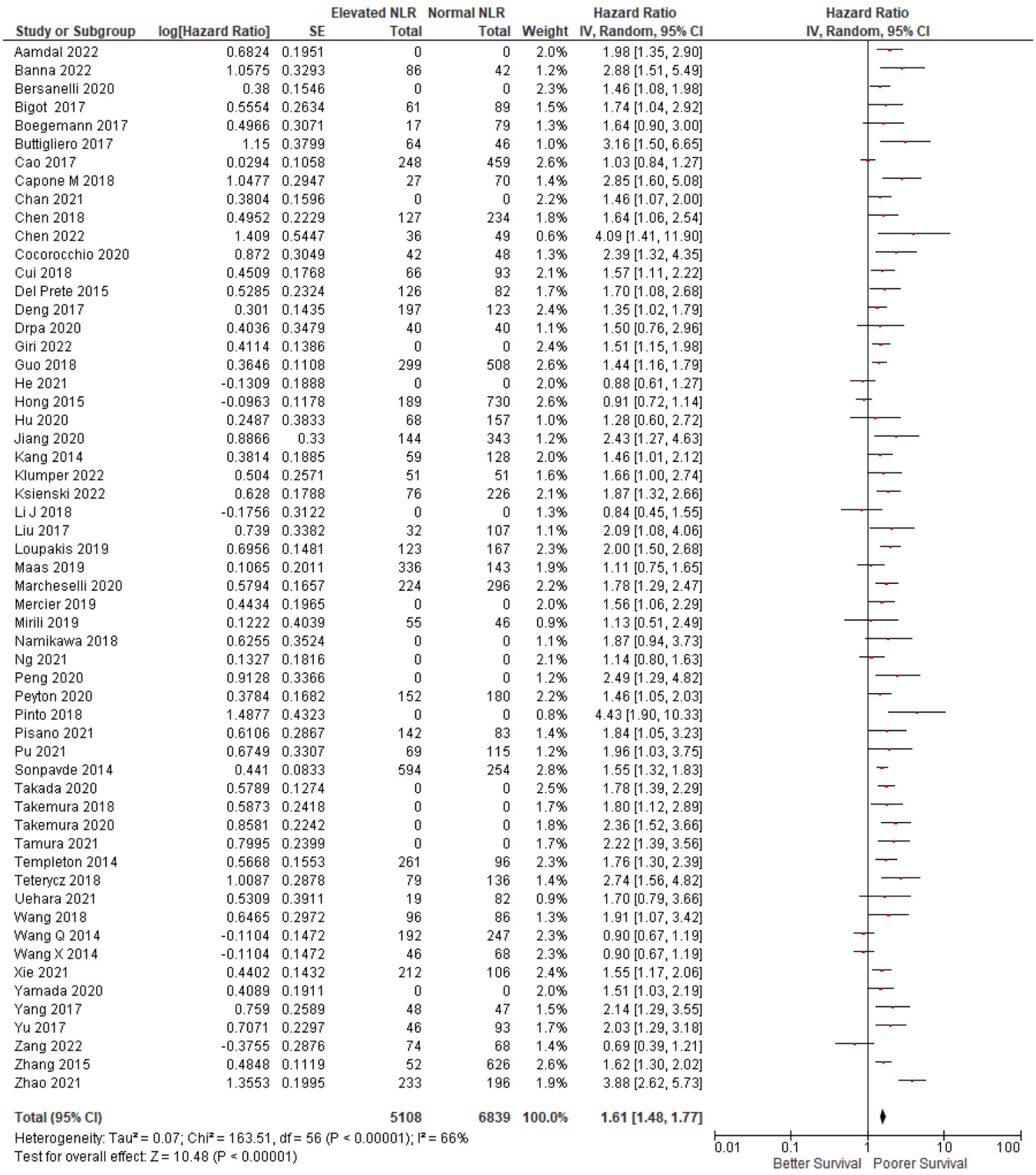


Fig. 8. Forest plot of pooled hazard ratios (HR) for overall survival (OS) associated with elevated neutrophil lymphocyte ratio (NLR)(aetiologic GLIM criterion) from studies reporting the prognostic value of both NLR and elevated lactate serum dehydrogenase (LDH) in cancer.

included in the meta-analysis (Aamdal, 2022b; Atzpodien, 2003; Berghoff, 2017; Casamassima, 2005; Desch, 2017; Di Blasi, 2022; Fukushima, 2015; Guo, 2018; Haas, 2013; Hartrampf, 2022; Hashimoto, 2009; Heppt, 2017; Ishioka, 2012; Jimenez-Zepeda, 2016; Kamba, 2014; Kanemasa, 2016; Klumper, 2022; Kripp, 2014; Li, 2013b, 2018; Ma, 2022b; Maas, 2019; Nakagawa, 2013, 2017; Nakai, 2010; Nakamura, 2016; Olgun and Diker, 2023; Reinert, 2020; Saito, 2009; Shibuki, 2022; Simmons, 2019a; Strijker, 2021; Suh and Ahn, 2007; Suzuki, 2020; Takada, 2020; Takemura, 2019, 2020; Tamura, 2021; Tanizaki, 2018; Tanrikulu, 2010; Tatsugami, 2015; Vogl, 2006; Wang et al., 2014b; Xie, 2021; Xue, 2014; Yamada, 2020; Zhou, 2015b) (renal=8, pancreatic=6, melanoma=5, urothelial=6, lung=5, various=5, lymphoma=3, prostate=2, glioblastoma=2, colorectal=1, gastric=1, breast=1, nasopharyngeal=1, myeloma=1). Thirty eight (n=13,768) of these only

included subjects with advanced, recurrent or metastatic cancer (Simmons et al., 2019a; Shibuki et al., 2022; Suzuki et al., 2020; Fukushima et al., 2015; Takemura et al., 2019; Berghoff et al., 2017; Vogl et al., 2006; Guo et al., 2018; Ma et al., 2022b; Wang et al., 2014b; Xie et al., 2021; Olgun and Diker, 2023; Di Blasi et al., 2022; Atzpodien et al., 2003; Haas et al., 2013; Hartrampf et al., 2022; Heppt et al., 2017; Klumper et al., 2022; Kripp et al., 2014; Reinert et al., 2020; Casamassima et al., 2005; Hashimoto et al., 2009; Ishioka et al., 2012; Kamba et al., 2014; Nakagawa et al., 2013; Nakai et al., 2010; Nakamura et al., 2016; Takemura et al., 2020; Tamura et al., 2021; Tanizaki et al., 2018; Tatsugami et al., 2015; Xue et al., 2014; Yamada et al., 2020; Suh and Ahn, 2007; Strijker et al., 2021; Aamdal et al., 2022b; Nakagawa et al., 2017; Saito et al., 2009). The remaining 9 papers (n=4156) included populations with all stages of disease (Tanrikulu et al., 2010; Jimenez-Zepeda et al., 2016; Li et al., 2013b; Zhou et al., 2015b; Desch et al., 2017; Kanemasa et al., 2016; Takada et al., 2020; Maas et al., 2019; Li et al., 2018). There were no studies of early cancer alone. Only 3 studies (n=308) took serial measurements of LDH and CRP (Klumper et al., 2022; Suh and Ahn, 2007; Saito et al., 2009), with all remaining studies (n=17,656) recording levels at diagnosis or baseline. Only six (n=1357) of the included studies measuring CRP and LDH were prospective (Simmons et al., 2019a; Di Blasi et al., 2022; Klumper et al., 2022; Kripp et al., 2014; Suh and Ahn, 2007; Aamdal et al., 2022b) (Supplementary Table). Forty-five studies used multivariable and 2 univariable survival analysis (Supplementary Table).

The median value used for raised CRP was >3 mg/L (range 0.3 – 50). This data was not available in 5 studies. Three papers (n=611) analyzed the log of CRP (Fukushima et al., 2015; Haas et al., 2013; Ishioka et al., 2012), 2 studies (Hartrampf et al., 2022; Nakai et al., 2010) analyzed CRP per unit increase (n=200) and 1 study (n=196) used the median CRP as the cutoff without stating the value (Yamada et al., 2020). Six studies (Aamdal, 2022b; Li, 2013a; Maas, 2019; Simmons, 2019a; Strijker, 2021; Zhou, 2015b) used a modified Glasgow Prognostic Score (mGPS) of >1 (n=6021) and as such the CRP cutoff in these papers was taken as >10 mg/L. One paper (n=130) did not state the value chosen for elevated CRP (Ma et al., 2022b).

