Abstract:

Introduction: Cancer remains a leading cause of death worldwide. While a curative intent is the aim of any surgical treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy with a palliative intent. Given their limited life expectancy appropriate allocation of treatment is vital. It is recognised that systemic chemoradiotherapy may shorten the quality/quantity of life in patients with advanced cancer. It is against this background that the present systematic review and meta-analysis of the prognostic value of markers of the systemic inflammatory response in patients with advanced cancer was conducted.

Methods: An extensive literature review using targeted medical subject headings was carried out in the MEDLINE, EMBASE, and CDSR databases until the end of 2016. Titles were examined for relevance and studies relating to duplicate datasets, that were not published in English and that did not have full text availability were excluded. Full texts of relevant articles were obtained and were then examined to identify any further relevant articles.

Results: The majority of studies were retrospective. The systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, was reported to have independent prognostic value, across tumour types and geographical locations. In particular, C-reactive protein (CRP, 63 studies), albumin (33 studies) the Glasgow Prognostic Score (GPS, 44 studies) and the Neutrophil Lymphocyte Ratio (NLR, 59 articles) were consistently validated across tumour types and geographical locations. There was considerable variation in the thresholds reported to have prognostic value when CRP and albumin were examined. There was less variation in the thresholds reported for NLR and still less for the GPS.

Discussion: The systemic inflammatory response, especially as evidenced by the GPS and NLR, has reliable prognostic value in patients with advanced cancer. Further prospective studies of their clinical utility in randomised clinical trials and in treatment allocation are warranted.

Introduction:

Cancer remains one of the leading cause of death worldwide and is responsible for 7.6 million deaths per year. Therefore, while a curative intent is the aim of any surgical treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy with a palliative intent. Given that patients with advanced cancer have a limited life expectancy appropriate treatment selection becomes vital. Indeed, the paradigm of precision medicine (right treatment, right patient, right time) is in the vanguard of oncology treatment, and if applied outcomes for all patients would improve irrespective of new treatment availability.[1]

However, optimal allocation of treatment remains elusive. There is increasing evidence that inappropriate anti-cancer treatment does not improve quality of life or survival[2-5]. A National Clinical Enquiry into Patient Outcome and Death (NCEPOD) reported that chemotherapy hastened or directly caused the death of over 25% of patients who died within 30 days of receiving treatment[4]. This need for caution has been further illustrated by a randomised control trial comparing early palliative and standard oncological care in patients with metastatic non-small cell lung cancer conducted by Temel *et al*[5]. In this randomised trial patients who received palliative care early not only maintained better quality of life scores but also had a significantly longer median survival[5]. These reports provide a persuasive argument for optimising the stratification of anti-cancer therapy in patients with advanced cancer. Therefore, it is important to examine the criteria that may be used to effectively stratify patients as to their likely survival prior to the allocation of treatment in patients with advanced cancer.

In the setting of patients with advanced cancer, Tumour, Node, Metastasis (TNM) staging has little discriminatory prognostic value and other patient related measures such as weight loss, performance status and quality of life have superior prognostic value. Therefore, the decision to

proceed with systemic therapy is frequently based on these parameters by an oncologist and primarily on the basis of subjective clinical observation. More recently, measurement of skeletal muscle mass made from CT scans has been proposed to be useful in this context[6]. Nevertheless, it is clear that the potential for sub-optimal allocation of anti-cancer therapy is considerable.

Recently, in a systematic review of prognostic tools in patients with advanced cancer, it was reported that a number of prognostic tools had been validated in different centres[7]. It was striking that the majority of these validated tools were based on subjective criteria, in particular the assessment of physical function. Only one validated prognostic tool the GPS (Glasgow Prognostic Score), assessing the magnitude of the systemic inflammatory response, was based exclusively on objective criteria. Indeed, there is now strong evidence that the chronic systemic inflammatory response results in classical features of cancer cachexia, including the preferential loss of lean muscle mass[8-10]. Indeed, studies have shown a direct relationship between systemic inflammation measured by the GPS and NLR (Neutrophil Lymphocyte Ratio) and elevation of inflammatory cytokines, adipokines and other biochemical disturbances associated with loss of lean muscle mass and reduced performance status[8;11-14]. Recently, Laird and co-workers showed that in a large cohort study in two international bio banks, the combination of performance status and the systemic inflammatory response (SIR) as measured by the mGPS (modified Glasgow Prognostic Score) improved the prediction of outcomes of patients with advanced cancer[15]. Furthermore, they showed that quality of life was independently associated with both performance and the GPS[16].

Therefore, from the above and with the introduction of immunotherapeutic agents for advanced inoperable cancer it is timely to review the role of the markers of systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer.

Methods:

The present systematic review and meta-analysis of published literature was undertaken according to a pre-defined protocol described in the PRISMA-P statement. The primary outcome was to assess the prognostic value of the SIR in patients with advanced inoperable cancer treated with chemotherapy, immunotherapy, radiotherapy, best supportive care or a combination of these treatment strategies.

This was carried out by a wide-ranging literature search to identify studies. Medical subject heading (MeSH) terms (Advanced Cancer, CRP, C-Reactive Protein, Albumin, White Cell Count, Neutrophil Count, Lymphocyte Count, Monocyte Count, Platelet Count, Red Blood Cell Count), were used in the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE) and the Cochrane Database of Systematic Reviews (CDSR) to identify articles.

