Chapter 8

Systemic Inflammatory Reaction in Gastric Cancer: Biology and Practical Implications of Neutrophil to Lymphocyte Ratio, Glasgow Prognostic Score and Related Parameters

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Abstract

Gastric cancer induces systemic inflammatory reaction (SIR) manifesting with changes in counts of white blood cell fractions and concentrations of acute phase proteins, clotting factors and albumins. Thus, protein-based scores or blood cell ratios (neutrophil to lymphocyte ratio (NLR); platelet to lymphocyte ratio (PLR)) are used to evaluate SIR. SIR tests are biologically justified by multiple clinically important and fascinating events including bone marrow activation, development of immune-suppressing immature myeloid cells, generation of pre-metastatic niches and neutrophil extracellular trap formation from externalised DNA network in bidirectional association with platelet activation. Despite biological complexity, clinical SIR assessment is widely available, patient-friendly and economically feasible. Here we present concise review on NLR, PLR, Glasgow prognostic score and fibrinogen – parameters that have prognostic role regarding overall, cancer-free and cancer-specific survival in early and advanced cases. Tumour burden can be predicted helping in preoperative detection of serosal or lymph node involvement. Practical consequences abound, including selection of surgical approach in respect to tumour burden, adjustments in treatment intensity by prognosis or evaluation of chemotherapy response. The chapter also scrutinises main controversies including different cut-off levels. Future developments should include elaboration of complex scores as described here. SIR parameters should be wisely incorporated in patients' treatment.

Keywords: gastric cancer, systemic inflammatory reaction, neutrophil to lymphocyte ratio, NLR, platelet to lymphocyte ratio, PLR, Glasgow prognostic score, fibrinogen

1. Introduction

Gastric cancer remains an important issue in world oncology. In 2013, it ranked fifth by the global incidence and second by mortality [1]. Although the death rates have decreased significantly in the USA and Europe over the previous 70 years, gastric cancer is characterised by poor prognosis and high mortality [2] except for early diagnosed cases. Thus, prognostic and predictive estimates are necessary to guide the intensity of treatment and to predict the efficacy of it. Different directions of prognostic evaluation have been studied, including classic means as tumour-node-metastasis (TNM) stage or patient's Eastern Cooperative Oncology Group (ECOG) performance status [3], or novel approaches as the molecular tests [4].

Many tumours, including gastric cancer, evoke systemic inflammatory reaction (SIR). The systemic effects of cancer include alterations in bone marrow function, especially myelopoiesis. The production and release of leukocytes increases. In addition, immature myeloid cells, including the precursors of granulocytes and monocytes, are retained in early stages of differentiation. Immature myeloid cells can act as immune suppressors and generate pre-metastatic niches, among other pathogenetic processes. Thus, it has even been stated that cancer is an inflammatory disease [5]. SIR shows complex associations with the local immune and inflammatory infiltrate in the tumour [6].

Cancer-related SIR involves cells of innate and adaptive immunity as well as soluble factors. Macrophages are recruited in tumour by hypoxia and tumour-released molecular agents including growth factors and cytokines [7]. Macrophage phenotype switch from tumour-suppressing classical M1 to tumour-promoting M2 subtype promotes angiogenesis and immunosuppression. Platelets undergo activation that contributes to cancer progression and patient mortality [8]. Neutrophil activation can stimulate angiogenesis and metastatic spread. Neutrophil extracellular traps formed from externalised DNA network are bidirectionally associated with platelet activation and can contribute to cancer progression via several mechanisms therefore neutrophil extracellular traps represent also an attractive treatment target [8]. Neutrophils are locally recruited in the cancer as well via chemokine signalling; they contribute to angiogenesis and increased blood vessel permeability. These molecular events highlight also the association between infection or surgery-induced inflammation [9, 10] and cancer relapse or metastatic spread. While innate immunity is generally thought to act as tumour enhancers, high numbers of infiltrating neutrophils [11] and macrophages [12] are shown to be protective in gastric cancer.

In contrast, lymphocytes representing the adaptive immunity are considered to have tumour suppressing effects [7] although contrary effects have been ascribed to certain subpopulations [13, 14].

There is increasing body of evidence that patients' survival can vary despite equal TNM parameters. In turn, cancer can cause systemic inflammatory response that might be associated with prognosis and/or response to treatment. SIR can be evaluated by number or ratio

of serum neutrophils, lymphocytes, monocytes and platelets as well as by concentrations of acute phase proteins. These blood tests represent patient-friendly, widely available, globally standardised and cheap information that should be wisely incorporated in patients' treatment [15]. Regarding the diagnostics of gastric cancer, several SIR parameters have been found to differ between gastric cancer patients and healthy controls. Such indicators include neutrophil to lymphocyte ratio [16–18], platelet to lymphocyte ratio, platelet count [18], mean platelet volume [18, 19] and red blood cell distribution width [18]. While these changes clearly indicate activation of systemic inflammatory reaction in gastric cancer, additional research is necessary to identify the diagnostic value of SIR parameters in the differential diagnosis between gastric cancer and other gastric pathologies, including precancerous, inflammatory and ulcerative changes.

The correlation between neutrophil to lymphocyte ratio (NLR) and poor survival of gastric cancer patients is the best-known finding regarding SIR in gastric cancer [16, 17, 20]. High NLR is associated not only with shorter overall survival but also with worse progression-free survival [21]. In addition to the general association with survival, the prognostic value of NLR has been tested in specific clinical groups. Thus, NLR predicts post-operative survival of surgically treated patients with resectable cancer [22] and retains independent prognostic role in elderly patients—an expanding group in Western population showing multiple ageing-related changes that could affect the immune and inflammatory processes [23]. For patients undergoing chemotherapy because of unresectable and recurrent advanced gastric cancer, NLR also shows independent prognostic significance [24]. NLR is an independent prognostic factor in metastatic gastric cancer [25] and in metastatic gastric cancer treated with chemotherapy [26]. The predictive value is limited in patients receiving palliative treatment for disseminated gastric cancer [21]. Some authors consider low NLR as an indicator for good prognosis and thus beneficial effect of surgical treatment in stage IV gastric cancer [27, 28].

Some research groups have found that complex assessment of SIR-related parameters has superior prognostic value. For instance, joint analysis of platelet count and NLR was found to predict post-operative survival more exactly [29]. Combined scoring of albumin and neutrophil to lymphocyte ratio was independently associated with overall survival and was especially accurate for patients with stage I–II gastric cancer [30]. Combined evaluation of pre-operative NLR and platelet to lymphocyte ratio (PLR) was independent predictor of survival after curative surgical resection of stage I–II gastric cancer [31].

SIR can highlight wider scope of clinical traits, including manifestations that are not directly related to surgery or oncologic treatment. For example, pre-operative anxiety and depression are significantly associated with NLR [32].

SIR assessment is more comprehensive than NLR analysis. Thus, pre-operative plasma fibrinogen increases with gastric cancer stage and predicts worse recurrence-free and overall survival [33]. Similarly, levels of plasma albumin or the characteristics of platelets can provide significant data. Levels of C-reactive protein, original or modified Glasgow prognostic score can be used for analysis [3, 15].

The systemic inflammatory reaction itself can be an adverse pathogenetic event, facilitating tumour angiogenesis or adhesion of circulating tumour cells to endothelium that would lead to the growth of metastasis. In addition, NLR correlates with other factors known to have adverse prognostic role. Among such parameters, presence of vascular and lymphatic invasion as well as positive resection lines have been reported [22]. In several studies, NLR has been found to correlate with the stage of gastric cancer [16, 20–22]. NLR negatively correlates with mismatch repair protein deficiency [34]. NLR is associated with post-operative infectious complications. Both factors show an independent significant association with poorer survival after gastrectomy [9].

The evaluation of SIR in gastric cancer patients is highly attractive. By increasing awareness of SIR parameters, simple and widely available blood tests can provide information that is helpful in shaping the care of gastric cancer patients from early stages to metastatic spread or locally advanced tumour.

However, unresolved issues remain. Except the prognostic value to NLR, many aspects as the correlation with tumour morphology, type by Lauren classification, invasive properties of cancer, grade, intensity of angiogenesis and microvascular density have been targeted by low number of studies. Only few meta-analyses have been conducted [21, 35–37]. Few data are available on SIR parameters after treatment although it is known that post-chemotherapy NLR correlates with the response in patients with unresectable gastric cancer [38].

The practical unsolved questions include the comparison between NLR and other indicators of systemic inflammatory response, e.g., platelet to lymphocyte ratio [39], the significance of post-treatment NLR as well as cut-off values for practical use. The ultimate goal would be to create and validate an algorithm for fine-tuning of the treatment strategy in gastric cancer from early to advanced stages. Inflammatory markers other than NLR should be included; complex assessment hypothetically could be advised.

Thus, considering the high incidence and mortality of gastric cancer and the need for prognostic and predictive data, the present chapter will be devoted to the assessment of SIR in gastric cancer in order to develop practical recommendations how to adjust gastric cancer treatment by easily available and economically feasible simple blood tests for SIR parameters. Increased awareness of SIR characteristics is important to reach this aim.