Thirteen studies (Suzuki et al., 2020; Takemura et al., 2019; Jimenez-Zepeda et al., 2016; Ma et al., 2022b; Di Blasi et al., 2022; Desch et al., 2017; Heppt et al., 2017; Hashimoto et al., 2009; Ishioka et al., 2012; Takada et al., 2020; Takemura et al., 2020; Li et al., 2018; Nakagawa et al., 2017) did not make clear what proportion of subjects fell into the raised CRP category (n=3985). Twelve studies (Aamdal, 2022b; Haas, 2013; Klumper, 2022; Kripp, 2014; Maas, 2019; Nakagawa, 2013; Nakamura, 2016; Olgun and Diker, 2023; Reinert, 2020; Strijker, 2021; Tatsugami, 2015; Xie, 2021) had incomplete data on CRP (n=2232). There were 11,934 deaths across all papers which looked at both raised LDH and CRP. Five studies did not declare the number of deaths in their cohort.

3.5. The association between elevated CRP and elevated LDH

Three papers (n=652) presented data on the association between an elevated serum CRP and LDH (Li et al., 2013a; Zhou et al., 2015b; Saito et al., 2009). The prevalence of raised CRP (38%, 251/652) and elevated LDH (38%, 250/652) was similar. Half of patients with an elevated CRP also had an elevated LDH (50%, 125/251), compared to 33% (125/382) of patients without a raised CRP. The largest of these studies, a retrospective analysis of the prognostic value of mGPS in 359 patients with small cell lung cancer, found that elevated LDH was present in 64% (74/115) of patients with an mGPS >1 (CRP>10) compared to only 42% (96/225) of patients with an mGPS of 0 (CRP<10) (Zhou et al., 2015b).

Meta-analysis showed a significant association (Fig. 9.) between elevated serum LDH and CRP (OR 2.58, 1.81 – 3.67, p<0.00001).

3.6. The prognostic value of elevated CRP

Meta-analysis (Fig. 10.) on the effect of raised CRP on OS showed a HR of 1.55 (95 per cent ci,1.43–1.69, p<0.00001).

3.7. The prognostic value of elevated LDH

Ninety-three studies, totaling 32,190 subjects, were included in the meta-analysis of elevated LDH and OS (Aamdal, 2022b; Atzpodien, 2003; Banna, 2022; Berghoff, 2017; Bersanelli, 2020; Bigot, 2017; Boegemann, 2017; Buttigliero, 2017; Cao, 2017; Capone, 2018; Casamassima, 2005; Chan, 2021; Chen, 2018, 2022; Cocorocchio, 2020; Cui, 2018; Del Prete, 2015; Deng, 2017; Desch, 2017; Di Blasi, 2022; Drpa, 2020; Fukushima, 2015; Giri, 2022; Guo, 2018; Haas, 2013; Hartrampf, 2022; Hashimoto, 2009; He, 2021; Heppt, 2017; Hong, 2015; Hu, 2020; Ishioka, 2012; Jiang, 2020; Jimenez-Zepeda, 2016; Kamba, 2014; Kanemasa, 2016; Kang, 2014; Klumper, 2022; Kripp, 2014; Ksienski, 2022; Li, 2013a, 2018; Liu, 2017; Loupakis, 2019; Ma, 2022b; Maas, 2019; Marcheselli, 2020; Mercier and Voutsadakis, 2019; Mirili, 2019; Nakagawa, 2013, 2017; Nakai, 2010; Nakamura, 2016; Namikawa, 2019; Ng, 2021; Olgun and Diker, 2023; Peng, 2020; Peyton, 2020; Pinto, 2018; Pisano, 2021; Pu, 2021; Reinert, 2020; Saito, 2009; Shibuki, 2022; Simmons, 2019a; Sonpavde, 2014; Strijker, 2021; Suh, 2010; Suh and Ahn, 2007; Suzuki, 2019; Takada, 2020; Takemura, 2019, 2020; Tamura, 2021; Tanizaki, 2018; Tanrikulu, 2010; Tatsugami, 2015; Templeton, 2014; Teterycz, 2018; Uehara, 2021; Vogl, 2006; Wang, 2018a,a; Wang et al., 2014b; Xie, 2021; Xue, 2014; Yamada, 2020; Yang, 2017; Yu, 2017; Zhang, 2015, 2022; Zhao, 2021; Zhou, 2015a,b). Eighty-six studies (n=26667) used cutoff values to determine elevated LDH. The median value chosen was 241 U/L (158.95 – 502 U/L). Twenty-six of these studies (n=8157) did not declare the value chosen for the upper limit of normal (Templeton et al., 2014; Hong et al., 2015; Liu et al., 2017; Ma et al., 2022b; Wang et al., 2018b; Zhao et al., 2021; Bigot et al., 2017; Di Blasi et al., 2022; Boegemann et al., 2017; Heppt et al., 2017; Klumper et al., 2022; Buttigliero et al., 2017; Cocorocchio et al., 2020; Del Prete et al., 2015; Kamba et al., 2014; Kanemasa et al., 2016; Nakagawa et al., 2013; Takemura et al., 2020; Tamura et al., 2021; Tatsugami et al., 2015; Yamada et al., 2020; Aamdal et al., 2022b; Teterycz et al., 2018; Giri et al., 2022; Peyton et al., 2020; Nakagawa et al., 2017). Four studies (n=4807) calculated

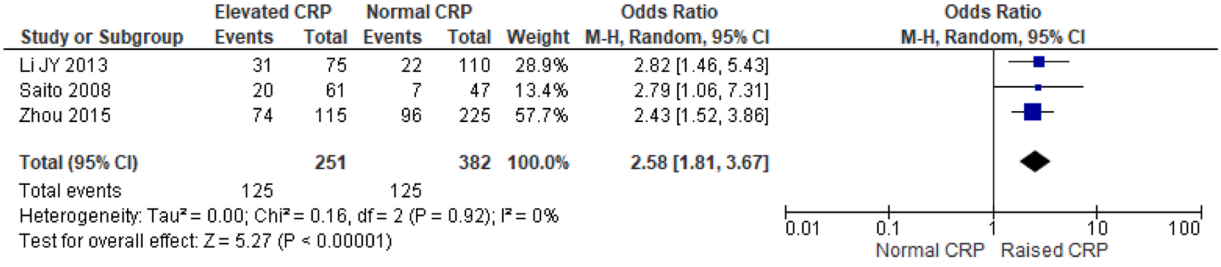


Fig. 9. Forest plot of odds ratios (OR) for the association between elevated serum lactate dehydrogenase (LDH) and elevated CRP (aetiologic GLIM criterion) in cancer.