On completion of the online search, the title and abstract of each identified study was examined for relevance. Studies relating to duplicate datasets, studies not available in English and those published in abstract form only were excluded. Full texts were obtained for all studies deemed potentially relevant. Once further exclusions outlined below were carried out the bibliographies of all included articles were subsequently hand searched to identify any additional studies.

Only articles that reported survival analysis and gave hazard ratios or odds ratios with associated confidence intervals were included in the review. Studies with patients who had failed resections and patients who underwent palliative symptom control procedures were also included.

Statistics

The HRs and 95 % CIs were directly retrieved from the article. If several estimates were reported for the same marker, the multivariate estimate was used in preference to the univariate analysis.

Interstudy heterogeneity among included studies was evaluated by I^2 statistics using the random-effects (DerSimonian – Laird method) model. All P values were 2-sided and $P < 0.05$ were considered statistical significant. Evidence of publication bias was evaluated using visual inspection of funnel plots. All analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Study selection process

Initial search strategy identified 9546 articles whose titles and abstracts were reviewed (Figure 1). Articles were excluded if initial curative surgery formed part of the treatment regimen (n=3114), where survival was not the primary outcome measure (n=1225), full articles were not available (n=1195), articles examining response to bacterial and viral infection (n=924), articles not carried out in humans (n=2021), articles not published in English (n=219), and those that were a systematic review/meta-analysis (n=149).

This led to a review of the full text of 699 articles. Further articles were excluded if surgery was part of the treatment regimen being examined (n=421), progression free survival (PFS) was the only outcome measured (n=62) and if survival was not expressed as HR (95%CI; n=47). The remaining 169 articles, had their bibliographies reviewed in a systematic manner and this identified a further 29 articles to be included in the final analysis leading to a final total of 198 articles.

Figure 1:

Studies of the prognostic value of C-reactive protein (CRP) in patients with advanced cancer:

Sixty-three articles with both overall survival (OS) and/or cancer specific survival (CSS) as their primary outcome measures were identified comprising data on 13,498 patients (8,466 deaths) (Supplementary Table). Fifty-four studies were carried out in a retrospective manner while eight were prospective with one study having both prospective and retrospective arms (Supplementary Table). Fifty-four studies used multivariate and nine used univariate survival analysis (Supplementary Table). On meta-analysis of the 55 retrospective studies including 11,761 patients (7,316 deaths) there was a significant association between elevated CRP and survival (HR: 1.97 95%CI 1.76-2.21, $p<0.00001$) with a considerable degree of heterogeneity ($I^2=92\%$). On meta-

analysis of the 9 prospective studies including 1,598 patients (1,009 deaths) there was a significant association between elevated CRP and survival (HR: 1.72 95%CI 1.31-2.26, p<0.00001) with a considerable degree of heterogeneity (I^2=88%).

Fifty-six studies examined the relationship with overall survival including 11,787 patients (7,477 deaths), as the primary outcome measure. On meta-analysis, there was a significant association between CRP and overall survival (HR 1.47 95%CI 1.40-1.54, p<0.00001) with a considerable degree of heterogeneity (I^2=90%, Figure 2). There was variation in the threshold of CRP used in the studies, the most common being >10 mg/L (n=19) followed by >5 mg/L (n=5). Other thresholds (n=32) were used in <5 studies and therefore meta-analysis was not carried out.

On meta-analysis those studies with a threshold of >10mg/L (n=19), including 3,883 patients (3,458 deaths), there was a significant association between CRP and overall survival (HR: 1.73 95%CI 1.55-1.93, p<0.00001) with a moderate degree of heterogeneity (I^2 = 35%). These included studies on cancer of the pancreas (n=6), lung (n=5), lymphoma (n=2), HCC (n=1), osteosarcoma (n=1), prostate (n=1), oesophagus (n=1), multiple cancers (n=1) and renal cells (n=1).

On meta-analysis of those studies with a threshold of >10mg/L and pancreatic cancer (n=6) 1,510 patients (1,446 deaths) there was a significant association between CRP and overall survival (HR: 1.64 95%CI 1.28-2.10, p<0.0001) with substantial heterogeneity (I^2=73%). In these six studies, there was a variation in their geographical locations including Japan (n=2), Korea (n=2), Germany (n=1) and Australia (n=1). The proportion of patients who had a CRP level >10mg/L with pancreatic cancer was 90% in Japan, 65% in Korea, 63% in Australia and 19% in Germany.

On meta-analysis of those studies with a threshold of >10mg/L and lung cancer (n=5) including 996 patients (960 deaths) there was a significant association between CRP and overall survival (HR: 1.58 95%CI 1.37-1.84, p<0.00001) with no heterogeneity (I^2=0%). In these 5 studies, there was a wide variation in their geographical locations including the Czech Rep (n=1), UK (n=1), Sweden (n=1), China (n=1) and Japan (n=1). The proportion of patients who had a CRP level >10mg/L and lung cancer was 98% in the Czech Rep, 80% in the UK, 71% in Sweden, 43% in China and 33% in

Japan. Remaining cancer types and geographical locations had <5 studies therefore further meta-analysis was not carried out.