2. Neutrophil to lymphocyte ratio in gastric cancer

Neutrophil to lymphocyte ratio is calculated as the ratio between the count of neutrophilic leukocytes and lymphocytes in peripheral blood. Thus, the parameter is easily available, especially in carefully examined cancer patients, and economically non-demanding. In fact, sufficient awareness and algorithm for interpretation are the only prerequisites to obtain an additional piece of information from routine blood tests.

Since the early reports [40, 41], NLR has been studied in relation to the prognosis of gastric cancer patients. Thus, Aliustaoglu et al. reported that high NLR was statistically

significantly associated with shorter median survival. In the same study, similar association was found regarding high platelet to lymphocyte ratio and high absolute number of lymphocytes but no difference was found for neutrophil count, platelet count and mean platelet volume [41]. In another early study devoted to the prognostic significance of host- and tumour-related factors in patients with gastric cancer, white blood cell count, NLR, C-reactive protein (CRP) and albumin was found to have prognostic impact, along with age, haemoglobin level, tumour size as well as T and N characteristics. By multivariate analysis, NLR was an independent prognostic factor along with tumour size and T parameter [42].

At present, the association between NLR and different aspects of survival (overall, cancer-specific, cancer-free or progression-free survival) remains one of the best substantiated aspects in the SIR research in gastric cancer.

2.1. NLR and survival: prognostic implications

The prognostic importance of NLR is shown over the whole course of gastric cancer, and is applicable to wide treatment spectrum—from surgically resectable cases, including early gastric cancer, to advanced, recurrent or metastatic tumours subjected to non-surgical treatment. Most researchers have demonstrated that NLR is an independent prognostic factor, based on multivariate analysis [17]. However, in few studies, the association with survival is confirmed by univariate but not multivariate analysis [43–45]. Some of the reports are on better scores, e.g. Glasgow prognostic score had higher informativity in a large and homogeneous group of 324 patients with stage III gastric cancer undergoing resection [43].

The prognostic value of NLR has been reported in different cancers, including lung, colorectal and breast carcinoma, among others [46]. Gastric cancer also follows the same mechanisms. In unselected cohort of patients diagnosed with gastric adenocarcinoma, high NLR (compared with the cut-off value 3) was a significant ($p = 0.016$), independent risk factor for poor survival [17].

Surgery is the mainstay of gastric cancer treatment, if the local and/or systemic tumour spread, or the general condition of the patient does not limit the possibilities of surgical intervention. In patients who have had curative surgery for gastric cancer, high NLR is significantly associated with poor prognosis [39], including overall survival [16, 47–49], cancer-specific survival [47], cancer-free survival [16, 47] and progression-free survival [25, 38, 50].

Thus, in a recent study of 162 patients with resectable gastric cancer, high pre-operative NLR (reaching or exceeding the median of 4.02) was associated with decreased overall and cancer-free survival, confirmed by Kaplan-Meier analysis [16]. In a significantly larger group of 1986 consecutive patients subjected to curative surgical treatment for gastric cancer, NLR was confirmed as an independent prognostic factor for overall survival, associated with hazard ratio of 1.4 [39]. Similarly, in 601 surgically treated gastric cancer patients, high NLR (reaching or exceeding 1.7) was a significant prognostic parameter for overall survival, confirmed as an independent factor by multivariate analysis. The hazard ratio was 2.12 [48]. Analogous observations were reported by Hsu et al. They assessed a large cohort of 1030 gastric cancer patients subjected to complex treatment. In accordance with clinical indications,

subtotal or total gastrectomy along with spleen- and pancreas-sparing D2 lymphadenectomy was performed, aiming to accomplish clear resection margins. Metastasectomy was considered depending on clinical symptoms and possibility of radical resections, and adjuvant or palliative chemotherapy was offered for stage II–IV patients. In such a large group, showing the routine clinical diversity of gastric cancer presentation, high NLR (exceeding 3.44) was an independent prognostic factor for overall survival, associated with hazard ratio of 1.57 [22].

In addition to significant statistical findings, the biological differences between groups also are remarkable. The 3- and 5-year survival rates in low versus (vs.) high NLR groups were 71.0% vs. 55.1% and 64.1% vs. 47.2%, respectively [22]. Even more, the 5-year survival was 29.9% in the high NLR group (reaching or exceeding 5.0) contrasting with statistically significantly different value of 85.6% in patients who had low NLR [51].

The overall survival was 86.1 months in patients presenting with low NLR vs. 64.0 months in high NLR (reaching or exceeding 2.3) group [30]. Evaluating 156 surgically treated gastric cancer patients, the median survival in high vs. low NLR groups was 36 vs. 60 months while the five-year survival was 35% and 60%, and the median cancer-free survival was 12 and 20 months, respectively. The survival differences retained significance in N0 patients: 5-year survival was 60% vs. 90%, $p < 0.05$. In this cohort, NLR was also recognised as an independent prognostic factor for overall survival [52].

In advanced gastric cancer (stage III–IV) patients subjected to gastrectomy with curative intent, high NLR was an independent predictor of overall survival at cut-off 2.0 corresponding to median while cut-off value 3.0 (the 75th percentile) was an independent predictor of cancer-free survival. The median overall survival in high vs. low NLR was 21.4 and 45.3 months while the progression-free survival in the redefined high and low NLR groups was 12.8 vs. 27.9 months [53].

NLR retains prognostic significance for surgically treated gastric cancer patients in specific subgroups. For instance, in elderly gastric cancer patients (aged 75 years or older) treated by gastrectomy, high NLR (reaching or exceeding 1.83) was associated with worse survival. Again, NLR was confirmed as an independent risk factor by multivariate analysis. The biological differences were remarkable: the median survival associated with low vs. high NLR was 1209 vs. 587 days, respectively [16]. High NLR is associated with older age in some studies [9, 20, 44, 47, 54, 55] while others report no association [22, 38].

It is very important to identify high risk of cancer progression in early diagnosed cases. Some promising reports have been published. Combined score including NLR and albumin level was shown to have independent prognostic value exceeding the informativity of NLR as justified by higher area under curve (AUC). This score, further described in detail, retained the prognostic ability in stage I–II gastric cancer [30]. A complex score comprising NLR and PLR is another prognostic option, successfully tested in a stage I–II gastric cancer. NLR-PLR score showed a clear trend to improve the prognostic value of TNM staging [31].

Mohri et al. has reported very interesting findings regarding NLR in surgically treatable gastric cancer cases. In 404 patients undergoing curative gastrectomy for gastric cancer, high NLR

was an independent risk factor of post-operative infectious complications while it was not predictive of non-infectious complications. In turn, both high NLR and post-operative infectious complications were independent risk factors of worse overall and cancer-specific survival [9]. The preceding NLR increase in patients later developing post-operative infectious complications but not in case of all complications was justified by Japanese scientists [10].

In contrast with the previously described findings, NLR was not informative regarding survival of gastric cancer patients having only local disease while it was significantly associated with survival in advanced cases [56]. Some negative findings, including the cited one, can be explained by small study group comprising only 53 patients with local disease and 50 with advanced cancer [56]. Evaluating Glasgow prognostic score, NLR and PLR in patients with resected stage III gastric adenocarcinoma, only Glasgow prognostic score along with TNM stage was independently associated with cancer-free and overall survival [43]. If the study design includes several SIR parameters, multivariate analysis could highlight only one of those.

Advanced or metastatic cancer represents a situation with continuously significant tumour burden, associated with ongoing inflammation, angiogenesis, antigenic stimulation and thus sustained SIR. The NLR has been evaluated in these situations as well. In 174 advanced gastric cancer patients treated with oxaliplatin/5-fluorouracil (FOLFOX), NLR was associated with overall survival but not with progression-free survival. NLR was also an independent predictor of overall survival. Normalisation of NLR after one cycle of chemotherapy was significant and independent predictor of overall and progression-free survival [57]. Similar findings are reported by Jin et al. [58].

In unresectable and recurrent advanced gastric cancer patients treated by chemotherapy, high NLR (exceeding 4) was associated with significantly lower median survival [24]. Similarly, in another cohort comprising 143 cases of metastatic gastric cancer, high NLR was an independent prognostic factor. The overall and progression-free survival was 11.6 and 7.9 months in low NLR (less than 3.34) group contrasting with 8.3 and 6.2 months in patients having high NLR [25]. In 120 unresectable metastatic and advanced gastric cancer cases, treated by chemoradiotherapy, baseline NLR predicted survival. The median overall and progression-free survival in high vs. low NLR group was 10 and 3 months vs. 18 and 6 months. Treatment-induced changes in NLR also predicted survival. Both baseline NLR and changes upon initiation of treatment predicted treatment outcomes [38]. This finding is in accordance with Cho et al., who also reported significantly higher chemotherapeutic disease control rate in metastatic advanced gastric cancer patients having low NLR, defined as less or equal to 3.0 [50]. Combined scores have been generated to evaluate the prognosis of metastatic gastric cancer as well [26].