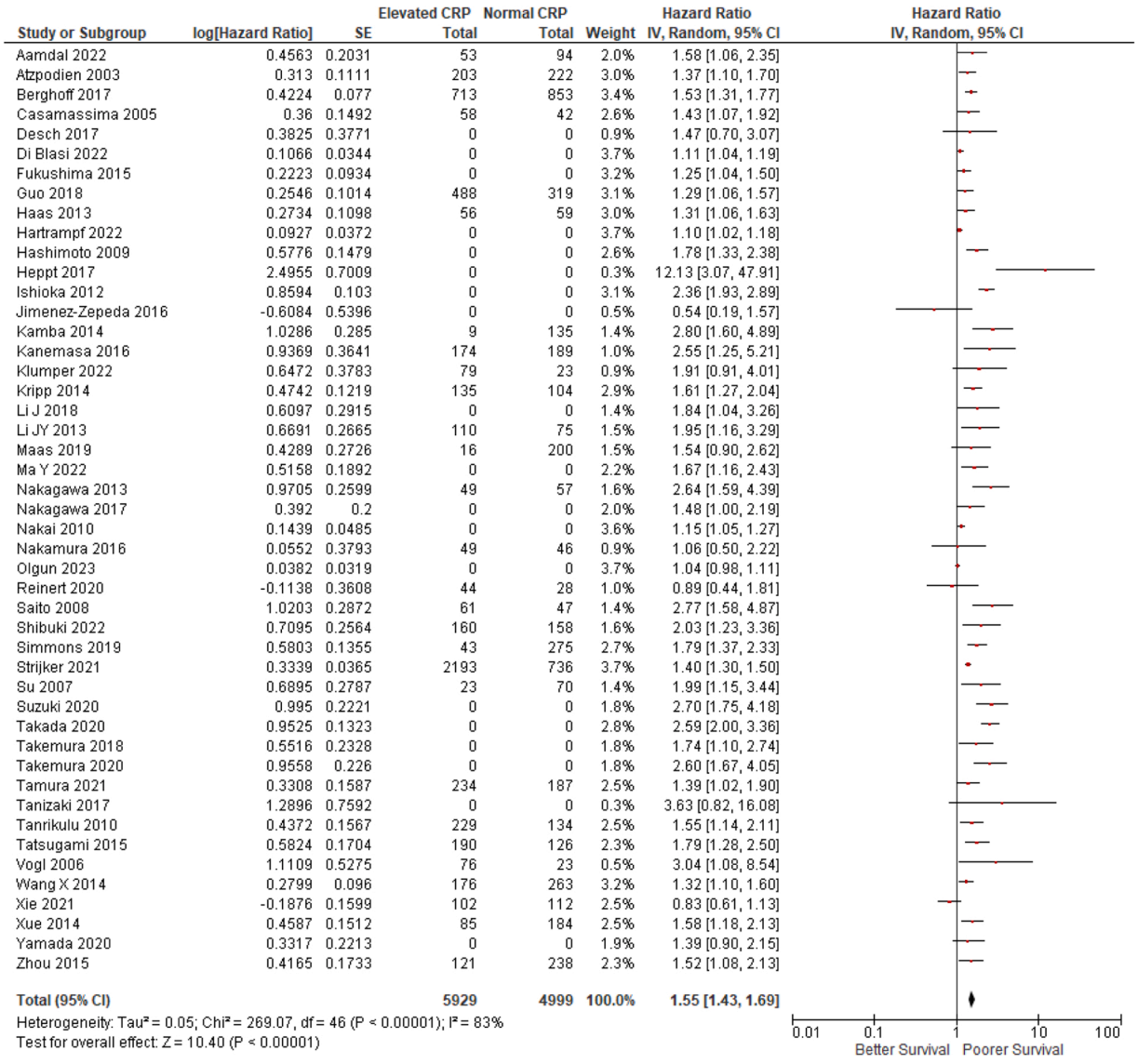


Fig. 10. Forest plot of pooled hazard ratios (HR) for overall survival (OS) associated with elevated CRP (aetiologic GLIM criterion) in studies reporting the prognostic value of both CRP and elevated serum lactate dehydrogenase (LDH) in cancer.

HRs based on per/unit increases in LDH (Zhou et al., 2015b; Hartrampf et al., 2022; Nakai et al., 2010; Strijker et al., 2021) and two studies (n=935) analyzed LDH on the logarithmic scale (Fukushima et al., 2015; Sonpavde et al., 2014).

Seventeen studies (n=4749) failed to provide the percentage of participants that were above their chosen cut off for elevated LDH (Suzuki et al., 2020; Takemura et al., 2019; Stangl-Kremser et al., 2020; Chan et al., 2021; Liu et al., 2017; Ma et al., 2022b; Desch et al., 2017; Bersanelli et al., 2020; Pisano et al., 2021; Hashimoto et al., 2009; Namikawa et al., 2019; Takada et al., 2020; Takemura et al., 2020; Tanizaki et al., 2018; Yamada et al., 2020; Ng et al., 2021; Nakagawa et al., 2017). Twenty-six studies (Aamdal, 2022b; Banna, 2022; Berghoff, 2017; Buttigliero, 2017; Capone, 2018; Casamassima, 2005; Cocorocchio, 2020; Giri, 2022; Haas, 2013; Hartrampf, 2022; Hashimoto, 2009; Heppt, 2017; Hong, 2015; Klumper, 2022; Kripp, 2014; Loupakis, 2019; Ma, 2022b; Maas, 2019; Mercier and Voutsadakis, 2019; Nakagawa, 2013; Olgun and Diker, 2023; Peyton, 2020; Reinert, 2020; Tatsugami, 2015; Xie, 2021; Yang, 2017) had incomplete data regarding serum LDH in their cohort (n=2687). There were 19,569 deaths across all studies. Five papers did not make clear the number of patients who died (Hong et al., 2015; Peng et al., 2020; Olgun and Diker, 2023; Takada et al., 2020; Maas et al., 2019).

Meta-analysis (Fig. 11.) of elevated LDH showed a HR for OS of 1.77 (95 per cent ci, 1.64 – 1.90, p<0.00001).

4. Discussion

The present review is the first to examine the association between LDH and GLIM criteria and compare their relative prognostic value on overall survival in cancer. The current results showed that an elevated serum LDH was associated with both an elevated NLR and an elevated CRP (both measures of systemic inflammation and aetiologic factors in GLIM criteria). In contrast, the association between an elevated LDH and a low BMI was weaker and not seen with weight loss or low skeletal muscle mass (phenotypic GLIM criterion). Furthermore, meta-analysis of 119 papers and more than 40,000 patients confirmed LDH as prognostic of overall survival in cancer when compared to both the phenotypic and aetiologic GLIM criteria. Therefore, the present results suggest that the measurement of LDH is a useful addition to GLIM criteria in patients with cancer.

The results of the present review are consistent with a recent study that, in 436 patients with advanced cancer, reported a direct association

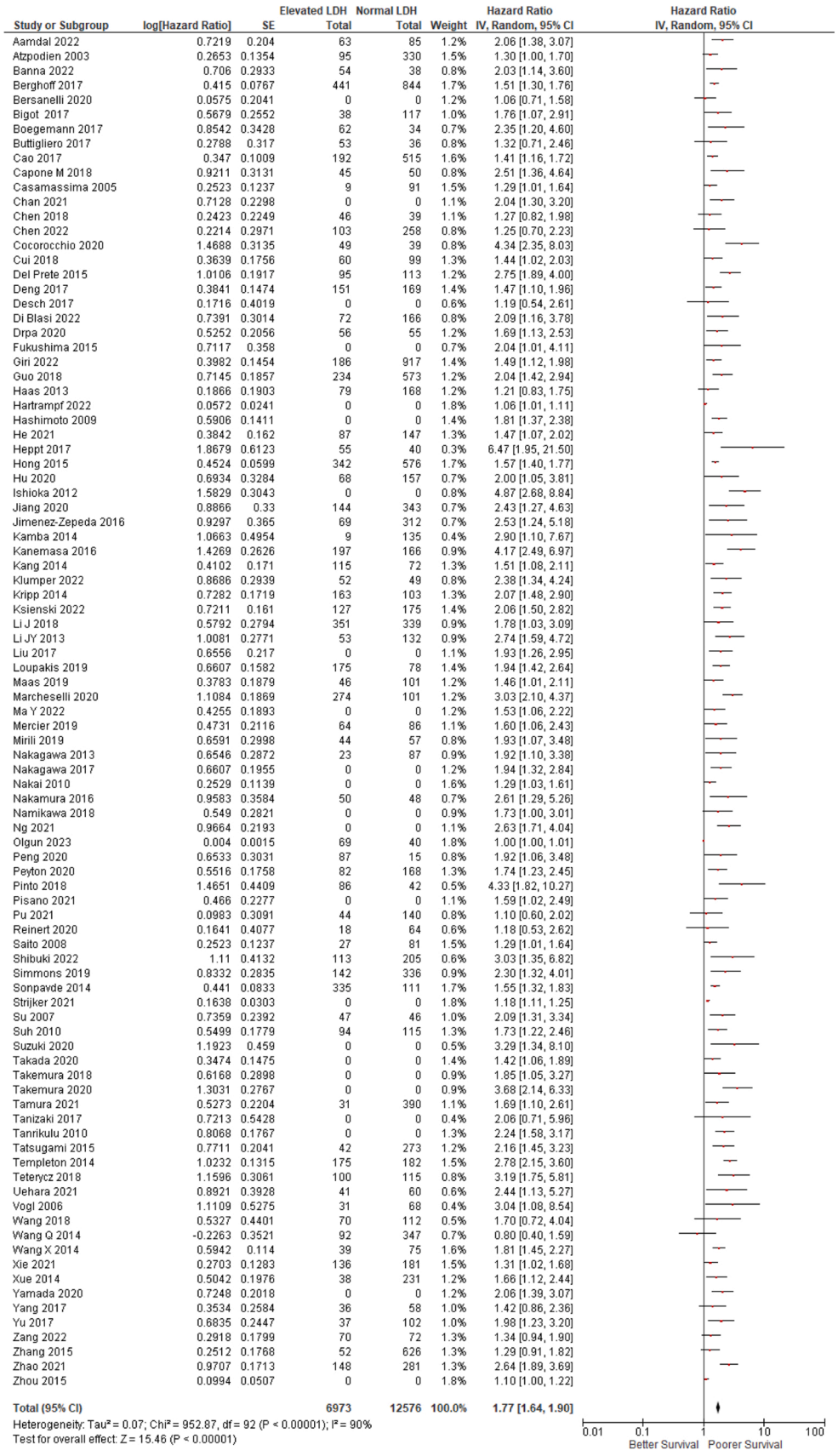


Fig. 11. Forest plot of pooled hazard ratios (HR) for overall survival (OS) associated with an elevated serum lactate dehydrogenase (LDH) in studies that presented the prognostic value of LDH and inflammation (neutrophil lymphocyte ratio or CRP) in cancer.

between LDH and aetiologic factors of GLIM criteria (systemic inflammation as evidenced by NLR and mGPS) but not phenotypic factors such as weight loss, low BMI and low muscle mass (McGovern et al., 2023). Therefore, the present results consolidate the relationship between lactate and the systemic inflammatory response in patients with cancer. In addition to LDH other potential biomarkers of cancer cachexia have been proposed but not incorporated into the GLIM criteria (Lipocalin-2, Angiotensin-II, HS6ST2, TGFB1 etc.). It remains to be determined whether, like LDH, a case can be made for their inclusion as a GLIM criterion for routine clinical measurement. Furthermore, whether normalizing lactate results in a reduction of systemic inflammation or vice versa is also unclear. However, this question is likely to become of increasing importance in the treatment of GLIM defined cancer cachexia.