On meta-analysis those studies with a threshold of >5mg/L (n=5), including 961 patients (515 deaths), there was a significant association between CRP and overall survival (HR: 1.66 95%CI 1.15-2.38, p=0.007) with a substantial degree of heterogeneity (I^2 = 83%). These included studies on cancer of the pancreas (n=2), prostate (n=1), renal cells (n=1) and colorectal (n=1). These included studies carried out in Japan (n=3), Belgium (n=1) and Sweden (n=1). The proportion of patients who had a CRP>5mg/L was 100% in Sweden, 66% in Belgium and 50% in Japan. Remaining cancer types and geographical locations had <5 studies therefore further meta-analysis was not carried out.

Ten studies examined the relationship with cancer specific survival including 1711 patients (989 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between CRP and cancer specific survival (HR 2.93 95%CI 2.14-4.01, p<0.00001) with a substantial degree of heterogeneity (I^2=66%). The most common thresholds used on the CSS group were >10 mg/L (n=4) including cancer of the prostate (n=1), breast (n=1), renal cells (n=1) and urothelial (n=1). All thresholds had <5 studies and therefore meta-analysis was not carried out. In the >10mg/L group studies were carried out in the UK (n=3) and Italy (n=1). The proportion of patients who had a CRP level >10mg/L was 64% in the UK and 50% in Italy.

Studies of the prognostic value of albumin (Alb) in patients with advanced cancer:

Thirty-three articles with both OS (n=29) and/or CSS (n=5) as their primary outcome measures were identified comprising data on 10,288 patients (8,740 deaths) (Supplementary Table). Twenty-eight studies were conducted in a retrospective manner while five were prospective. Twenty-nine articles used multivariate and four univariate survival analysis (Supplementary Table).

Thirty-one studies examined the relationship with overall survival including 9,753 patients (8,493 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between low albumin and overall survival (HR 1.77 95%CI 1.54-2.03, p<0.00001) with a considerable degree of heterogeneity (I^2=84%, Figure 3). There was variation in the threshold of albumin examined. The most common thresholds examined were <35g/L (n=13) and <30 mg/L (n=5). Other thresholds were used in <5 studies (n=15) and therefore meta-analysis was not carried out.

On meta-analysis those studies with a threshold of <35g/L (n=13), including 2,127 patients (1,831 deaths), there was a significant association between low albumin and overall survival (HR: 2.21 95%CI 1.60-3.06, p<0.00001) with a considerable degree of heterogeneity (I^2 = 79%). These included studies on cancer of the pancreas (n=5), biliary tract (n=2), multi anatomical sites (n=1), breast (n=1), lung (n=1), HCC (n=1), colorectal (n=1) and multiple myeloma (n=1) These included studies carried out in Korea (n=6), Japan (n=3), Singapore (n=1), Canada (n=1), Belgium (n=1), France (n=1), Spain (n=1), Australia (n=1), and the UK (n=1). The proportion of patients who had an albumin <35g/L was 51% in Korea, 49% in Spain, 31% in Belgium, 26% in the UK and 16% in France.

On meta-analysis of those studies with a threshold of <35g/L and pancreatic cancer (n=5) 910 patients (834 deaths) there was a significant association between reduced albumin and overall survival (HR: 1.96 95%CI 1.04-3.69, p=0.04) with substantial heterogeneity (I^2=85%). In these five studies, there was a variation in their geographical locations including Korea (n=2), Japan (n=1), Australia (n=1) and Belgium (n=1). The proportion of patients who had an albumin level <35g/L with pancreatic cancer was 31% in Belgium and 42% in Australia.

On meta-analysis of those studies with a threshold of <30g/L (n=5), including 1,319 patients (1,192 deaths), there was a significant association between low albumin and overall survival (HR: 1.57 95%CI 1.26-1.95, p<0.0001) with a minimal degree of heterogeneity (I^2 =14%). These included studies on cancer of the lung (n=2), gastric (n=1), renal cells (n=1), and multiple

anatomical sites (n=1). These included studies carried out in the US (n=1), Taiwan (n=1), Japan (n=1), Turkey (n=1) and Sweden (n=1). The proportion of patients who had an albumin <30g/L was 49% on Taiwan, 39% in the Japan, 20% in Turkey and 17% in Sweden.

Studies of the prognostic value of white cell count (WCC) in patients with advanced cancer:

Four articles with both OS (n=3) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 1,593 patients (1,440 deaths) (Supplementary Table). All four were retrospective multivariate survival studies carried out in cancer of the lung (n=2), renal cells (n=1) and multiple anatomical sites (n=1). There was variation in the level of WCC used between different papers including $>10x10^9$/L (n=2), $>10.2x10^9$/L for males and $>10.6x10^9$ /L for females (n=1), and $>11 \times 10^9$ /L for both sexes (n=1). Geographically studies were carried out in the UK (n=2), US (n=1) and Italy (n=1). The proportion of patients who had an elevated WCC was 24% in the US, 28% in the UK and 28% in Italy. Due to the small number of studies, meta-analysis was not carried out.

Studies of the prognostic value of neutrophils in patients with advanced cancer:

Nine articles with both OS (n=7) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 2,870 patients (2,266 deaths) (Supplementary Table). Seven studies were conducted in a retrospective manner while two were prospective. (Supplementary Table). Five articles reported significance on multivariate and two articles reported significance on univariate survival analysis. There was variation in the levels of neutrophils used in individual papers including neutrophil count ≥ upper limit of normal (ULN) without defining it explicitly (n=3), neutrophil count $>7.5x10^9$ cells/ml (n=1), neutrophil count $>3.41x10^9$ cells/ml (n=1),

absolute neutrophil count (ANL) >4.7 x 10^9 L (n=1), ANC≥7500 (n=1), log of readings above normal which was defined as >7x10^9/L (n=1) and >8x10^9/L (n=1), .