Occasionally NLR shows association with survival by univariate but not multivariate analysis. Thus, in a small group of 70 patients affected by locally advanced gastric cancer (stage III–IV) and treated by neoadjuvant chemotherapy, NLR was an independent predictor of overall survival. It was significantly associated with progression-free survival but was not an independent factor [59]. In a large group of 439 patients affected by metastatic or recurrent gastric cancer, NLR was significantly associated with overall survival in univariate but not multivariate analysis. Complex score was favoured by authors [60].

The prognostic findings regarding NLR in gastric cancer have been summarised in **Table 1**.

Study group		Survival				References
Characteristics	**Size**	**Overall**	**Cancer-specific**	**Cancer-free**	**Progression-free**	
Unselected gastric adenocarcinoma	706	X Multivariate				[17]
GC	245	X Kaplan-Meier analysis of multicentre study data				[61]
Gastric adenocarcinoma	236	X Multivariate				[62]
Surgically treated GC						
Consecutive GC patients undergoing curative gastrectomy	404	X Multivariate	X Multivariate			[9]
Curative surgery for GC	288	X Multivariate				[49]
Resectable GC	162	X Kaplan-Meier analysis		X Kaplan-Meier analysis		[16]
GC, subjected to curative surgery	1986	X Multivariate				[39]
Surgically treated GC (R0)	601	X Multivariate				[48]
GC patients undergoing gastrectomy	389	X Multivariate	X Multivariate	X Multivariate		[47]
Surgically treated GC patients	207		X Multivariate	X Multivariate		[63]
GC subjected to radical surgery	291	X Multivariate				[20]

Study group		Survival				References
Characteristics	**Size**	**Overall**	**Cancer-specific**	**Cancer-free**	**Progression-free**	
GC subjected to gastrectomy	632	X Univariate (significant) Multivariate (NS)				[45]
GC subjected to potentially curative gastrectomy	156	X Multivariate				[52]
Patients with resectable GC, including advanced cases	377	X Multivariate				[64]
Surgically treated (total or subtotal gastrectomy) GC patients	220	X Univariate (significant) Multivariate (NS)				[44]
Gastrectomy with curative intent for stage III–IV GC	293	X Multivariate		X Multivariate		[53]
Curative gastrectomy	157		X Multivariate			[65]
GC patients, undergoing gastrectomy	1028	X Multivariate				[66]
Elderly patients (at least 75 years old) undergoing gastrectomy	160	X Multivariate				[23]
Curative resection, D2 lymphadenectomy, adjuvant chemotherapy in stage II–III	873	X Kaplan-Meier analysis				[30]
Resectable GC subjected to combined treatment	1030	X Multivariate				[22]

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Study group		Survival				References
Characteristics	**Size**	**Overall**	**Cancer-specific**	**Cancer-free**	**Progression-free**	
Advanced, unresectable and/or metastatic GC						
Unresectable and recurrent advanced GC, treated by chemotherapy	224	X Multivariate				[24]
Metastatic GC treated by chemotherapy	256	X Multivariate				[26]
Metastatic GC	143	X Multivariate			X Multivariate	[25]
Unresectable, advanced GC, treated by chemotherapy	120	X Kaplan-Meier analysis			X Kaplan-Meier analysis	[38]
Metastatic GC treated by chemotherapy	109	X Kaplan-Meier analysis			X Kaplan-Meier analysis	[67]
GC, stage IV with synchronous distant MTS	123	X Multivariate				[27]
Metastatic advanced GC treated by palliative chemotherapy	268	X Multivariate			X Multivariate	[50]
Locally advanced GC treated by neoadjuvant chemotherapy	70	X Multivariate			X Univariate (significant) Multivariate (NS)	[59]
Metastatic or recurrent GC	439	X Univariate (significant) Multivariate (NS)				[60]

Study group		Survival				References
Characteristics	**Size**	**Overall**	**Cancer-specific**	**Cancer-free**	**Progression-free**	
Inoperable advanced or metastatic GC patients receiving chemotherapy	384	X Univariate (significant) Multivariate (NS)				[68]
Advanced GC patients treated by chemotherapy	174	X Multivariate			X (dynamics, not baseline) Multivariate	[57]
Advanced GC treated with neoadjuvant chemotherapy	46	X (baseline and dynamics) X Univariate (significant) Multivariate (NS)			X (baseline and dynamics) Multivariate	[58]
Metastatic unresectable advanced GC patients treated with palliative chemotherapy	104	X Multivariate				[69]

Abbreviations: GC, gastric cancer; R0, resection line free of cancer; NS, not significant; MTS, metastasis.

Table 1. The prognostic value of NLR in gastric cancer patients.

The cut-off levels vary widely among the studies. Most frequently, either the median value is selected as the cut-off [16, 70], or the relevant level is found by receiver operating characteristic curve (ROC) analysis [30, 39]. Youden Index has been successfully employed to detect the optimal cut-off during ROC analysis [30]. This index is defined as the cut-off value showing the highest sum of specifity and sensitivity at the considered value; minus 1 [71]. Less frequently, the 75th percentile is used as the cut-off [44, 53]. Some research groups have applied more complex approach, e.g. combining the patients groups with similar survival [17, 20]. The reported cut-off levels for NLR in gastric cancer patients are summarized in **Table 2**.

Interestingly, different cut-off values can reveal different information. Thus, Jung et al. has reported that cut-off 2.0 based on the median value was valuable in order to show that higher NLR is an independent risk factor for worse overall survival. However, when studying cancer-free survival, NLR was an independent risk factor by cut-off 3.0 corresponding to the 75th percentile [53]. The necessity for different cut-offs in regard to the question of interest is indirectly demonstrated by mean NLR in different patient groups: 4.02 in T1–2; 6.54 in T3–4; 4.81 in N0; 6.41 in N+; 5.00 in M0; 7.82 in M1; 4.74 in stage I–II cancers and 7.07 in stage III–IV cancers [47]. Jung et al. also observed statistically significant differences in median NLR by gastric cancer stage: 1.88 in stage III and 2.17 in stage IV [53].

2.2. Association with tumour features

2.2.1. Local tumour spread: T

Significant association between NLR and the invasion depth of gastric cancer is recognised since the early studies [65] and confirmed by more recent research [20]. The applied cut-off levels again vary widely. Thus, the association with increased depth of invasion has been demonstrated in patients whose high preoperative NLR level was defined as higher than or equal to 4.02 [16] or as exceeding the ROC-set cut-off value of 1.59 [55]. Significant difference in T1–2 vs. T3–4 distribution was reported by Deng et al. The mean NLR was 4.02 in T1–2 cases and 6.54 in T3–4 cases [47].

Many studies have highlighted the association between NLR and serosal invasion that is classified as T4a. Such invasion represents a potential limit to surgical treatment if followed by extensive peritoneal spread. NLR studies in regard to the tumour spread have led to the development of complex predictive scores to forecast serosal invasion. Hence, high NLR can be used as an independent predictive factor for T4 using cut-off 3.2 [73]. The high NLR (exceeding 3.44) group had significantly higher proportion of T4 when 1030 patients with resectable gastric cancer were assessed [22]. Serosal invasion was significantly more frequent in elderly patients having high NLR: 75.5% vs. 57.4% [23]. Finally, in a large prospective study enrolling 1131 surgically treated patients, high NLR (exceeding the median 3.5) was associated with deeper invasion: T3–T4 tumours. The mean NLR was 2.51 in T3–T4 tumours vs. 2.19 in T1–T2 tumours. Within the frames of a complex score, NLR can be used to predict inappropriateness of gastrectomy [54].

The capacity of NLR to predict such tumour spread that would limit surgical treatment has been explored in combined model searching for either peritoneal or metastatic spread due to either gastric or oesophageal adenocarcinoma. Authors concluded that NLR reaching or exceeding

Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Unselected gastric adenocarcinoma	706	3	Complex	OS	Multivariate	Higher NLR is associated with worse OS	[17]
GC	245	2.56	Ref. [40]	OS	Kaplan-Meier analysis Multicentre study	High NLR is significantly associated with worse OS, presence of N+ and higher stage	[61]
Surgically treated GC							
Operable GC	231	2.97	ROC analysis	N	Multivariate	High NLR shows significant association with N+ in early GC but is not an independent factor	[72]
Stage I–II GC, subjected to radical (R0) surgery including D2 lymphadenectomy	305	2.1	ROC analysis	OS	Multivariate	Within the frames of complex NLR-PLR score is an independent predictor of OS in stage I–II GC	[31]
Stage I–II GC, subjected to radical (R0) surgery including D2 lymphadenectomy	305	3	Ref. [29]	OS	Multivariate	Within the frames of complex score, including platelet count and NLR, is not the most informative predictor of OS by AUC assessment	[31]
Surgically treated T2 GC	230	2.18	Median	N	Multivariate	Higher NLR is associated with higher number of LN MTS and higher N	[70]