Recently, the cachexia community has focused on the prognostic value of body composition in cancer. Indeed, the foundation of earlier cachexia definitions centered around weight loss, low BMI and low muscle mass (McGovern et al., 2022; Fearon et al., 2011). Each of these phenotypes confer poor prognostic value in cancer (Abbass et al., 2019, 2020a, 2020b), but without a causal link, may represent surrogate markers of an underlying aetiologic process and therefore not a useful clinical therapeutic target. In particular, each component of body composition must be considered in the context of the patient's constitution, comorbidity and conditioning prior to diagnosis. The increasing prevalence of old age and obesity in the cancer population leaves the importance of clinically relevant definitions of cancer associated weight loss, low BMI and low muscle mass unclear since there is the potential confounding of primary sarcopenia and sarcopenic obesity respectively to consider. Furthermore, there is the potential confounding of the presence of the systemic inflammatory response on the prognostic value of low muscle mass to consider. A recent paper by Hacker et al. examined the relationship between systemic inflammation (as measured by mGPS) and skeletal muscle index in patients with advanced gastric and esophageal cancer. They reported that tumor associated systemic inflammation was associated with low muscle mass and was the dominant prognostic factor and postulated that there was no direct relationship between sarcopenia and survival (Hacker et al., 2022).

Recently, the definition of cancer cachexia has evolved to include measurement of the systemic inflammatory response and indeed some have argued that cancer cachexia is primarily a systemic inflammatory syndrome rather than a nutritional syndrome (Maccio et al., 2023). In the present review it was of particular interest that an elevated serum LDH was associated with an elevated systemic inflammatory response and had comparative prognostic value in patients with cancer. Therefore, it may be that LDH will be a clinically useful addition to the GLIM etiological criteria and a useful therapeutic target.

It has long been recognized that all mammalian cells abhor poor perfusion and hypoxia. The precocious and chaotic vasculature within tumors can result in areas of both hypoxia and necrosis. This will result in increased lactate production, mediated by LDH, which leaks into the TME. Furthermore, as first observed by Warburg, cancer cells are predisposed to aerobic glycolysis and the production of lactate despite the presence of oxygen. This results in rising levels of lactate throughout the TME with various pro-tumorigenic consequences having been demonstrated (Ippolito et al., 2019; Certo et al., 2021). Although much remains unclear this would support the comparative prognostic value and association between inflammation and LDH highlighted by this review.

In the present review the median percentage weight loss was 5%, in keeping with the GLIM criteria. However, this represented a small number of studies. This is likely explained by the lack of available data on weight loss in retrospective cohorts as this requires an accurate baseline weight and serial measurement. In contrast, a larger number of studies provided data on BMI. GLIM classifies a low BMI as <20 kg/m^2 if <70 years old (Asia:<18.5) and <22 kg/m^2 if >70 years old (Asia: <20). The average value of <20 used to determine low BMI in this review was consistent with GLIM and other commonly used malnutrition screening tools such as MUST. In the present review there were no studies that examined the association between, or prognostic value of, food intake and LDH in patients with cancer. This is perhaps not surprising given the difficulty involved in accurately measuring food intake. Nevertheless, this association is of considerable interest given the above discussion on the phenotypic and aetiologic criteria in the GLIM definition of cancer cachexia and the current approach to replacing or surpassing any calorie deficit in cancer patients. Recent studies have shown the effectiveness of supplementing nutritional intake amongst cancer patients is much reduced in the presence of inflammation (Merker et al., 2020; Bargetzi et al., 2021). In terms of low muscle mass the GLIM criteria allow the identification of muscle mass by any "valid body composition assessment method". These broad criteria can include anything from physical examination and bioelectrical impedance to advanced imaging techniques. However, these methodologies are likely to be inferior to the extensively validated computed tomography (CT) measurement of muscle mass at the level of the 3rd lumbar vertebra (Hansen et al., 2021). All studies in the present review assessed muscle mass in this way and therefore the comparison of the LDH with BMI and low muscle mass is likely to be a valid one.

The present systematic review and meta-analysis had several limitations. In particular, the random-effects model utilised by RevMan, compared with other more elaborate models in R packages and Stata, have been shown to generate confidence intervals that are too narrow and p-values that are low. This may result in false positive results. Similarly, publication bias was assessed by visual inspection of funnel plots. This showed that larger studies had effects that were symmetrically distributed around the effect line however smaller studies were more likely to have a skewed effect, perhaps suggesting an element of non-reporting bias. Furthermore, there are innate shortcomings associated with retrospective studies. This introduces bias due to missing data, loss to follow up and potential confounding. Additionally, routinely available serum biomarkers represent attractive tools in prognostication, however they require standardized and validated use. The current review includes papers which used very different values to represent elevated LDH, NLR and CRP. Some studies did not state the value chosen and only declared that LDH was elevated above the locally assigned upper limit of normal. The mGPS (CRP >10 and Albumin <35) has been extensively validated as a tool for studying systemic inflammation in cancer (Abbass et al., 2020a; McMillan, 2013; Proctor et al., 2015, 2011; Dolan et al., 2020), however only 8 out of 106 included studies on inflammation used this tool (supplementary tables). Future work on the etiology and prognosis of cancer cachexia should aim to utilize standardized tool such as the mGPS. Furthermore, few of the included studies presented data on the association between elevated LDH and the GLIM criteria which constrained this aspect of the meta-analysis. The decision to use survival data (represented by hazard ratios) as an inclusion criteria may have missed some studies which presented data on the association alone. As such, there was limited data on the association between LDH and GLIM to perform subgroup analysis by tumor type or stage. However, the majority of HRs were based on multivariable survival analyses (109 out of 119 studies, 92%) univariable survival analysis was unlikely to be a major source of error in the present review. Further prospective studies are required to show that LDH has substantial added prognostic value, after adjusting for all other GLIM criteria. Finally, it is possible that ethnicity and geographical location result in different tumor-host interactions. A large proportion of included studies originated from Japan, Korea and China. A recent review of inflammatory markers in breast cancer (Savioli et al., 2022) found that Asian studies often use lower thresholds for NLR which may reflect differences in levels of inflammation between geographical locations. It might be reasonable to expect a similar difference in the levels of serum LDH present in advanced cancer between Asian and Western populations.

The present review confirms the prognostic value of LDH, in the context of GLIM, in patients with cancer. Additional studies should aim

to confirm the independent prognostic value of LDH by correcting for the GLIM criteria. Given that it is an objective measure of metabolic dysfunction, LDH may prove to be a useful addition to the GLIM criteria to improve treatment stratification and response. Future prospective work is required to define the interactions between LDH and the GLIM criteria and in early or resectable disease. Additionally, further work on LDH in the tumor microenvironment may define mechanisms by which the tumor and host interact resulting in the cancer cachexia state.

5. Conclusion

Elevated serum LDH was associated with the systemic inflammatory response in patients with cancer (an aetiologic GLIM criterion). This supports previous work proposing elevated LDH become the 3rd aetiologic criteria of GLIM. Additionally, LDH had similar prognostic value when compared to GLIM criteria including weight loss, low BMI, low muscle mass and systemic inflammation.

Declaration of Competing Interest

None to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104378.

References

Baracos, V.E., et al., 2018. Cancer-associated cachexia. Nat. Rev. Dis. Prim. 4, 17105.

McGovern, J., et al., 2022. Cancer cachexia: a nutritional or a systemic inflammatory syndrome? Br. J. Cancer 127 (3), 379–382.

Cederholm, T., et al., 2019. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. J. Cachex Sarcopenia Muscle 10 (1), 207–217.