Seven studies examined the relationship with overall survival including 2,364 patients (1,999 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between elevated neutrophils and overall survival (HR 1.89 95%CI 1.25-2.85, p=0.002) with a considerable degree of heterogeneity (I^2=87%). Studies were in melanoma (n=2), renal (n=1), lung (n=1), breast (n=1), mesothelioma (n=1) and lung (n=1) cancer. Geographically studies were carried out in France (n=2) and Italy (n=2), USA (n=1), China (n=1) and Australia (n=1). The proportion of patients who had elevated Neutrophils was 32% in Australia, 28% in France, 19% in the USA and 12% in Italy.

Two studies examined the relationship with cancer specific survival including 506 patients (267 deaths), as its primary outcome measure. Due to the small number of studies, meta-analysis was not carried out.

Studies of the prognostic value of lymphocytes in patients with advanced cancer:

Eleven articles with OS as their primary outcome measures were identified comprising data on 2,517 patients (2,148 deaths) (Supplementary Table). Ten studies were conducted in a retrospective manner and one prospectively. Nine studies reported significance on multivariate survival analysis and two on univariate survival analysis. (Supplementary Table). On meta-analysis, there was a significant association between lower lymphocyte levels and overall survival (HR 1.68 95%CI 1.35-2.09, p<0.00001) with a substantial degree of heterogeneity (I^2=68%).

There was considerable variation in the lymphocyte thresholds used in each study including continuous readings (n=1), <0.5x10^9/L (n=1), <0.7x10^9/L (n=1), >2x10^9/L (n=2) , <1x$10^{9/}$L (n=2), ≥0.45x10^9/L (n=1), <2.25x10^9/L (n=1), <1.4x1x$10^{9/}$L (n=1), and 2.70x10^9/L (n=1). These included

studies on cancer of the pancreas (n=3), lymphoma (n=1), lung (n=1), nasopharyngeal (n=1), mesothelioma (n=1), colorectal (n=1), cervical (n=1), melanoma (n=1) and multiple cancer types (n=1). Geographically studies were carried out in China (n=3), US (n=3), France (n=2), Japan (n=2) and Korea (n=1), The proportion of patients who had low lymphocytes was 75% in Korea, 48% in US, 47% in China, 45% in Japan and 32% in France. All eleven studies used chemotherapy as the treatment modality. No specific lymphocyte thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of monocytes in patients with advanced cancer:

Five articles with OS as their primary outcome measures were identified comprising data on 1,367 patients (1,152 deaths) (Supplementary Table). All five studies were conducted in a retrospective multivariate manner, used chemotherapy as the treatment regime of choice and conducted their analysis in a multivariate manner. On meta-analysis of there was a significant association between elevated monocytes and survival (HR: 1.40 95%CI 1.05-1.87, p=0.02) with a substantial degree of heterogeneity (I^2=66%). There was considerable variation in the levels of monocytes used including >0.8x10^9/L (n=1), ≥0.64x10^9/L (n=1), ≥0.45x10^9/L (n=1), ≥0.35x10^9/L (n=1) and ≥0.55x10^9/L (n=1). There was also variation in the types of cancer examined including lung (n=2), lymphoma (n=1), nasopharyngeal (n=1) and colorectal metastasis (n=1). In terms of geographical locations, the studies were carried out in China (n=3), Korea (n=1) and Italy (n=1). The proportion of patients who had high monocytes was 57% in China, 50% in Korea, and 23% in Italy. No specific monocyte thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of platelets in patients with advanced cancer:

Eight articles with both OS (n=7) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 4,850 patients (2,422 deaths) (Supplementary Table). Seven studies were conducted in a retrospective manner while one was prospective (Supplementary Table). All eight articles reported multivariate survival analysis.

Seven studies examined the relationship with overall survival including 4,653 patients (2,293 deaths), as its primary outcome measure. On meta-analysis of there was a significant association between elevated platelets and survival (HR: 1.47 95%CI 1.12-1.93, p=0.006) with a considerable degree of heterogeneity (I^2=92%). There was variation in the thresholds of platelets examined including a platelet count >300 × 10^9 /L (n=1), >360 x 109 /L (n=1), <130 g/L (n=1), >350 × 10^9 /L (n=1), >450 × 10^9 /L (n=1), ≥ULN (n=1) and continuous readings (n=1). There was also variation in the type of cancers being examined including lung (n=1), oropharyngeal (n=1), pleural mesothelioma (n=1), nasopharyngeal (n=1), pancreatic (n=1), renal (n=1) and multiple cancers (n=1). Geographically studies were carried out in US (n=3), China (n=2), France (n=1) and Sweden (n=1). The proportion of patients who had elevated platelet counts was 30% in Sweden, 24% in the US, 15% in China and 11% in France. However, no specific platelet thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of the Glasgow Prognostic Score (GPS/mGPS) in patients with advanced cancer:

Forty-four articles with both OS (n=37) and/or CSS (n=9) as their primary outcome measures were identified comprising data on 12,578 patients (10,745 deaths) (Supplementary Table). Thirty-two studies were conducted in a retrospective manner while twelve were prospective

(Supplementary Table). Forty studies reported multivariate and four reported univariate survival analysis (Supplementary Table). On meta-analysis of the 32 retrospective studies including 9,472 patients (7,936 deaths) there was a significant association between elevated GPS/mGPS and survival (HR: 1.93 95%CI 1.76-2.13, p<0.00001) with a moderate degree of heterogeneity (I^2=42%). On meta-analysis of the 12 prospective studies including 3,244 patients (2,809 deaths) there was a significant association between elevated GPS/mGPS and survival (HR: 2.09 95%CI 1.69-2.57, p=0.0001) with a substantial degree of heterogeneity (I^2=69%).