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Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Consecutive patients undergoing curative gastrectomy	404	3.0	ROC analysis	OS CSS Post-operative complications	Multivariate	Higher NLR is an independent risk factor for worse OS, CSS and post-operative infectious complications	[9]
Curative surgery for gastric cancer	288	2.7	ROC analysis for survival	OS Immune cell density within cancer	Multivariate	Higher NLR is an independent risk factor for worse OS Density of CD4 Ly is decreased in high NLR group while CD3 and CD8 + Ly density shows no differences	[49]
Operable GC	492	1.59	ROC analysis	N	Multivariate	High NLR is an independent factor, associated with N+	[55]
Curative resection, D2 lymphadenectomy, adjuvant chemotherapy in high-risk stage II–III	873	2.3	ROC analysis	OS	Kaplan-Meier analysis Multivariate	Although NLR is associated with OS, a complex score including NLR and albumin is more potent predictor of OS based on higher AUC in ROC analysis	[30]
Elderly patients (at least 75 years old) undergoing gastrectomy	160	1.83	ROC analysis	OS	Multivariate	Higher NLR is an independent risk factor for worse OS	[23]
Surgically treated GC	601	1.7	ROC analysis	OS	Multivariate	Higher NLR is an independent risk factor for worse OS	[48]

Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Total or subtotal gastrectomy with lymphadenectomy	389	2.36	ROC analysis	OS, CFS, CSS	Multivariate	Higher NLR is a significant risk factor for worse OS, CFS, CSS	[47]
Resectable GC	162	4.02	Median	OS, CFS	Kaplan-Meier analysis	Higher NLR is an associated with worse OS and CFS	[16]
Resectable gastric cancer subjected to combined treatment	1030	3.44	Survival tree assessment by R software	3 and 5-year OS rate	Multivariate	Higher NLR is an independent risk factor for worse OS	[22]
Surgically treated GC	207	5/4	ROC analysis	OS CFS	Multivariate	Higher NLR is an independent risk factor for worse OS. However, GPS has higher prognostic value	[63]
GC subjected to radical surgery	291	3.5	Complex assessment of survival by NLR intervals	OS Tumour and patients characteristics	Multivariate	High NLR is an independent prognostic factor for overall survival and is significantly associated with, age, tumour size, T and TNM stage	[20]
GC subjected to gastrectomy	632	1.83	ROC analysis	OS	Multivariate	High NLR shows significant association with OS but is not an independent factor. Complex score preferred	[45]
GC subjected to potentially curative gastrectomy	156	2.34	Median	OS	Multivariate	Higher NLR is an independent risk factor for worse OS	[52]

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Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Surgically treated GC, including non-radical cases	1131	3.5	Median	Resection line status Tumour characteristics	Mann Whitney test Fisher test Univariate analysis	High NLR is associated with T3-4, G3-4, larger tumours, higher N and TNM stage Within frames of complex score NLR can be used to predict inappropriateness of gastrectomy	[54]
Surgically treated GC patients	220	2.15	75th percentile	OS	Multivariate	Higher NLR is a significant risk factor for OS by univariate but not multivariate analysis	[44]
Surgically treated GC, T2–4	262	3.2	ROC analysis	T4	Multivariate	High NLR is an independent factor, associated with T4	[73]
Gastrectomy with curative intent for stage III–IV GC	293	2.0	Median	OS	Multivariate	Higher NLR is an independent risk factor for worse OS	[53]
Gastrectomy with curative intent for stage III–IV GC	293	3.0	75th percentile	CFS	Multivariate	Higher NLR is an independent risk factor for worse CFS	[53]
Curative gastrectomy	157	5.0	Refs. [74, 75]	CSS	Multivariate	Higher NLR is an independent risk factor for worse CSS	[65]
Advanced, unresectable and/or metastatic GC							
Metastatic gastric adenocarcinoma treated by chemotherapy	256	3	Refs. [53, 66]	OS	Multivariate	NLR is an independent risk factor	[26]

Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Metastatic GC	143	3.34	Median	OS	Multivariate	Higher NLR is an independent risk factor for worse OS	[25]
Metastatic GC treated by chemotherapy	109	2.5	Refs. [40, 58]	OS PFS	Kaplan-Meier analysis	High NLR is significantly associated with worse OS and PFS	[67]
Unresectable, advanced GC, treated by chemotherapy	120	4.62	Median	OS PFS	Kaplan-Meier analysis	Higher baseline NLR or increase of NLR after first-line chemotherapy is associated with worse OS and CFS	[38]
Unresectable, advanced GC, treated by chemotherapy	120	4.62	Median	Response to chemotherapy	χ^2 test	Lower baseline NLR or lower NLR after first-line chemotherapy was associated with improved response to chemotherapy	[38]
Advanced GC treated by chemotherapy// Local GC treated by surgery and adjuvant chemoradiotherapy	50//53	2.75	Median	OS	Kaplan-Meier analysis	High NLR is significantly associated with worse OS in advanced but not local GC	[56]
GC (stage IV) with synchronous distant MTS	123	3.1	Median	OS	Multivariate	Higher NLR is a significant risk factor for worse OS in the whole group and in surgically treated patients	[27]

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Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Metastatic advanced GC treated by palliative chemotherapy	268	3.0	Median	OS, PFS Response to chemotherapy	Multivariate	Higher NLR is an independent risk factor for worse response to chemotherapy, OS and PFS	[50]
Inoperable advanced and metastatic GC patients receiving palliative chemotherapy	384	2.75	Median	OS	Multivariate	High NLR shows significant association with OS but is not an independent factor	[68]
Advanced GC patients treated with chemotherapy	174	3	OS curve analysis	OS PFS	Multivariate	Low baseline NLR and normalisation of NLR were independent predictors of better OS. Normalisation of NLR was an independent predictor of better PFS.	[57]
Advanced GC treated by neoadjuvant chemotherapy	46	2.5	Ref. [40]	OS PFS	Multivariate		[58]

Abbreviations: OS, overall survival; NLR, neutrophil to lymphocyte ratio; GC, gastric cancer; Ref., reference; N+, presence of metastases in regional lymph nodes; ROC, receiver operating characteristic curve; N, regional lymph node status in respect to metastases by tumour-nodes-metastasis (TNM) classification; R0, resection line free of tumour; PLR, platelet to lymphocyte ratio; AUC, area under the curve; T, local spread of primary gastric cancer by TNM classification; LN, lymph node; MTS, metastasis; CSS, cancer-specific survival; CD, cluster of differentiation; Ly, lymphocyte; CFS, cancer-free survival; GPS, Glasgow prognostic score; TNM, tumour-nodes-metastasis classification; G, grade; PFS, progression-free survival.

Table 2. Cut-offs of NLR in gastric cancer studies.

the cut-off value of 3.28 is an independent predictor of undesirable tumour spread. The median NLR in operable patients vs. those having peritoneal or metastatic disease was 2.2 vs. 3.3 [76].

Negative findings have been published. Some of them could be easily explained by small group size, e.g. only 61 gastric cancer patients were enrolled in the study of Pietrzyk et al. [18]. However, no differences in T distribution by NLR were found by Kim et al. who analysed a large group of 601 patients [48]. No association between invasion depth and NLR was found in a multicentre study [61].

Large tumour size has shown association with high NLR [20, 22, 38, 53–55, 65, 77]. As T in gastric cancer is not defined by size, tumour size could become a confounding factor.

2.2.2. Metastases in regional lymph nodes: N

Metastatic involvement of regional lymph nodes is associated with worse prognosis, being especially important in the early stages of gastric cancer. Presence of lymph node metastases also limits and changes the treatment options as endoscopic resection is not feasible anymore but D2 lymphadenectomy becomes more appropriate than D1 lymphadenectomy. In addition, neoadjuvant treatment can be offered now to gastric cancer patients affected by lymph node metastases [55]. NLR can be used to predict lymph node metastasis. In a retrospective study of 230 surgically treated patients, affected by T2 gastric cancer, NLR exceeding the median value of 2.18 was associated with higher number of lymph node metastases and higher N characteristics. The findings were confirmed by multivariate analysis. The relative risk was as high as 4.15 and 7.09 in regard to high number of metastases and N stage, respectively [70]. NLR at the cut-off level 1.59 (detected by ROC) was an independent factor associated with lymph node metastasis; however, higher informativity reflected by higher AUC was achieved by complex score (see further) including NLR, PLR and tumour-related factors [55]. The conclusions are justified by other researchers reporting correlation between NLR and N parameter since the early reports [65] until recent studies [77]. Thus, high NLR (exceeding the ROC-set cut-off value of 1.59) was associated with high N [55] while low preoperative NLR level (less than 4.02) was associated with lower number of lymph node metastases [16]. The variability of applied cut-off values is evident.

Lymph node metastases were significantly more frequent in elderly patients having high NLR: 83.0% vs. 55.6% [23]. In a large cohort of 1030 patients with resectable gastric cancer, high ratio of metastatic to examined lymph nodes defined as exceeding 0.18 was more frequent in those who had high NLR (greater than 3.44). Interestingly, in the same study N distribution showed only a trend to differences [22]. Significant difference in N0 vs. N+ distribution was reported by Deng et al. In addition, the mean NLR was 4.81 in N0 patients and 6.41 in N+ cases [47]. Statistically significant correlation between presence of lymph node metastasis, high NLR was confirmed in a multicentre study [61]. In a prospective study of 1131 surgically treated cases, high NLR (exceeding the median 3.5) was associated with higher N. The mean NLR was 2.31 in N0; 2.32 in N1; 2.43 in N2 and 2.75 in N3 cases [54].