McGovern, J., et al., 2023. Lactate dehydrogenase: relationship with the diagnostic GLIM criterion for cachexia in patients with advanced cancer. Br. J. Cancer 128 (5), 760–765.

Farhana, A. and S.L. Lappin, Biochemistry, Lactate Dehydrogenase, in StatPearls. 2023: Treasure Island (FL) ineligible companies. Disclosure: Sarah Lappin declares no relevant financial relationships with ineligible companies.

Warburg, O., 1956. Origin of cancer cells. Oncologia 9 (2), 75–83.

Walenta, S., Mueller-Klieser, W.F., 2004. Lactate: mirror and motor of tumor malignancy. Semin Radiat. Oncol. 14 (3), 267–274.

Claps, G., et al., 2022. The multiple roles of LDH in cancer. Nat. Rev. Clin. Oncol. 19 (12), 749–762.

Masi, T., Patel, B.M., 2021. Altered glucose metabolism and insulin resistance in cancer-induced cachexia: a sweet poison. Pharm. Rep. 73 (1), 17–30.

McAllister, S.S., Weinberg, R.A., 2014. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nat. Cell Biol. 16 (8), 717–727.

Roxburgh, C.S., McMillan, D.C., 2014. Cancer and systemic inflammation: treat the tumour and treat the host. Br. J. Cancer 110 (6), 1409–1412.

Roxburgh, C.S., McMillan, D.C., 2012. The role of the in situ local inflammatory response in predicting recurrence and survival in patients with primary operable colorectal cancer. Cancer Treat. Rev. 38 (5), 451–466.

Ippolito, L., et al., 2019. Lactate: a metabolic driver in the tumour landscape. Trends Biochem Sci. 44 (2), 153–166.

Certo, M., et al., 2021. Lactate modulation of immune responses in inflammatory versus tumour microenvironments. Nat. Rev. Immunol. 21 (3), 151–161.

Dolan, R.D., et al., 2018. The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: a systematic review. Crit. Rev. Oncol. Hematol. 132, 130–137.

Dolan, R.D., et al., 2017a. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: systematic review and meta-analysis. Sci. Rep. 7 (1), 16717.

Dolan, R.D., et al., 2017b. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 116, 134–146.

Shimoyama, R., et al., 2024. Inflammation-based prognostic markers of metastatic pancreatic cancer using real-world data in Japan: the Tokushukai REAl-world Data (TREAD) project. Oncol. Lett. 27 (3), 136.

Vandenbroucke, J.P., et al., 2007. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Ann. Intern Med 147 (8).

Bremnes, R.M., et al., 2003. The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5 year follow-up. Lung Cancer 39 (3), 303–313.

Knetki-Wroblewska, M., et al., 2021. Thymic epithelial tumors: do we know all the prognostic factors? Thorac. Cancer **02**.

Lara, P.N., et al., 2015. Relevance of platinum-sensitivity status in relapsed/refractory extensive-stage small-cell lung cancer in the modern era: a patient-level analysis of Southwest Oncology Group trials. J. Thorac. Oncol. 10 (1), 110–115.

Simmons, C., et al., 2019a. How long have i got?"-a prospective cohort study comparing validated prognostic factors for use in patients with advanced cancer. Oncologist 24 (9), e960–e967.

Shibuki, T., et al., 2022. Prognostic nomogram for patients with unresectable pancreatic cancer treated with gemcitabine plus nab-paclitaxel or FOLFIRINOX: a post-hoc analysis of a multicenter retrospective study in Japan (NAPOLEON study). BMC Cancer 22 (1), 19.

Sougioultzis, S., et al., 2011. Palliative gastrectomy and other factors affecting overall survival in stage IV gastric adenocarcinoma patients receiving chemotherapy: a retrospective analysis. Eur. J. Surg. Oncol. 37 (4), 312–318.

Tanrikulu, A.C., et al., 2010. A clinical, radiographic and laboratory evaluation of prognostic factors in 363 patients with malignant pleural mesothelioma. Respiration 80 (6), 480–487.

Tanriverdi, O., et al., 2014. Prognostic significance of the baseline serum uric acid level in non-small cell lung cancer patients treated with first-line chemotherapy: a study of the Turkish Descriptive Oncological Researches Group. Med. Oncol. 31 (10), 1–7.

Viganó, A., et al., 2000. Clinical survival predictors in patients with advanced cancer. Arch. Intern Med 160 (6), 861–868.

Tsai, C.K., et al., 2021. Underweight as a risk factor of mortality in patients with newly diagnosed multiple myeloma. Support. Care Cancer 29 (7), 3991–3999.

Hoang, T., et al., 2012. Prognostic models to predict survival in non-small-cell lung cancer patients treated with first-line paclitaxel and carboplatin with or without bevacizumab. J. Thorac. Oncol. 7 (9), 1361–1368.

Kim, E.Y., et al., 2015. Prognostic Significance of CT-Determined Sarcopenia in Patients with Small-Cell Lung Cancer. J. Thorac. Oncol. 10 (12), 1795–1799.

Kim, E.Y., et al., 2018. Prognostic significance of cachexia score assessed by CT in male patients with small cell lung cancer. Eur. J. Cancer Care 27 (1).

Li, Y.J., et al., 2017. Increased body mass index is associated with improved overall survival in extranodal natural killer/T-cell lymphoma, nasal type. Oncotarget 8 (3), 4245–4256.

Liu, J., et al., 2016. Body mass index as a prognostic factor in patients with extranodal natural killer/T-cell lymphoma, nasal type. Oncotarget 7 (47), 78159–78167.

Lu, Z., et al., 2013. Advanced or metastatic gastric cancer in elderly patients: Clinicopathological, prognostic factors and treatments. Clin. Transl. Oncol. 15 (5), 376–383.

Tang, L.Q., et al., 2016. Establishment and validation of prognostic nomograms for endemic nasopharyngeal carcinoma. J. Natl. Cancer Inst. 108, 1.

Zeng, Q., et al., 2016a. Nomograms for predicting long-term survival in patients with non-metastatic nasopharyngeal carcinoma in an endemic area. Oncotarget 7 (20), 29708–29719.

Abdel-Rahman, O., 2018. Impact of baseline characteristics on extensive-stage SCLC patients treated with etoposide/carboplatin: a secondary analysis of a phase III study. Clin. Respir. J. 12 (10), 2519–2524.

Banna, G.L., et al., 2022. Host immune-inflammatory markers to unravel the heterogeneous outcome and assessment of patients with PD-L1 >/=50% metastatic non-small cell lung cancer and poor performance status receiving first-line immunotherapy. Thorac. Cancer 13 (3), 483–488.

Gravis, G., et al., 2015. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. Eur. Urol. 68 (2), 196–204.

Huang, P.Y., et al., 2015. Ten-year outcomes of a randomised trial for locoregionally advanced nasopharyngeal carcinoma: a single-institution experience from an endemic area. Eur. J. Cancer 51 (13), 1760–1770.

Smith, M.R., et al., 2011. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer 117 (10), 2077–2085.

Suzuki, H., et al., 2020. Prognostic significance of the controlling nutritional status (CONUT) score in advanced urothelial carcinoma patients. Urol. Oncol. Semin. Orig. Investig. 38 (3), 76.e11–76.e17.

Suzuki, H., et al., 2019. Prognostic significance of controlling nutritional status (CONUT) score in advanced urothelial carcinoma patients. Eur. Urol. Suppl. 18 (1), e637.

Zeng, Z., et al., 2016b. A nomogram for predicting survival of nasopharyngeal carcinoma patients with metachronous metastasis. Medicine 95 (27).

Aben, K.K., et al., 2011. Better survival in patients with metastasised kidney cancer after nephrectomy: a population-based study in the Netherlands. Eur. J. Cancer 47 (13), 2023–2032.

Song, Y., et al., 2016. Body mass index and age are additional prognostic factors in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Urol. Oncol.: Semin. Orig. Investig. 34 (6), e15–e258.

Wang, Q.Q., et al., 2018a. Pretreatment controlling nutritional status score and lactate dehydrogenase as predictive markers of survival in patients with malignant peritoneal mesothelioma. Nutr. Cancer 70 (8), 1264–1274.

Wang, X., et al., 2019. Development and validation of a prognostic nomogram in AFP-negative hepatocellular carcinoma. Int. J. Biol. Sci. 15 (1), 221–228.

Rutkowski, P., et al., 2020. Body mass index (BMI) and outcome of metastatic melanoma patients receiving targeted therapy and immunotherapy: a multicenter international retrospective study. J. Immunother. Cancer 8 (2) (no pagination).