Thirty-six studies examined the relationship with overall survival including 11,441 patients (10,022 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between GPS and overall survival (HR 2.06 95%CI 1.86-2.28, p<0.00001) with a substantial degree of heterogeneity (I^2=56%, Figure 4). These included studies on cancer of multiple anatomical sites (n=7), gastric (n=7), lung (n=5), pancreas (n=5), colon (n=3), lymphoma (n=1), biliary tract (n=1), bladder (n=1), haematological (n=1), prostate (n=1), renal cell (n=1), oesophagus (n=1), HCC (n=1) and cervix (n=1).

On meta-analysis those studies carried out in multiple anatomical sites (n=7), including 5,804 patients (5,139 deaths), there was a significant association between elevated GPS/mGPS and overall survival (HR: 2.22 95%CI 1.81-2.71, p<0.00001) with a moderate degree of heterogeneity (I^2 = 65%). These included studies carried out in the UK (n=2), Australia (n=2), Japan (n=1), Norway (n=1) and Brazil (n=1). The proportion of patients who had an elevated GPS was 93% in Japan, 77% in the UK, 69% in Norway, 46% in Australia and 20% in Brazil.

On meta-analysis those studies carried out in gastric cancer (n=7), including 1,283 patients (5139 deaths), there was a significant association between elevated GPS/mGPS and overall survival (HR: 2.08 95%CI 1.58-2.74, p<0.00001) with a moderate degree of heterogeneity (I^2 = 40%). These included studies carried out in the Japan (n=2), Korea (n=2), Taiwan (n=1), UK (n=1) and Czech

Rep (n=1). The proportion of patients who had an elevated GPS was 74% in Taiwan, 73% in the UK, 52% in the Czech Rep, 49% in Japan and 42% in Korea.

On meta-analysis those studies carried out in lung cancer (n=5), including 1,104 patients (708 deaths), there was a significant association between elevated GPS and overall survival (HR: 2.05 95%CI 1.52-2.77, p<0.00001) with a substantial degree of heterogeneity (I^2 = 55%). These included studies carried out in the UK (n=2), China (n=2) and Greece (n=1). The proportion of patients who had an elevated GPS was 76% in the UK, 33% in China and 29% in Greece.

On meta-analysis those studies carried out in pancreatic cancer (n=5), including 735 patients (719 deaths), there was a significant association between elevated GPS and overall survival (HR: 1.91 95%CI 1.29-2.83, p=0.001) with a substantial degree of heterogeneity (I^2 = 70%). These included studies carried out in the Japan (n=3), Australia (n=1) and the UK (n=1). The proportion of patients who had an elevated GPS was 70% in the UK, 63% in Australia and 36% in Japan.

Nine studies examined cancer specific survival including 1,137 patients (723 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between elevated GPS and cancer specific survival (HR 1.69 95%CI 1.48-1.92, p<0.00001) with a minimal degree of heterogeneity (I^2=4%). These included studies on cancer of the colon (n=3), lung (n=2), gastro-oesophageal (n=2), breast (n=1) and renal cells (n=1). These included studies carried out in the UK (n=5), Japan (n=2) and China (n=2). The proportion of patients who had an elevated GPS was 77% in China, 65% in the UK and 43% in Japan. However, since no cancer type or country had more than four studies further meta-analysis was not carried out.

Studies of the prognostic value of neutrophil lymphocyte ratio (NLR) in patients with advanced cancer:

Fifty-nine articles with both OS (n=58) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 16,921 patients (12,801 deaths) (Supplementary Table). Forty-three of these were conducted in a retrospective manner while sixteen were prospective. Fifty-five studies reported multivariate and four reported univariate survival analysis (Supplementary Table). On meta-analysis of the 43 retrospective studies including 10,870 patients (8,044 deaths) there was a significant association between elevated NLR and survival (HR: 1.78 95%CI 1.59-1.98, p<0.00001) with a considerable degree of heterogeneity (I^2=77%). On meta-analysis of the 16 prospective studies including 5,898 patients (4,733 deaths) there was a significant association between elevated NLR and survival (HR: 1.63 95%CI 1.41-1.88, p<0.00001) with a substantial degree of heterogeneity (I^2=67%).

Fifty-eight studies examined the relationship with overall survival including 16,405 patients (12,675 deaths) as its primary outcome measure. On meta-analysis, there was a significant association between NLR and overall survival (HR 1.71 95%CI 1.57-1.86, p<0.00001) with a substantial degree of heterogeneity (I^2=79%, Fig 5). The most common NLR thresholds used were ≥5 (n=19), ≥4 (n=5) and ≥3 (n=12). Other thresholds were used in <5 studies and therefore meta-analysis was not carried out (n=23).

On meta-analysis those studies with a threshold of ≥5 (n=19), including 5,506 patients (4,613 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.64 95%CI 1.42-1.89, p<0.00001) with a substantial degree of heterogeneity (I^2 = 57%). These included cancer of the pancreas (n=5), lung (n=4), colorectal (n=3), multiple anatomical sites (n=2), mesothelioma (n=1), prostate (n=2), cholangiocarcinoma (n=1) and HCC (n=1).