Negative findings have been published as well. Some of them could be easily explained by small group size, e.g. only 61 gastric cancer patients were enrolled in the study of Pietrzyk

et al. [18]. No differences in N distribution by NLR were found by Kim et al. who analysed a large group of 601 patients [48] and Yu et al. who assessed another significant cohort of 291 patients. In the same study, association with T and TNM stage was significant [20]. There was no correlation between NLR and N in a reasonable group of 262 surgically treated patients affected by T2–T4 gastric cancer while correlation with T in the same study was meaningful. The cut-off in this study was detected by ROC and was 3.2 [73].

Some reports have re-evaluated the meaning of NLR in predicting N status, arriving to less positive conclusions. In early gastric cancer (T1a–T1b), NLR was significantly associated with presence of lymph node metastases. The mean NLR was 2.07 in N0 group while it increased to 2.60 in N+ group. However, by multivariate analysis NLR was not an independent prognostic factor. Complex score not including NLR was more informative for preoperative estimation of lymph node metastases [72].

2.2.3. Presence of distant metastases: M

Presence of distant metastasis has also been associated with higher NLR [38, 77]. Metastatic tumours were significantly more frequent in patients who had high NLR (exceeding 3.44) assessing 1030 patients with resectable gastric cancer [22]. Significant difference in M0 vs. M1 frequencies by NLR groups was reported by Deng et al. In addition, the mean NLR was 5.00 in M0 cases and 7.82 in M1 cases [47].

In a large study of 491 gastric cancer patients, NLR was significantly associated with peritoneal metastasis. However, it was not an independent predictive factor for peritoneal spread, while tumour morphology, serum level of carbohydrate antigen CA19-9 and lymphocyte count retained independent predictive value [78]. In contrast, evaluating CRP, activated partial thromboplastin time, NLR and hypoalbuminemia, NLR was identified as an independent risk factor of the presence of peritoneal metastasis. The cut-off level was set at 2.37 [79].

2.2.4. TNM stage

Considering the previously discussed links between NLR and TNM parameters, correlation with TNM stage could be expected as well. Indeed, advanced TNM stage was significantly associated with high NLR [9, 20, 44, 47, 65, 77]. High NLR (exceeding the ROC-set cut-off value of 1.59) was associated with high TNM stage [55]. The mean NLR was 4.73 in stage I–II and 7.07 in stage III–IV [47]. In advanced gastric cancer (stage III–IV) patients, there still was difference between stage III and IV [53].

Statistically significant correlation between cancer stage and high NLR was confirmed also by multicentre [61] and prospective study design [54]. In a prospective study of 1131 surgically treated patients, high NLR (exceeding the median 3.5) was associated with higher TNM stage. The mean NLR was 2.13 in stage I, 2.40 in stage II, 2.53 in stage III and 2.60 in stage IV [54].

Regarding negative reports, no NLR differences by TNM stage were found by Kim et al. who analysed a large group of 601 patients [48].

2.2.5. Histological type and grade (G)

The association between NLR and cancer grade is more controversial. The cancer grade was not different between high and low NLR groups in a cohort of 143 metastatic gastric cancer cases as well as in 389 patients who underwent gastrectomy or in 293 gastric cancer patients diagnosed in stage III–IV [22, 25, 47, 53]. No difference by differentiation degree (G1–2 vs. G3) was found by Yu et al. [20].

In contrast, high NLR was associated with differentiated (vs. undifferentiated) gastric cancer [9]. High differentiation degree (vs. moderate and poorly differentiated cases) was associated with low NLR. In the same study, no differences were observed regarding proliferation fraction by Ki-67 [38]. High NLR (exceeding the ROC-set cut-off value of 1.59) was associated with high grade [55]. In a prospective study of 1131 surgically treated patients, high NLR (exceeding the median 3.5) was associated with poor differentiation or undifferentiated tumours while low NLR—with high and moderate differentiation. The relevant mean NLR values were 2.46 in G3–G4 vs. 2.31 in G1–G2 cancers [54].

There was no correlation between NLR and histological differentiation in a large group of 262 surgically treated patients affected by T2–T4 gastric cancer while correlation with T in the same study was meaningful. The cut-off in this study was detected by ROC and was 3.2 [73]. No correlation between histological type of cancer and NLR was observed in a prospective study of 1131 surgically treated patients [54]. No differences in histology distribution by NLR were found by Kim et al. who analysed a large group of 601 patients [48]. Histological types (papillary, tubular, poorly differentiated, mucinous, signet ring cell carcinoma) were scrutinized by Deng et al., also finding no association with NLR level [47].

No NLR differences were observed between Lauren types: intestinal vs. diffuse [38, 53, 65] that might explain the lack of association with HER-2 protein expression [38].

Low NLR shows significant correlations with mismatch repair deficiency [34]. In cancer tissues, the density of CD4-positive lymphocytes was significantly decreased in high NLR group while the density of CD3 and CD8-positive lymphocytes was not associated with NLR [49]. Although NLR correlated with survival, it did not correlate with tumour-infiltrating lymphocytes [62]. Regarding cytokines and angiogenic factors, serum levels of osteopontin and interleukin 6 were significantly associated with NLR in gastric cancer patients [80]. NLR is significantly associated with helper T lymphocyte Th1/Th2 ratio in blood [65].

2.2.6. Manifestations of invasive growth

Only few scientists have assessed the relations between NLR and such manifestations of invasive growth as perineural, lymphatic and vascular invasion. Theoretically, such association could be hypothesised on the basis of prognostic value of NLR and the correlations between NLR and metastatic cancer spread. However, at present, negative reports predominate although are not unequivocal.

The frequency of perineural growth was not different between high and low NLR groups [22]. The frequency of lymphovascular invasion also was not different between high and low NLR groups in a cohort of 143 metastatic gastric cancer cases [25]. In contrast, vascular or lymphatic invasion was significantly more frequent in patients who had high NLR (exceeding 3.44) assessing 1030 cases of resectable gastric cancer. Hypothetically, the higher capacity for invasive growth could be the reason of more frequent occurrence of R1 in patients presenting with high NLR. However, association between NLR and resection line status (R0 vs. R1 vs. R2) was found by Jung et al., who observed no differences in the frequency of lymphatic, vascular and perineural growth regarding NLR level [53].

2.3. The diagnostic role of NLR and confounding factors

Several haematological parameters, including NLR, are significantly higher in gastric cancer patients than in healthy individuals [18]. A number of studies have confirmed that patients affected by gastric carcinoma have significantly higher NLR than healthy controls [16, 17]. NLR was also higher in gastric cancer patients if compared with persons having adenoma or benign gastrointestinal stromal tumour: 2.17 vs. 1.62. Excluding the confounding factors, NLR was an independent predictor of gastric cancer, associated with the odds ratio of 1.446, $p = 0.005$ [77].

NLR is influenced by smoking [81]. Such differences are reported in gastric cancer patients as well [25] while other researchers have found no difference [47]. Non-oncological diseases, including both inflammations and such frequent non-inflammatory pathologies as diabetes mellitus and atrial fibrillation, among others, can also influence NLR [82]. Thus, SIR should be assessed within the frames of complex patient evaluation.

2.4. Meta-analyses of NLR in gastric cancer

Several meta-analyses of NLR in gastric cancer have been carried out. Sun et al. have assessed 19 studies of NLR in gastric cancer. They confirmed the association between high NLR and worse overall, progression- or cancer-free survival, and higher stage. The predictive role was lost for stage IV patients who received palliative surgery only [21]. Nineteen studies were subjected to meta-analysis by Xin-Ji et al. [37]. Elevated NLR was associated with shorter overall (odds ratio (OR) 1.65; 95% CI = 1.47–1.83) and shorter cancer-free survival (OR 1.61; 95% CI = 1.28–1.94). Regarding the tumour characteristics, NLR was associated with presence of lymph node metastasis, and high T (T3 + T4) and high stage (III–IV). The odds ratio for lymph node metastasis, 1.70 (95% CI = 1.05–2.75), for T3 or T4 cancer 2.93 (95% CI = 2.27–3.78) and for stage III–IV: 1.87 (95% CI = 1.48–2.35) as reported by Xin-Ji et al. [37]. By meta-analysis performed by Chen et al. [36], high NLR was associated with poor overall survival (hazard ratio (HR) 2.16; 95% CI = 1.86–2.51) and progression-free survival (HR 2.78; 95% CI = 1.95–3.96). In a meta-analysis of 10 studies, higher NLR was associated with worse overall (HR 1.83; 95% CI = 1.62–2.07), progression-free (HR 1.54; 95% CI = 1.22–1.95) and cancer-free (HR 1.58; 95% CI = 1.12–2.21) survival [35].

3. Platelet to lymphocyte ratio in gastric cancer

3.1. PLR and survival: prognostic implications

Similarly to NLR, platelet to lymphocyte ratio (PLR) has been evaluated as a prognostic and diagnostic marker of gastric cancer. Although the prognostic role has been shown both in surgically treatable and advanced gastric cancer cases, the data are controversial.