Abdel-Rahman, O., 2019. Prognostic value of baseline ALBI score among patients with colorectal liver metastases: a pooled analysis of two randomized trials. Clin. Colorectal Cancer 18 (1), e61–e68.

Kanemasa, Y., et al., 2018. Geriatric nutritional risk index as a prognostic factor in patients with diffuse large B cell lymphoma. Ann. Hematol. 97 (6), 999–1007.
Okamoto, T., et al., 2019. Impact of nutritional status on the prognosis of patients with metastatic hormone-naive prostate cancer: a multicenter retrospective cohort study in Japan. World J. Urol. 37 (9), 1827–1835.
Shah, M.S., et al., 2015. Joint prognostic effect of obesity and chronic systemic inflammation in patients with metastatic colorectal cancer. Cancer 121 (17), 2968–2975.
Simmons, C., et al., 2019b. How long have i got?"-a prospective cohort study comparing validated prognostic factors for use in patients with advanced cancer. Oncologist 24 (9), e960–e967.
Fukushima, H., et al., 2015. Sarcopenia as a prognostic biomarker of advanced urothelial carcinoma. PLoS ONE 10 (1).
Takemura, K., et al., 2019. Prognostic significance of serum gamma-glutamyltransferase in patients with advanced urothelial carcinoma. Urol. Oncol. 37 (2), 108–115.
Jung, S.H., et al., 2014. Decreased body mass index is associated with poor prognosis in patients with multiple myeloma. Ann. Hematol. 93 (5), 835–840.
Hwang, H.S., et al., 2015. Body mass index as a prognostic factor in Asian patients treated with chemoimmunotherapy for diffuse large B cell lymphoma, not otherwise specified. Ann. Hematol. 94 (10), 1655–1665.
Park, I., et al., 2016. Prognostic factors for risk stratification of patients with recurrent or metastatic pancreatic adenocarcinoma who were treated with gemcitabine-based chemotherapy. Cancer Res Treat. 48 (4), 1264–1273.
Veasey Rodrigues, H., et al., 2013. Body composition and survival in the early clinical trials setting. Eur. J. Cancer 49 (15), 3068–3075.
Go, S.I., et al., 2016. Prognostic impact of sarcopenia in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J. Cachex Sarcopenia Muscle 7 (5), 567–576.
Burkart, M., et al., 2019. Evaluation of the impact of cachexia on clinical outcomes in aggressive lymphoma. Br. J. Haematol. 186 (1), 45–53.
Berghoff, A.S., et al., 2017. Combining standard clinical blood values for improving survival prediction in patients with newly diagnosed brain metastases-development and validation of the LabBM score. Neuro Oncol. 19 (9), 1255–1262.
Stangl-Kremser, J., et al., 2020. Development of a prognostic model for survival time prediction in castration-resistant prostate cancer patients. Urol. Oncol. 38 (6).
Vogl, U.M., et al., 2006. Prognostic factors in metastatic renal cell carcinoma: metastasectomy as independent prognostic variable. Br. J. Cancer 95 (6), 691–698.
Chan, S.W.S., et al., 2021. Systemic inflammatory markers of survival in epidermal growth factor-mutated non-small-cell lung cancer: single-institution analysis, systematic review, and meta-analysis. Clin. Lung Cancer 22 (5), 390–407.
Jimenez-Zepeda, V.H., et al., 2016. Revised international staging system applied to real world multiple myeloma patients. Clin. Lymphoma Myeloma Leuk. 16 (9), 511–518.
Ksienski, D., et al., 2022. Immune related adverse events and treatment discontinuation in patients older and younger than 75 years with advanced melanoma receiving nivolumab or pembrolizumab. J. Geriatr. Oncol. 13 (2), 220–227.
Mercier, J., Voutsadakis, I.A., 2019. Comparison of hematologic and other prognostic markers in metastatic colorectal cancer. J. Gastrointest. Cancer 50 (3), 493–506.
Nicholas, M.N., et al., 2018. Prognostic factors for first-line therapy and overall survival of metastatic uveal melanoma: the princess margaret cancer centre experience. Melanoma Res 28 (6), 571–577.
Templeton, A.J., et al., 2014. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. Cancer 120 (21), 3346–3352.
Pinto, M.P., et al., 2018. Patient inflammatory status and CD4+/CD8+ intraepithelial tumor lymphocyte infiltration are predictors of outcomes in high-grade serous ovarian cancer. Gynecol. Oncol. 151 (1), 10–17.
Cao, S., et al., 2017. Selected patients can benefit more from the management of etoposide and platinum-based chemotherapy and thoracic irradiation-a retrospective analysis of 707 small cell lung cancer patients. Oncotarget 8 (5), 8657–8669.
Chen, J., et al., 2022. Clinical significance of serum biomarkers in stage IV non-small-cell lung cancer treated with PD-1 inhibitors: LIPI score, NLR, dNLR, LMR, and PAB. Dis. Markers 2022, 7137357.
Chen, L., et al., 2018. Survival and prognostic analysis of preoperative inflammatory markers in patients undergoing surgical resection for laryngeal squamous cell carcinoma. BMC Cancer 18 (1), 816.
Cui, X., et al., 2018. Long-term outcomes and prognostic markers in gallbladder cancer. Med. (Baltim.) 97 (28), e11396.
Deng, M., et al., 2017. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? Oncotarget 8 (23), 37200–37207.
Guo, G., et al., 2018. Establishment of inflammation biomarkers-based nomograms to predict prognosis of advanced colorectal cancer patients based on real world data. PLoS One 13 (12), e0208547.
He, M., et al., 2021. Value of pretreatment serum lactate dehydrogenase as a prognostic and predictive factor for small-cell lung cancer patients treated with first-line platinum-containing chemotherapy. Thorac. Cancer 12 (23), 3101–3109.
He, X., et al., 2015. Advanced lung cancer inflammation index, a new prognostic score, predicts outcome in patients with small-cell lung cancer. Clin. Lung Cancer 16 (6), e165–e171.
Hong, X., et al., 2015. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J. Exp. Med 236 (4), 297–304.
Hu, C., et al., 2020. Prognostic value of systemic inflammatory factors NLR, LMR, PLR and LDH in penile cancer. BMC Urol. 20 (1), 57.
Jiang, Y., et al., 2020. Prognostic nomogram for locoregionally advanced nasopharyngeal carcinoma. Sci. Rep. 10 (1), 861.
Li, A.C., et al., 2015. Risk factors and prediction-score model for distant metastasis in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy. Tumour Biol. 36 (11), 8349–8357.
Li, Y.J., et al., 2013a. The glasgow prognostic score (GPS) as a novel and significant predictor of extranodal natural killer/T-cell lymphoma, nasal type. Am. J. Hematol. 88 (5), 394–399.
Li, Y.J., et al., 2013b. Serum C-reactive protein (CRP) as a simple and independent prognostic factor in extranodal natural killer/T-cell lymphoma, nasal type. PLoS One 8 (5), e64158.
Liu, D., et al., 2017. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. BMC Cancer 17 (1), 882.
Ma, Y., et al., 2022a. The prognostic value of albumin-globulin ratio and eosinophil-neutrophil ratio in patients with advanced tumors undergoing treatment with PD-1/PD-L1 inhibitors. Nutr. Cancer 74 (8), 2815–2828.
Ma, Y.Y., et al., 2022b. Prognostic value of combined lactate dehydrogenase, C-reactive protein, cancer antigen 153 and cancer antigen 125 in metastatic breast cancer. Cancer Control 29, 10732748211053150.
Peng, L., et al., 2020. Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Immunol. Immunother. 69 (9), 1813–1822.
Pu, D., et al., 2021. Inflammation-nutritional markers of peripheral blood could predict survival in advanced non-small-cell lung cancer patients treated with PD-1 inhibitors. Thorac. Cancer 12 (21), 2914–2923.
Wang, Q., et al., 2014a. Prognostic value of carbohydrate tumor markers and inflammation-based markers in metastatic or recurrent gastric cancer. Med Oncol. 31 (12), 289.
Wang, S., et al., 2018b. Prognostic significance of pretreatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with diffuse large B-cell lymphoma. Biomed. Res Int 2018, 9651254.
Wang, X., Jiang, R., Li, K., 2014b. Prognostic significance of pretreatment laboratory parameters in combined small-cell lung cancer. Cell Biochem Biophys. 69 (3), 633–640.
Xie, T., et al., 2021. Prognostic value of modified systemic inflammatory score in patients with newly diagnosed high-grade gliomas. Clin. Neurol. Neurosurg. 201, 106428.
Yang, J., et al., 2017. Pre-treatment inflammatory indexes as predictors of survival and cetuximab efficacy in metastatic colorectal cancer patients with wild-type RAS. Sci. Rep. 7 (1), 17166.
Yu, S.L., et al., 2017. Serum lactate dehydrogenase predicts prognosis and correlates with systemic inflammatory response in patients with advanced pancreatic cancer after gemcitabine-based chemotherapy. Sci. Rep. 7, 45194.
Zhang, Y., et al., 2022. Prognostic nutritional index predicts outcome of PD-L1 negative and MSS advanced cancer treated with PD-1 inhibitors. Biomed. Res Int 2022, 6743126.
Zhang, H., et al., 2015. Clinical significance of preoperative neutrophil-lymphocyte vs platelet-lymphocyte ratio in primary operable patients with non-small cell lung cancer. Am. J. Surg. 210 (3), 526–535.
Zhao, L., et al., 2022. Association of blood biochemical indexes and antibiotic exposure with severe immune-related adverse events in patients with advanced cancers receiving PD-1 Inhibitors. J. Immunother. 45 (4), 210–216.
Zhao, Q., et al., 2021. Three models that predict the efficacy of immunotherapy in Chinese patients with advanced non-small cell lung cancer. Cancer Med 10 (18), 6291–6303.
Zhou, T., et al., 2015a. Ratio of C-reactive protein/albumin is an inflammatory prognostic score for predicting overall survival of patients with small-cell lung cancer. Sci. Rep. 5, 10481.
Zhou, T., et al., 2015b. A systemic inflammation-based prognostic scores (mGPS) predicts overall survival of patients with small-cell lung cancer. Tumour Biol. 36 (1), 337–343.
Drpa, G., et al., 2020. Neutrophil-to-lymphocyte ratio can predict outcome in extensive-stage small cell lung cancer. Radio. Oncol. 54 (4), 437–446.
Olgun, P., Diker, O., 2023. Prognostic value of pretreatment immune inflammation indices in patients with immune-related tumors. Curr. Med Res Opin. 39 (3), 425–431.
Jorgensen, S.F., et al., 2017. Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study. BMC Cancer 17 (1), 809.
Bigot, F., et al., 2017. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: the Gustave Roussy Immune Score (GRIm-Score). Eur. J. Cancer 84, 212–218.
Chasseuil, E., et al., 2018. Blood predictive biomarkers for nivolumab in advanced melanoma. Acta Derm. Venereol. 98 (4), 406–410.
Di Blasi, R., et al., 2022. Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis. Blood 140 (24), 2584–2593.
Atzpodien, J., et al., 2003. Metastatic renal carcinoma comprehensive prognostic system. Br. J. Cancer 88 (3), 348–353.
Boegemann, M., et al., 2017. The role of the neutrophil to lymphocyte ratio for survival outcomes in patients with metastatic castration-resistant prostate cancer treated with abiraterone. Int J. Mol. Sci. 18 (2).
Desch, A., et al., 2017. D-dimers in malignant melanoma: association with prognosis and dynamic variation in disease progress. Int J. Cancer 140 (4), 914–921.
Haas, M., et al., 2013. Prognostic value of CA 19-9, CEA, CRP, LDH and bilirubin levels in locally advanced and metastatic pancreatic cancer: results from a multicenter, pooled analysis of patients receiving palliative chemotherapy. J. Cancer Res Clin. Oncol. 139 (4), 681–689.