On meta-analysis of those studies with a threshold of ≥5 and pancreatic cancer (n=5) 1009 patients (942 deaths) there was a significant association between an NLR≥5 and overall survival (HR: 1.78 95%CI 1.30-2.44, p=0.0003) with substantial heterogeneity (I^2=56%). In these five

studies, there was a variation in their geographical locations including Japan (n=2), Australia (n=1), Korea (n=1) and China (n=1). The proportion of patients who had an NLR≥5 with pancreatic cancer 48% in Australia, 29% in Korea, and 20% in Japan. No country had more than 4 studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥4 (n=5), including 834 patients (588 deaths), there was a significant association between elevated NLR and overall survival (HR: 2.08 95%CI 1.45-3.00, p<0.0001) with a substantial degree of heterogeneity (I^2 = 57%). These included cancer of the lung (n=1), colorectal (n=1), B-cell lymphoma (n=1), T-cell lymphoma (n=1) and gastric (n=1). In these five studies, there was a variation in their geographical locations including Japan (n=2), UK (n=1), Peru (n=1) and Austria (n=1). The proportion of patients who had an NLR≥4 was 40% in Japan, 35% in Peru, 32% in the UK and 19% in Austria.

On meta-analysis those studies with a threshold of ≥3 (n=12), including 4,195 patients (3,130 deaths), there was a significant association between elevated NLR and overall survival (HR: 1.75 95%CI 1.53-2.01, p<0.00001) with a substantial degree of heterogeneity (I^2=56%). These included cancer of the renal cells (n=3), prostate (n=3), gastric (n=3), melanoma (n=1), colorectal (n=1) and multiple anatomical sites (n=1). These included studies carried out in the Korea (n=2), US/Israel (n=2), China (n=2), Italy (n=2), Australia (n=1), Canada (n=1), Taiwan (n=1) and the UK (n=1). The proportion of patients who had an NLR≥3 was 71% in the US/Israel, 53% in Korea, 52% in Australia, 51% in Taiwan, 47% in the UK, 42% in China and 30% in Italy. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of lymphocyte monocyte ratio (LMR) in patients with advanced cancer:

Eleven articles with both OS (n=11) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 5,043 patients (3,842 deaths) (Supplementary Table). All 11 studies were retrospective and multivariate analysis was carried out. On meta-analysis, there was a significant association between a low LMR and overall survival (HR 1.84 95%CI 1.64-2.07, p<0.00001) with minimal heterogeneity (I^2=8%, Figure 6). There was a variety of LMR thresholds used in each study including ≤2.6 (n=1), <2.8 (n=1), ≥2.475 (n=1), <2.11 (n=1), >5.22 (n=1), ≤4.56 (n=1), ≤5.07 (n=1), ≤3.4 (n=1), ≤2.11 (n=1), ≤3.11 (n=1) and low LMR but no figures given (n=1). These included studies on lung cancer (n=2), lymphoma (n=2), nasopharyngeal cancer (n=3) Hodgkin's lymphoma (n=2), and colorectal (n=2). Geographically the studies were carried out in China (n=5), Korea (n=3), Taiwan (n=1), Hungary (n=1) and Italy (n=1). The proportion of patients who had low LMRs was 53% in Italy, 52% in Korea 45% in China and 41% in Taiwan. No specific LMR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of platelet lymphocyte ratio (PLR) in patients with advanced cancer:

Twelve articles with both OS (n=12) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 5,733 patients (2,611 deaths) (Supplementary Table). Ten studies were conducted in a retrospective manner and two prospectively. Eleven studies were also conducted in a multivariate and one in a univariate manner (Supplementary Table). On meta-analysis, there was a significant association between an elevated PLR on overall survival (HR 1.49 95%CI 2.10-1.84, p=0.0003) with considerable heterogeneity (I^2=82%, Figure 7). There was a variety of PLR thresholds used in each study including >111.23 (n=1), ≥190 (n=1), >153.44 (n=1), >322 (n=1), >146 (n=1), >200 (n=1), ≥152.6 (n=1), ≥250 (n=1), >119.50 (n=1), ≥150 (n=1), >162 (n=1) and one study which simply stated elevated PLR without given a numerical value. These included studies on cancer of the lung (n=5), nasopharynx (n=1), cervix (n=1), prostate (n=1), pancreas (n=2), colorectal (n=1) and liver (n=1). Geographically studies were located in China (n=6), Japan (n=2), Turkey (n=1), Austria (n=1), Australia (n=1) and the US (n=1). The proportion

of patients who had an elevated PLR was 61% in Australia, 59% in Japan, 50% in Turkey, 31% in China, 29% in Austria and 20% in the US. No specific PLR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of other markers/scores of the systemic inflammatory response in patients with advanced cancer:

During the course of this review several studies (n=6) were identified which could not be assigned to one of the above groupings (Supplementary Table). Two studies focused on the CRP/Albumin ratio (CAR). The first such study was by Zhou et al[17] from China. In this multivariate survival analysis on patients with small cell lung cancer a CRP/Alb ratio ≥0.441 was shown to be related to a statistically significant worse OS (HR: 1.34 95%CI 1.04-1.73 p=0.025). The second such study by Yamashita et al[18] from Japan. In this multivariate survival analysis on patients with prostate cancer a CRP/Alb ratio ≥7 was shown to be related to a statistically non-significant worse overall survival (HR: 2.34 95%CI 0.91-6.05 p=0.08).