Some research groups have demonstrated that PLR could help to predict overall and cancer-free survival of surgically treated gastric cancer patients. Thus, in 377 patients who underwent curative resection for gastric cancer, high PLR was an independent predictive factor for worse overall survival [64]. In 162 patients diagnosed with resectable gastric cancer, high PLR correlated with decreased both overall and cancer-free survival [16].

Later, evaluating several blood test parameters (PLR, NLR, absolute count and relative proportion of neutrophils and lymphocytes, counts of platelets, white and red blood cells as well as mean platelet volume) in 451 surgically treated gastric cancer patients, high PLR was the only independent prognostic marker for poor overall survival, associated with hazard ratio of 1.4 (95% CI = 1.0–1.9). Hence, in this study preoperative PLR was more informative than NLR [83].

PLR has been successfully implemented in complex prognostic score (along with NLR, see also the further description) in order to assess the prognosis in stage I–II gastric cancer. The created score was an independent predictor of overall survival and retained prognostic significance both in stage I and stage II [31].

In contrast, several studies either preferred the NLR as more informative SIR marker, or failed to identify the independent prognostic role of PLR although significant association with survival parameters was found by univariate analysis. In 389 gastric cancer patients who have undergone gastrectomy, elevated PLR was significantly associated with worse overall, cancer-specific and cancer-free survival. The cut-off was estimated by ROC analysis and was 132. However, as a prognostic factor for overall survival, cancer-specific survival and cancer-free survival, PLR was not superior to NLR [47]. PLR was not an independent prognostic factor for overall survival in large Chinese cohort of 591 gastric cancer patients although it was significantly associated with survival by univariate analysis. In the same study, NLR along with age and TNM stage was shown to be an independent prognostic factor [84]. Assessing 207 gastric cancer patients treated by resection, univariate analysis disclosed significant association of PLR (along with serum CRP, albumin, Glasgow prognostic score (GPS), NLR, cancer grade and TNM stage) with overall survival and cancer-specific survival. However, by multivariate analysis, PLR was not an independent predictor of survival, contrasting with NLR, GPS, TNM stage and cancer grade. Glasgow prognostic score and TNM stage were the most robust of the assessed prognostic parameters [63]. Evaluating different SIR markers, namely, GPS, NLR and PLR, as prognostic variables in 324 patients with resected stage III gastric adenocarcinoma, only Glasgow prognostic score along with TNM stage was independently associated with cancer-free and overall survival while PLR

was associated with GPS [43]. By univariate analysis, both NLR and PLR were associated with overall survival of gastric cancer patients after gastrectomy. However, none of these parameters was identified as an independent factor by multivariate analysis in this study [45]. A study of 1986 consecutive gastric cancer patients was directly targeting the issue if PLR of NLR is better as a prognostic factor of gastric cancer. Although high PLR was significantly associated with poor prognosis it was not an independent risk factor for decreased overall survival in contrast to NLR. Thus, NLR was preferred [39].

Finally, negative results are reported. In a multicentre study of 245 gastric cancer patients, PLR was not associated with survival [61].

In advanced gastric cancer, many studies have revealed significant and independent association between PLR and survival. However, controversial findings still are reported.

High PLR (exceeding 160) along with high NLR (reaching or exceeding 2.57) and high absolute number of lymphocytes (reaching or exceeding 1500/mm^3) were significantly associated with shorter median overall survival of 168 locally advanced gastric cancer patients. The median survival in high vs. low PLR groups was 27 vs. 45 months [41].

In advanced unresectable gastric cancer, low PLR (less than 235) correlated with less metastasis and improved response to chemotherapy, longer overall survival and progression-free survival. Changes in PLR after first-line chemotherapy also were indicative of prognosis: survival and response to treatment was better in cases that retained low PLR or switched to low PLR group during treatment [38].

In a cohort of 109 metastatic gastric cancer patients treated by chemotherapy, high PLR (exceeding the cut-off 160) was associated with significantly shorter progression-free and overall survival [67].

In 174 advanced gastric cancer cases treated by chemotherapy, low PLR and normalisation of PLR after one cycle of chemotherapy were independent prognostic markers for better overall survival. Normalisation of PLR was also associated with longer progression-free survival: 5.6 months vs. 3.4 months [57].

In a relatively small study group, PLR lacked prognostic role in 53 patients affected by local gastric cancer and treated with surgery and adjuvant chemotherapy while it had significant prognostic meaning in 50 advanced cases treated by chemotherapy. Interestingly, high platelet count was associated with better overall survival in patients having local disease [56].

Again, many studies have identified significant but not independent association between PLR and survival. In 439 patients affected by metastatic or recurrent gastric cancer, PLR (along with NLR, modified Glasgow prognostic score, previous histology with neural and vascular invasion, albumin, CRP and haemoglobin level) was significantly associated with overall survival, but it was not an independent prognostic factor. In this study design, modified Glasgow prognostic score was the only inflammation-related parameter that was independently associated with survival by multivariate analysis [60]. In 384 patients affected by inoperable advanced or metastatic gastric cancer and treated by palliative chemotherapy, PLR (as well as NLR, leucocytosis, elevated number of neutrophils or platelets, decreased lymphocyte count, hypoalbuminemia, high CRP and Glasgow prognostic score) showed association with

overall survival by univariate analysis. By multivariate assessment, PLR had no independent meaning. Only elevated count of neutrophils and Glasgow prognostic score were independent survival predictors by multivariate analysis [68].

As the prognostic role of PLR in gastric cancer is controversial, meta-analyses also have brought contrary opinions. Thus, in a meta-analysis of 8 studies comprising 4513 patients with gastric cancer, there was no association between elevated PLR and overall survival: the hazard ratio was 0.99 (95% CI = 0.9–1.1) as described by Xu et al. [85]. In another meta-analysis comprising 14 cohorts and 6280 cases, PLR was associated with poor overall survival (HR 1.3; 95% CI 1.1–1.5) but not with worse cancer-free survival (HR 1.6; 95% = CI 0.9–2.9). High PLR predicted poor survival in Caucasians, patients receiving chemotherapy and patients at advanced stage [86].

In parallel with NLR research, diversity of cut-off levels have been applied in PLR studies (**Table 3**).

In 377 patients who underwent curative resection for gastric cancer, PLR was independently associated with the development of post-operative complications [64].

3.2. Association with tumour features

3.2.1. Local tumour spread: T

PLR has been evaluated for the association with tumour features, mainly—TNM parameters, representing the oncological mainstay. The association between high PLR and deeper invasion has been confirmed in 162 patients diagnosed with resectable gastric cancer [16], in a larger cohort of 451 surgically treated gastric cancer patients [83] and in a multicentre study of 245 gastric cancer patients [61]. In a meta-analysis of 8 studies comprising 4513 patients with gastric cancer, elevated PLR also showed association with deeper invasion (T3–T4). The relevant odds ratios was 2.01 (95% CI 1.49–2.73) as reported by Xu et al. [85]. In addition, in a large cohort of 451 surgically treated gastric cancer patients, high PLR was associated with larger tumour size [83].

3.2.2. Metastases in regional lymph nodes: N

In patients diagnosed with resectable gastric cancer, high PLR correlated with higher number of lymph node metastases [16]. The association between high PLR and presence of lymph node metastasis was re-confirmed by a meta-analysis of 8 studies comprising 4513 patients with gastric cancer. Elevated PLR showed association with lymph node metastasis with the relevant odds ratio of 1.50 (OR 1.24–1.82) as reported by Xu et al. [85]. In another meta-analysis comprising 14 cohorts and 6280 cases, elevated PLR also was significantly associated with lymph node metastases [86]. However, in a multicentre study of 245 gastric cancer patients, PLR was not associated with N [61].