Hartrampf, P.E., et al., 2022. Baseline clinical characteristics predict overall survival in patients undergoing radioligand therapy with [(177)Lu]Lu-PSMA I&T during long-term follow-up. Eur. J. Nucl. Med Mol. Imaging 49 (12), 4262–4270.
Heppt, M.V., et al., 2017. Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte antigen-4 inhibition. Eur. J. Cancer 82, 56–65.
Klumper, N., et al., 2022. C reactive protein flare predicts response to checkpoint inhibitor treatment in non-small cell lung cancer. J. Immunother. Cancer 10 (3).
Kripp, M., et al., 2014. Patients with malignant hematological disorders treated on a palliative care unit: prognostic impact of clinical factors. Ann. Hematol. 93 (2), 317–325.
Reinert, C.P., et al., 2020. Clinical and prognostic value of tumor volumetric parameters in melanoma patients undergoing (18)F-FDG-PET/CT: a comparison with serologic markers of tumor burden and inflammation. Cancer Imaging 20 (1), 44.
Bersanelli, M., et al., 2020. Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study. Lung Cancer 150, 123–131.
Buttigliero, C., et al., 2017. Prognostic impact of pretreatment neutrophil-to-lymphocyte ratio in castration-resistant prostate cancer patients treated with first-line docetaxel. Acta Oncol. 56 (4), 555–562.
Capone, M., et al., 2018. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J. Immunother. Cancer 6 (1), 74.
Casamassima, A., et al., 2005. C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy. J. Urol. 173 (1), 52–55.
Cocorocchio, E., et al., 2020. Baseline neutrophil-to-lymphocyte ratio (NLR) is associated with outcome of patients treated with BRAF inhibitors. Clin. Transl. Oncol. 22 (10), 1818–1824.
Del Prete, M., et al., 2015. Prognostic clinical factors in pretreated colorectal cancer patients receiving regorafenib: implications for clinical management. Oncotarget 6 (32), 33982–33992.
Loupakis, F., et al., 2019. A validated prognostic classifier for (V600E)BRAF-mutated metastatic colorectal cancer: the 'BRAF BeCool' study. Eur. J. Cancer 118, 121–130.
Marcheselli, R., et al., 2020. Improving the international prognostic index score using peripheral blood counts: Results of a large multicenter study involving 520 patients with diffuse large B cell lymphoma. Hematol. Oncol. 38 (4), 439–445.
Pisano, C., et al., 2021. Prognostic role of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with metastatic castration resistant prostate cancer treated with abiraterone or enzalutamide. Minerva Urol. Nephrol. 73 (6), 803–814.
Hashimoto, K., et al., 2009. Do recurrent and metastatic pancreatic cancer patients have the same outcomes with gemcitabine treatment? Oncology 77 (3-4), 217–223.
Ishioka, J., et al., 2012. Development of a nomogram incorporating serum C-reactive protein level to predict overall survival of patients with advanced urothelial carcinoma and its evaluation by decision curve analysis. Br. J. Cancer 107 (7), 1031–1036.
Ito, K., et al., 2019. Impact of inflammatory marker levels one month after the first-line targeted therapy initiation on progression-free survival prediction in patients with metastatic clear cell renal cell carcinoma. Jpn. J. Clin. Oncol. 49 (1), 69–76.
Kamba, T., et al., 2014. Improvement of prognosis in patients with metastatic renal cell carcinoma and Memorial Sloan-Kettering Cancer Center intermediate risk features by modern strategy including molecular-targeted therapy in clinical practice. Int J. Clin. Oncol. 19 (3), 505–515.
Kanemasa, Y., et al., 2016. A convenient prognostic score consisting of the Glasgow prognostic score and serum lactate dehydrogenase predicts clinical outcome in patients with diffuse large B-cell lymphoma. Leuk. Lymphoma 57 (10), 2460–2463.
Nakagawa, T., et al., 2013. Prognostic risk stratification of patients with urothelial carcinoma of the bladder with recurrence after radical cystectomy. J. Urol. 189 (4), 1275–1281.
Nakai, Y., et al., 2010. Impact of S-1 in patients with gemcitabine-refractory pancreatic cancer in Japan. Jpn. J. Clin. Oncol. 40 (8), 774–780.
Nakamura, Y., et al., 2016. Nivolumab for advanced melanoma: pretreatment prognostic factors and early outcome markers during therapy. Oncotarget 7 (47), 77404–77415.
Namikawa, T., et al., 2019. Prognostic significance of serum alkaline phosphatase and lactate dehydrogenase levels in patients with unresectable advanced gastric cancer. Gastric Cancer 22 (4), 684–691.
Takada, K., et al., 2020. Clinical significance of preoperative inflammatory markers in non-small cell lung cancer patients: a multicenter retrospective study. PLoS One 15 (11), e0241580.
Takemura, K., et al., 2020. Impact of serum gamma-glutamyltransferase on overall survival in patients with metastatic renal cell carcinoma in the era of targeted therapy. Target Oncol. 15 (3), 347–356.
Tamura, K., et al., 2021. External validation of the albumin, C-reactive protein and lactate dehydrogenase model in patients with metastatic renal cell carcinoma receiving second-line axitinib therapy in a Japanese multi-center cohort. Jpn. J. Clin. Oncol. 51 (5), 810–818.
Tanizaki, J., et al., 2018. Peripheral blood biomarkers associated with clinical outcome in non-small cell lung cancer patients treated with Nivolumab. J. Thorac. Oncol. 13 (1), 97–105.
Tatsugami, K., et al., 2015. Role of cytoreductive nephrectomy for Japanese patients with primary renal cell carcinoma in the cytokine and targeted therapy era. Int J. Urol. 22 (8), 736–740.
Uehara, T., et al., 2021. Serum lactate dehydrogenase is a predictive biomarker in patients with oropharyngeal cancer undergoing radiotherapy: retrospective study on predictive factors. Head. Neck 43 (10), 3132–3141.
Xue, P., et al., 2014. Comparative outcomes between initially unresectable and recurrent cases of advanced pancreatic cancer following palliative chemotherapy. Pancreas 43 (3), 411–416.
Yamada, Y., et al., 2020. Prognostic value of an inflammatory index for patients with metastatic castration-resistant prostate cancer. Prostate 80 (7), 559–569.
Yamazaki, N., et al., 2021. Prospective observational study of the efficacy of nivolumab in Japanese patients with advanced melanoma (CREATIVE study). Jpn. J. Clin. Oncol. 51 (8), 1232–1241.
Kang, M.H., et al., 2014. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br. J. Cancer 111 (3), 452–460.
Suh, S.Y., Ahn, H.Y., 2007. Lactate dehydrogenase as a prognostic factor for survival time of terminally ill cancer patients: a preliminary study. Eur. J. Cancer 43 (6), 1051–1059.
Suh, S.Y., et al., 2010. Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. Support Care Cancer 18 (2), 151–157.
Maas, S.L.N., et al., 2019. Routine blood tests do not predict survival in patients with glioblastoma-multivariable analysis of 497 patients. World Neurosurg. 126, e1081–e1091.
Strijker, M., et al., 2021. Readily available biomarkers predict poor survival in metastatic pancreatic cancer. Biomarkers 26 (4), 325–334.
Aamdal, E., et al., 2022a. Health-related quality of life in patients with advanced melanoma treated with ipilimumab: prognostic implications and changes during treatment. ESMO Open 7 (5), 100588.
Aamdal, E., et al., 2022b. Ipilimumab in a real-world population: a prospective Phase IV trial with long-term follow-up. Int J. Cancer 150 (1), 100–111.
Baicus, C., et al., 2014. Cancer and involuntary weight loss: failure to validate a prediction score. PLoS One 9 (4), e95286.
Teterycz, P., et al., 2018. High baseline neutrophil-to-lymphocyte ratio predicts worse outcome in patients with metastatic BRAF-positive melanoma treated with BRAF and MEK inhibitors. Melanoma Res 28 (5), 435–441.
Ng, I.K., et al., 2021. Development, internal validation and calibration of a risk score to predict survival in patients with EGFR-mutant non-small cell lung cancer. J. Clin. Pathol. 74 (2), 116–122.
Mirili, C., et al., 2019. Clinical significance of prognostic nutritional index (PNI) in malignant melanoma. Int J. Clin. Oncol. 24 (10), 1301–1310.
Giri, S., et al., 2022. Pre-treatment neutrophil to lymphocyte ratio as a biomarker of frailty and predictor of survival among older adults with multiple myeloma. J. Geriatr. Oncol. 13 (4), 486–492.
Peyton, C.C., et al., 2020. The value of neutrophil to lymphocyte ratio in patients undergoing cytoreductive nephrectomy with thrombectomy. Eur. Urol. Focus 6 (1), 104–111.
Sonpavde, G., et al., 2014. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. Clin. Genitourin. Cancer 12 (5), 317–324.
Li, J., et al., 2018. Prognostic nomogram for patients with Nasopharyngeal Carcinoma incorporating hematological biomarkers and clinical characteristics. Int J. Biol. Sci. 14 (5), 549–556.
Nakagawa, T., et al., 2017. Nomogram for predicting survival of postcystectomy recurrent urothelial carcinoma of the bladder. Urol. Oncol. 35 (7).
Artac, M., et al., 2017. Prognostic impact of neutrophil/lymphocyte ratio, platelet count, CRP, and albumin levels in metastatic colorectal cancer patients treated with FOLFIRI-Bevacizumab. J. Gastrointest. Cancer 48 (2), 176–180.
Saito, K., et al., 2009. Impact of C-reactive protein kinetics on survival of patients with metastatic renal cell carcinoma. Eur. Urol. 55 (5), 1145–1153.
Shao, N., Cai, Q., 2015. High pretreatment neutrophil-lymphocyte ratio predicts recurrence and poor prognosis for combined small cell lung cancer. Clin. Transl. Oncol. 17 (10), 772–778.
Fearon, K., et al., 2011. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 12 (5), 489–495.
Abbass, T., et al., 2019. The relationship between imaging-based body composition analysis and the systemic inflammatory response in patients with cancer: a systematic review. Cancers 11 (9).
Abbass, T., et al., 2020a. Comparison of the prognostic value of MUST, ECOG-PS, mGPS and CT derived body composition analysis in patients with advanced lung cancer. Clin. Nutr. ESPEN 40, 349–356.
Abbass, T., et al., 2020b. The relationship between computed tomography derived skeletal muscle index, psoas muscle index and clinical outcomes in patients with operable colorectal cancer. Clin. Nutr. ESPEN 39, 104–113.
Hacker, U.T., et al., 2022. Modified Glasgow prognostic score (mGPS) is correlated with sarcopenia and dominates the prognostic role of baseline body composition parameters in advanced gastric and esophagogastric junction cancer patients undergoing first-line treatment from the phase III EXPAND trial. Ann. Oncol. 33 (7), 685–692.
Maccio, A., et al., 2023. Cancer cachexia and chronic inflammation: an unbreakable bond. Br. J. Cancer 128 (9), 1609–1610.
Merker, M., et al., 2020. Association of baseline inflammation with effectiveness of nutritional support among patients with disease-related malnutrition: a secondary analysis of a randomized clinical trial. JAMA Netw. Open 3 (3), e200663.
Bargetzi, L., et al., 2021. Inflammation reduces the effect of nutritional therapy on clinical outcomes in cancer patients. Ann. Oncol. 32 (11), 1451–1452.
Hansen, C., et al., 2021. Measurement of body composition: agreement between methods of measurement by bioimpedance and computed tomography in patients with non-small cell lung cancer. Clin. Nutr. ESPEN 44, 429–436.
McMillan, D.C., 2013. The systemic inflammation-based glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat. Rev. 39 (5), 534–540.