Two further studies focused on the relationship between globulin, albumin and survival. Shibutani et al[19] in Japan reported that the albumin/globulin ratio predicted overall survival (HR: 2.247, 95%CI 1.069-4.722, p=0.033) independent of the NLR. Yao et al[20] in China reported that in patients with advanced NSCLC, the globulin/albumin ratio (GAR) >0.58 and an Alb<35g/L was associated with poorer OS (GAR HR 1.65, 95%CI 1.20-2.26, p=0.002, Alb HR 1.92, 95%CI ,1.10-3.36, p=0.022). Chan et al[21] in China reported that, in patients with HCC, the albumin-to-alkaline phosphatase ratio (AAPR) >0.68 predicted poorer OS (HR 2.185, 95%CI, 1.780-2.683, p<0.001).

Finally, Zhou et al[17] in China reported that, in patients with SCLC, the CRP/Globulin ratio ≥1.29 predicted poorer OS in both the testing (HR 1.35, 95%CI, 1.61-1.81, p=0.046) and validated (HR 1.43, 95%CI, 1.052-1.95, p=0.022) cohorts. Due to the small number of these studies meta-analysis was not carried out.

Discussion

The results of the present systematic review and meta-analysis show clearly that the systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, have independent prognostic value, across tumour types and geographical locations, in patients with advanced cancer. In particular, C-reactive protein, albumin and neutrophil count and the scores derived from them (GPS and NLR) have been consistently validated worldwide. There was considerable variation in the thresholds reported to have prognostic value when CRP, albumin and neutrophil counts were examined. There was less variation in the thresholds reported for NLR and still less for the GPS. The majority of studies were retrospective and therefore further prospective studies are warranted. In particular, there is a need to determine their clinical utility in the context of randomised clinical trials and thereby inform the appropriate treatment selection for patients with advanced cancer.

In the present review, the majority of studies reported overall survival as the end-point. However, for some markers of the systemic inflammatory response such as C-reactive protein and GPS there were also multiple studies using cancer specific survival as an end-point. It was of interest therefore that, on meta-analysis, the degree of heterogeneity appeared to be greater for overall survival as an endpoint compared with cancer specific survival (C-reactive protein 90% vs. 66% and GPS 56% vs. 4% respectively). This observation may be explained by previous observations that markers of the systemic inflammatory response have a stronger relationship with the cancer survival compared with the overall survival[22;23]. Therefore, it would appear that the optimal prognostic utility of markers of the systemic inflammatory response such as C-reactive protein and the GPS is in the prediction of cancer specific survival.

With reference to overall survival as an end-point, heterogeneity was greater in studies with a variety of thresholds compared to those with a standard threshold (e.g. C-reactive protein 90% (all) vs. 35% (>10mg/l), albumin 84% (all) vs. 79% (<35g/l) and NLR 79% (all) vs. 57% ($\geq$5)

respectively). In studies with these specific thresholds (e.g. in C-reactive protein threshold >10mg/l), compared with all tumour types, heterogeneity was less in specific tumour types (e.g. lung cancer heterogeneity was lower, 0% vs. 35% for all). Therefore, it would appear that the threshold used and the specific cancer studied influence the consistency of the association between markers of the systemic inflammatory response and overall survival in patients with advanced cancer. This has implications for the routine clinical application of markers such as C-reactive protein and NLR where a number of different thresholds have been reported in the literature. However, the GPS/mGPS have internationally recognised thresholds and are the preferred measure of the systemic inflammatory response amongst those investigators active in the field[24] and therefore are likely to have reproducible clinical utility in the context of randomized trials in patients with advanced cancer.

In the present review it was of interest that, across different markers of the systemic inflammatory response, when comparing using the same threshold and tumour type, the geographical prevalence of an elevated systemic inflammatory response varied. In particular, there was a trend towards a greater proportion of patients who had elevated markers in Western countries compared with Eastern Asian countries. Given the objective nature of these measurements there may be genetic or environmental causes of such a consistent difference. Indeed, there are well known ethnic differences in the normal range of neutrophils and lymphocytes[25-27]. Azab and co-workers recently reported that in a review of >9,000 patients, there were ethnic differences in NLR ratios in the United States[27]. Overall, the mean NLR was 2.15, whereas black Americans had a mean NLR of 1.76, Hispanic Americans had a mean NLR of 2.08 and white Americans had a mean NLR of 2.24[27]. Also, within ethnicities, patients who had diabetes, cardiovascular disease, a high BMI and were smokers had a significantly higher NLR[27]. Given that the most common thresholds used for NLR were >5 and >3 it is likely that a combination of genetic and environmental factors are responsible for such consistent East/West differences. To date, similar data for the GPS/mGPS has not appeared in the literature. Therefore, differences in the magnitude of systemic

inflammatory responses may explain, in part, the East/West split often observed in overall survival independent of tumour stage alone. Irrespective, the present results point to the value of not only staging the tumour but also the host systemic inflammatory response[28] in patients with advanced disease.

The systemic inflammatory response in patients with advanced cancer can be thought of as a result of a chronic inflammatory cascade. From the initial innate immune activation, as a result of the invasive tumour, due to the interaction of neutrophils and platelets at the site of tissue injury[29], to the chronic wounding of tissues around the body in metastatic disease. This chronic activation of inflammatory processes results in profound changes at the genomic, intracellular, cellular and systemic levels in the patient with cancer[9]. In particular, at the systemic level, markers of a systemic inflammatory response are associated with a progressive nutritional and functional decline[8] and a profound deterioration in quality of life[16].