PLR has been investigated as predictive factor for lymph node metastases in a cohort of surgically treatable gastric cancer comprising 492 patients. PLR was identified as an independent predictive factor for lymph node metastasis and along with other independent prognostic factors that can be determined preoperatively was included in scoring system. This complex

Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Patients with confirmed GC diagnosis	103	170	Median	OS	Kaplan-Meier analysis	PLR is associated with worse OS in advanced but not local GC	[56]
Patients with confirmed GC diagnosis	245	160	Ref. [87]	OS	Kaplan-Meier analysis Multicentre study	PLR correlated with T and stage but not survival	[61]
Surgically treated GC							
GC patients subjected to curative resection	873	117	ROC analysis	OS	Kaplan-Meier analysis	Higher PLR is associated with worse OS	[30]
Operable GC patients	492	155.67	ROC analysis	N	Multivariate	PLR was an independent factor predicting N+ and was incorporated in complex score	[55]
Operable patients with early GC	312	106	ROC analysis	N	Multivariate	PLR was an independent factor predicting N+ and was incorporated in complex score	[72]
Surgically treated GC	207	3-tiered complex scoring	ND	OS CFS	Multivariate	PLR was associated with OS and CFS by univariate but not multivariate analysis	[63]
GC patients undergoing gastrectomy	632	140	ROC analysis	OS	Multivariate	PLR was associated with OS by univariate but not multivariate analysis	[45]

Study group		Cut-off		Study target	Level of justification	Main conclusions	References
Characteristics	Size	Value	Approach				
Resectable GC	162	208	Median	OS, CFS	Kaplan-Meier analysis	Higher PLR is associated with worse OS and CFS	[16]
GC treated by total or subtotal gastrectomy with lymphadenectomy	389	132	ROC analysis	OS, CFS, CSS	Multivariate	Higher PLR is significantly associated with worse OS, CFS, CSS	[47]
Advanced, unresectable and/or metastatic GC							
Unresectable, advanced GC, treated by chemotherapy	120	235	Median	OS PFS	Kaplan-Meier analysis Multivariate	Higher baseline PLR or increase of PLR after first-line chemotherapy is associated with worse OS and CFS	[38]
Unresectable, advanced GC, treated by chemotherapy	120	235	Median	Response to chemotherapy	χ^2 test	Lower baseline PLR or lower PLR after first-line chemotherapy was associated with improved response to chemotherapy	[38]
Metastatic GC treated by chemotherapy	109	160	Refs. [40, 58]	OS PFS	Kaplan-Meier analysis	High PLR is significantly associated with worse OS and PFS	[67]

Abbreviations: GC, gastric cancer; OS, overall survival; PLR, platelet to lymphocyte ratio; Ref, reference; T, local spread of primary gastric cancer by tumour-nodes-metastasis (TNM) classification; ROC, receiver operating characteristic curve; N, regional lymph node status in respect to metastases by (TNM) classification; N+, presence of metastases in regional lymph nodes; ND, no data available; CFS, cancer-free survival; CSS, cancer-specific survival.

Table 3. Cut-offs of PLR in gastric cancer studies.

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score consisted of NLR (cut-off 1.59), PLR (cut-off 155.67), T/depth of invasion, macroscopic type according to Bormann and tumour size [55].

As previously outlined, lymph node status is crucial to select the most appropriate treatment in early gastric cancer. PLR has been analysed in this context. In a retrospective assessment of 312 early gastric cancer cases subjected to surgical treatment, high PLR along with high NLR was significantly associated with lymph node metastases. Although both PLR and NLR showed this association by univariate analysis, only PLR was identified as an independent risk factor by multivariate analysis. Thus PLR, but not NLR was included in a complex score. The scoring system was based on the identified independent risk factors: PLR (cut-off 106, based on ROC analysis), age, tumour size, grade and depth of invasion and successfully validated in a prospective training set [72].

3.2.3. TNM stage

In patients diagnosed with resectable gastric cancer, high PLR correlated with higher stage [16]. The association between high PLR and higher stage was confirmed in a multicentre study of 245 gastric cancer patients [61]. When a meta-analysis of 8 studies was performed comprising data on 4513 patients with gastric cancer, elevated PLR showed association with advanced cancer stage (III–IV). The relevant odds ratios was 1.99 (95% CI 1.60–2.46) as reported by Xu et al. [85].

Generally, PLR can accurately reflect tumour burden. In the study carried out by Cetinkunar et al., the 228 cases were classified as early vs. advanced and non-metastatic vs. metastatic ones. PLR could discriminate the groups in both models. The mean PLR values were 160.3 in early and 231.6 in advanced gastric cancer; 192.7 in non-metastatic and 251.0 in metastatic cases [88].

3.3. The diagnostic role of PLR

The diagnostic role of PLR has been explored as well. Thus, the mean values of PLR were significantly higher in gastric cancer patients than in healthy controls [16, 18]. The parameter might seem promising as it is not affected by smoking in contrast to NLR [81].

3.4. Meta-analyses of PLR in gastric cancer

Several meta-analyses of PLR have been devoted to PLR in gastric cancer, yielding partially conflicting results. In a meta-analysis of 8 studies comprising 4513 cases of gastric carcinoma, elevated PLR correlated with lymph node metastasis, deeper invasion (T3–T4) and advanced cancer stage (III–IV) but it was not predictor of overall survival. The relevant odds ratios were 1.50 (95% CI = 1.24–1.82) for N+, 2.01 (95% CI = 1.49–2.73) for T3–T4 and 1.99 (95% CI = 1.60–2.46) for stage III–IV [85].

Fourteen cohorts and 6280 cases were re-evaluated within the frames of another meta-analysis. Authors found out that PLR was associated with poor overall survival but not with cancer-free survival. High PLR predicted poor survival in Caucasians, patients receiving

chemotherapy and patients at advanced stage. Despite the controversies regarding survival, the association with lymph node metastases was reconfirmed [86].

Zhou et al. carried out a general meta-analysis devoted to the prognostic value of PLR in different cancers [89]. There was significant association between elevated PLR and worse overall survival (hazard ratio 1.60; 95% CI = 1.35–1.90). In the subgroup of gastric cancer, the HR was 1.35 (95% CI 0.80–2.25).

4. Peripheral blood monocytes in gastric cancer assessment

Although macrophages are a significant component of tumour microenvironment, quite few studies have been devoted to the prognostic role of monocytes in relation with other cells in peripheral blood of gastric cancer patients.

However, in a recent large study enrolling 3243 gastric cancer patients, high monocyte to white cell ratio (MWR) was identified as an independent prognostic factor of poor survival. In the same study, high NLR, high PLR, high monocyte to lymphocyte ratio, high neutrophil to white cell ratio, low lymphocyte to white cell ratio (LWR) were associated with survival in univariate analysis, but only low LWR and high MWR were independent prognostic factors for poor survival [90].

In gastric cancer patients who have undergone gastrectomy, decreased lymphocyte to monocyte ratio (LMR) was significantly associated with worse overall survival, cancer-specific survival and cancer-free survival. The cut-off was estimated by ROC analysis and was 4.95. However, as a prognostic factor for overall survival, cancer-specific survival and cancer-free survival, LMR was not superior to NLR [47].

5. Glasgow prognostic score in gastric cancer

Glasgow prognostic score is considered the prognostic milestone of SIR assessment in malignant tumours [91]. It is detected on the basis of the prototypic acute phase protein, C-reactive protein and albumin levels in blood serum. CRP is a non-specific, but sensitive marker of systemic inflammatory response, produced as a response to pro-inflammatory cytokines including interleukins IL-1 and IL-6 as well as tumour necrosis factor TNF. Hypoalbuminemia can be caused by malnutrition and cancer cachexia or by systemic inflammation [68]. GPS includes both estimates of elevated acute phase response and malnutrition, resulting in considerable sensitivity [68]. Later, two alterations of Glasgow prognostic score have been developed—the modified GPS and high-sensitivity GPS. In the modified GPS, albumin level influences the score only if CRP is increased [31]. However, the definitions also show variability between authors [92]. High-sensitivity GPS differs from the original GPS by lower cut-off level for CRP [93]. The definitions of GPS and its modifications are summarised in **Table 4**.

5.1. Glasgow prognostic score and survival

Glasgow prognostic score has high informativity both in surgically treatable and advanced, unresectable and/or metastatic gastric cancer. Thus, evaluating Glasgow prognostic score, NLR and PLR in 324 patients with resected stage III gastric adenocarcinoma, only Glasgow prognostic score along with TNM stage was independently associated with overall and cancer-free survival [43]. In 207 gastric cancer patients who underwent surgery, GPS along with NLR, PLR, CRP, albumin and TNM stage were significantly associated with overall and cancer-free

Score	Definition	References
Glasgow prognostic score		[68]
0	CRP < 10 mg/L AND albumin ≥ 35 g/L	
1	One high-risk finding: CRP ≥ 10 mg/L OR albumin < 35 g/L	
2	Both high-risk findings: CRP ≥ 10 mg/L AND albumin < 35 g/L	
Modified Glasgow prognostic score		[31] [94]
0	CRP ≤ 10 mg/L irrespective of albumin level	
1	Increased CRP on the background of normal albumin level: CRP > 10 mg/L AND albumin ≥ 35 g/L	
2	Increased CRP and hypoalbuminemia: CRP > 10 mg/L AND albumin < 35 g/L	
Modified Glasgow prognostic score by Hirashima et al.		[92]
0	CRP ≤ 5 mg/L AND albumin ≥ 38 g/L	
1	One high-risk finding: CRP > 5 mg/L OR albumin < 38 g/L	
2	Both high-risk findings: CRP > 5 mg/L AND albumin < 38 g/L	
High-sensitivity Glasgow prognostic score		[93]
0	CRP ≤ 3 mg/L AND albumin ≥ 35 g/L	
1	One high-risk finding: CRP > 3 mg/L OR albumin < 35 g/L	
2	Both high-risk findings: CRP > 3 mg/L AND albumin < 35 g/L	

Abbreviations: CRP, C-reactive protein.

Table 4. Glasgow prognostic score and its modifications.

survival. However, only GPS and TNM were independent prognostic factors; therefore in this study, GPS was favoured as the most informative SIR parameter [63]. By multivariate analysis, GPS was independent predictor of overall survival in 425 surgically treated gastric cancer patients who had normal serum levels of carcinoembryonic antigen [91]. In a large cohort of 1017 patients subjected to curative resection of gastric cancer, GPS was an independent prognostic factor for overall survival [95].