Proctor, M.J., et al., 2015. Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. PLoS One 10 (3), e0116206.
Proctor, M.J., et al., 2011. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br. J. Cancer 104 (4), 726–734.
Dolan, R.D., et al., 2020. The relationship between ECOG-PS, mGPS, BMI/WL grade and body composition and physical function in patients with advanced cancer. Cancers 12 (5).
Savioli, F., et al., 2022. Prognostic role of preoperative circulating systemic inflammatory response markers in primary breast cancer: meta-analysis. Br. J. Surg.

Joshua Thompson, MBChB. Surgical resident and PhD candidate whose work focuses on the role of lactate dehydrogenase and the systemic inflammatory response in driving cancer related cachexia, both systemically and in the tumour microenvironment.

Josh McGovern, MBChB. Surgical resident and PhD candidate who has published extensively on the role of body composition and systemic inflammation in cancer related cachexia.

Campbell Roxburgh, MBChB, PhD. Professor of Colorectal Surgical Oncology at the University of Glasgow and consultant robotic surgeon. Recipient of numerous awards and grants from bodies such as the Chief Scientific Officer and Cancer Research UK to fund ongoing work into the tumour micro-environment in colorectal cancer.

Joanne Edwards, PhD. Professor of Translational Cancer Pathology at the University of Glasgow. Professor Edward's group focuses on the determinants of long- and short-term outcomes in patients with colorectal cancer. In particular, the relationship between the local and systemic inflammatory responses, tumour microenvironment and cell signalling.

Ross D Dolan, MBChB, PhD. Colorectal surgeon who has published extensively on the prognostic value of the systemic inflammatory response in cancer with an ongoing interest in the IL6/JAK/STAT pathway in cancer.

Donald C McMillan PhD, OBE. As Professor of Surgical Science at the University of Glasgow, work carried out by Professor McMillan and his collaborators has highlighted the importance of the systemic inflammatory response in weight loss, poor physical function, poor quality of life and poor survival in the patient with cancer. This work carried out over a 20-year period has been summarised in a series of published reviews. This has led to the introduction of the modified Glasgow Prognostic Score (mGPS), a tumor stage independent tool for predicting survival in patients with either localised or advanced cancer. The mGPS has been validated worldwide.