A key pathway connecting the genomic, intracellular, cellular and systemic levels is the IL-6/JAK/STAT pathway[30]. Indeed, it is now increasingly recognised that genomic changes result in the chronic activation of the JAK/STAT pathway in the tumour and its microenvironment resulting in unregulated IL-6 production that produces an unregulated inflammatory cascade at cellular and systemic levels (increased C-reactive protein, neutrophil and platelet counts and decreased albumin). At the cellular and systemic level, IL-6 would appear to be the ideal marker of chronic systemic inflammation activation. Indeed, IL-6 in the circulation reflects the magnitude of tissue injury following surgery.[31] However, the strong correlation of IL-6 and C-reactive protein, the relative expense of IL-6 measurement has resulted in IL-6 not being routinely measured despite its central position in the systemic inflammatory cascade. Indeed, in the use of anti-IL-6 treatments, inhibition of the production and the fall in circulating concentrations of C-reactive protein is often used as a surrogate for IL-6 activity. Finally, that IL-6 is produced in most tissues including the tumour means that compared with C-reactive protein and albumin (produced in the liver only) and

neutrophils and platelets (myeloid tissue only), its use as a marker of the systemic inflammatory responses is perhaps suboptimal.

While little work has focused on the use of SIR monitoring to track treatment response in the setting of advanced disease this is not the case in the neoadjuvant and adjuvant settings[32-34]. Carruthers *et al* (2012) showed a direct relationship between an NLR ≥ 5 and decreased time to local recurrence (HR 3.8 95%CI 1.3–11.2 p=0.014) in patients with locally advanced rectal cancers receiving chemoradiotherapy[33]. Dreyer *et al* (2016) showed that an elevated mGPS was associated with a poorer pathological response (p=0.022) in patients treated with neoadjuvant chemoradiotherapy[34], while Crozier *et al* (2006) showed that a CRP≥10mg/l was associated with worse survival in patients receiving adjuvant chemotherapy following surgery for colorectal cancer (HR 5.57 95%CI 1.32–23.51 p=0.019)[32]. It has been widely reported that the toxicity caused by chemotherapy and/or radiotherapy has its basis in the inflammatory response[35]. This suggests that immune system modulation could be the key mechanism in their therapeutic activity and a potential therapeutic target[35-37].

Furthermore, there is increasing evidence that the SIR is a central mediator of the negative symptoms associated with both chemotherapy and radiotherapy[35;38]. Animal models have suggested that the administration of chemotherapeutic agents induces IL-6 production and illness behaviours in mice[35;39]. Several common chemotherapeutic agents have been shown to be associated with the production of proinflammatory cytokines and the presence of natural killer (NK) cells, and activated T cell in patients with cancer[35;40-42]. In a recent observational study in patients being treated with chemoradiotherapy for advanced disease there was a dose-dependent rise in IL 6, IL 10, and TNF, correlating with symptoms such as pain, fatigue, and anorexia[35;43].

The development of immune-oncology medications such as iplimumab provides a potential means to target the activated inflammatory cascades to treat patients[44;45]. Indeed in a recent study in pancreatic cancer ruxolitinib, a strong downregulator of the inflammatory JAK/STAT pathway, was shown to increase median survival from 1.8 to 2.7 months in patients with high CRP readings[46]. This suggests a possible innovative means to treat patients with advanced cancers[46].

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The present systematic review and meta-analysis has a number of limitations. Intrinsic to the process and the high proportion of retrospective studies is the potential for publication bias. However, the volume of studies examined in the present review would mitigate, in part, against such publication bias. In the meta-analysis there was considerable heterogeneity that could be accounted for in part by differing thresholds and tumour type. It may be that as there is greater threshold standardisation in prospective studies the degree of heterogeneity will be reduced in subsequent meta-analysis of prospective studies.

In summary, the present systematic review and meta-analysis shows clearly that the systemic inflammatory response, as evidenced by a number of markers, has independent prognostic value in patients with advanced cancer. Of these markers, the GPS and NLR have been consistently validated worldwide. Therefore, it can be concluded that the systemic inflammatory response is an important predictor of outcome and is likely to inform treatment decisions in patients with advanced cancer. Further prospective studies are warranted.

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Figure and Table Legends Section:

Figure 1: PRISMA flowchart demonstrating study selection

Figure 2: Forrest Plot of Studies investigating the prognostic value of CRP in an unselected cohort of patients with advanced cancer

Figure 3: Forrest Plot of Studies investigating the prognostic value of Albumin in an unselected cohort of patients with advanced cancer

Figure 4: Forrest Plot of Studies investigating the prognostic value of GPS/mGPS in an unselected cohort of patients with advanced cancer

Figure 5: Forrest Plot of Studies investigating the prognostic value of NLR in an unselected cohort of patients with advanced cancer

Figure 6: Forrest Plot of Studies investigating the prognostic value of LMR in an unselected cohort of patients with advanced cancer

Figure 7: Forrest Plot of Studies investigating the prognostic value of PLR in an unselected cohort of patients with advanced cancer

Supplementary Table: Studies investigating the prognostic value of all markers of the SIR in an unselected cohort of patients with advanced cancer