In a homogeneous group of 88 gastric cancer patients undergoing only surgical treatment, increasing GPS was an independent predictor of worse overall survival and perioperative mortality. The median survival by GPS 0 vs. 1 vs. 2 was 25.2 vs. 15.3 vs. 5.8 months. The perioperative mortality in the same subgroups was 0.0% vs. 20.0% vs. 80.0% [96]. However, the GPS capacity to predict complications is not straightforward. In contrast with the previous report, assessing 1017 patients subjected to curative resection of gastric cancer, GPS was not associated with the incidence of complications [95].

Variations of GPS have been successfully tested. In a large group of 236 gastric cancer patients who underwent gastrectomy, high-sensitivity GPS after surgery was a significant prognostic factor for overall survival while the pre-operative level was less informative [93]. Modified Glasgow prognostic score was an independent prognostic factor for overall and cancer-free survival in 102 consecutive gastric cancer patients treated with resection [97]. Modified GPS was independent predictor of cancer-specific survival in 120 surgically treated gastric cancer patients [98]. The role of modified GPS in stage IV gastric cancer was confirmed by Mimatsu et al., who evaluated cancer-specific survival in 42 patients at stage IV, treated by palliative gastrectomy and chemotherapy. The modified GPS was associated with cancer-specific survival [99]. Pre-operative modified GPS retained prognostic value in elderly patients [92]. Assessing 1710 surgically treated patients with gastric cancer, modified GPS was associated with postoperative mortality [94]. However, high-sensitivity modified GPS was found to be superior prognostic predictor for overall survival compared to modified GPS having especially high prognostic importance in stage I and IV [100].

By some study designs, the informativity of GPS has been estimated lower. In comparison with NLR-PLR score, modified Glasgow prognostic index was not an independent prognostic factor for survival of stage I–I gastric cancer patients [31]. In 224 patients receiving chemotherapy for advanced gastric cancer, NLR and diffuse type histology were independent prognostic factors for overall survival while GPS was not. However, the median survival still was significantly longer in patients having GPS 0 in contrast to those having GPS 1 or 2 [24].

GPS and its variations retain the prognostic value in advanced cases. In 402 patients with advanced gastric adenocarcinoma treated by palliative chemotherapy, GPS was an independent predictor of overall survival [101]. GPS was an independent predictor of cancer-specific and progression-free survival in 83 patients having advanced gastric cancer and receiving chemotherapy. In low GPS group, favourable response to chemotherapy can be obtained [102]. In patients affected by stage IV gastric cancer and treated by chemotherapy, higher modified Glasgow prognostic score was associated with shorter overall survival (along with

lower level of albumin, elevated concentration of C-reactive protein, high absolute number of neutrophilic leukocytes and elevated NLR). In multivariate analysis, modified Glasgow prognostic score was identified as an independent prognostic factor along with NLR, presence of lymph node metastasis and histological subtype [69]. In 68 patients affected by advanced gastric cancer and treated by chemotherapy with or without irradiation, high GPS predicted shorter survival [103]. High GPS was an independent prognostic factor in 384 inoperable advanced or metastatic gastric cancer patients treated with chemotherapy. The value of GPS was higher than that of NLR, PLR or CRP [68]. In 125 patients with recurrent or metastatic gastric cancer placed on single agent chemotherapy because of poor performance status, GPS had independent prognostic value [104]. In 91 metastatic or recurrent gastric cancer patients treated by palliative chemotherapy, GPS was significantly associated with survival. The differences were also biologically remarkable: the median survival was 12.3 months if GPS was 0 but only 2.9 if GPS was 2 [105].

Recently, a meta-analysis was carried out including 14 studies and 5579 gastric cancer patients. High GPS was significantly associated with poor overall survival (hazard ratio 1.51; 95% CI 1.37–1.66), and disease-free survival (HR 1.45; 95% CI = 1.26–1.68) as reported by Zhang et al. [106].

Glasgow prognostic score has been further developed into different complex scores. Thus, complex predictive score regarding survival was elaborated, based on NLR and modified Glasgow prognostic score in patients with metastatic gastric adenocarcinoma treated by chemotherapy, after independent prognostic value of both parameters was justified in a group of 256 patients [26]. The design of studies devoted to GPS in gastric carcinoma is summarised in **Table 5**.

5.2. Association with tumour features

5.2.1. Local tumour spread: T

In 88 patients undergoing only surgical treatment, increasing GPS was associated with higher T and resection line status [96]. In a recent meta-analysis, association between high GPS and high TNM stage was found. Although the association with lymph node metastases (OR 4.60; 95% CI = 3.23–6.56) was significant, there was no association with T [106].

5.2.2. Metastases in regional lymph nodes: N

In a recent meta-analysis including 14 studies and 5579 gastric cancer patients, high GPS was significantly associated with presence of lymph node metastases (OR 4.60; 95% CI = 3.23–6.56) as well as with lymphatic (OR 3.04; 95% CI = 2.00–4.62) invasion [106].

5.2.3. Presence of distant metastases: M

In a homogeneous group of 88 gastric cancer patients undergoing only surgical treatment, increasing GPS was associated with presence of synchronous distant metastases and venous invasion [96].

Group		Score	Target	References
Characteristics	**Size**			
Meta-analysis	14 studies 5579 patients	GPS	OS, CFS TNM stage, N Lymphatic invasion Venous invasion	[106]
Meta-analysis	7 studies 3206 patients	mGPS	OS Lymphatic invasion Venous invasion	[109]
Original studies of surgically treated GC				
Stage I–II GC, treated by curative resection	305	mGPS	OS	[31]
GC undergoing surgical treatment only	88	GPS	T, M, R; Venous invasion Perioperative mortality OS	[96]
GC patients subjected to surgical treatment	207	GPS	OS	[63]
Surgically treated GC patients with normal CEA level	425	GPS	OS	[91]
GC patients subjected to gastrectomy	236	HS-GPS	Clinical and pathological parameters OS	[93]
GC patients subjected to gastrectomy	552	GPS HS-GPS	Clinical and pathological parameters OS	[100]
Consecutive GC patients undergoing surgical treatment	102	mGPS	OS CFS	[97]
GC patients subjected to gastrectomy	294	mGPS	OS	[92]
Surgically treated GC patients	1017	GPS	OS Post-operative complications	[95]
Surgically treated GC patients	1710	mGPS	OS	[94]
Surgically treated GC patients	120	mGPS	CSS	[98]
Surgically treated GC patients, stage III	324	GPS	CFS OS	[43]

Group		Score	Target	References
Characteristics	**Size**			
Original studies of advanced GC				
Chemotherapy for advanced GC	224	GPS	OS	[24]
Advanced GC treated with chemo- or chemoradiotherapy	68	GPS	OS	[103]
Metastatic GC treated by chemotherapy	256	mGPS	OS	[26]
GC patients at stage IV, treated by palliative gastrectomy	42	mGPS	CSS	[99]
Metastatic or recurrent GC patients considered for palliative chemotherapy	91	GPS	OS	[105]
Inoperable advanced or metastatic GC patients receiving first-line chemotherapy	384	GPS	OS	[68]
Advanced GC patients treated by single agent palliative chemotherapy due to poor performance	125	GPS	OS	[104]
Metastatic GC treated by palliative chemotherapy	104	mGPS	OS	[69]
Advanced GC treated by chemotherapy	83	GPS	CSS, PFS	[102]
Advanced recurrent or metastatic GC patients receiving first-line palliative chemotherapy	402	GPS	PFS OS	[101]
GC patients with vs. without cachexia vs. controls	90 (30 vs. 30 vs. 30)	GPS	Cachexia, adipokines	[107]
Inoperable GC subjected to chemotherapy	71	GPS	Predicting metastasis	[108]

Abbreviations: GC, gastric cancer; mGPS, modified Glasgow prognostic score; OS, overall survival; GPS, Glasgow prognostic score; T, local tumour spread by tumour-nodes-metastasis (TNM) classification; M, presence of distant metastasis by TNM classification; R, resection line status; CEA, carcinoembryonic protein; HS-GPS, high sensitivity Glasgow prognostic score; CFS, cancer-free survival; CSS; cancer-free survival; PFS, progression-free survival; TNM, tumour-nodes-metastasis classification; vs, versus; N, regional lymph node status by TNM classification.

Table 5. The design of studies devoted to Glasgow prognostic score in gastric cancer.

5.2.4. TNM stage

Assessing 1710 patients with gastric cancer, modified GPS was associated with advanced stage [94]. Elevated GPS has been reported in gastric cancer patients having cachexia; higher stage was also observed in cachectic patients [107]. However, GPS did not differ between metastatic and non-metastatic gastric cancer cases. Although the study group was small consisting of only 43 metastatic and 28 non-metastatic cases, a novel score based on pre-albumin and CRP, showed significant differences [108]. In a recent meta-analysis including 14 studies and 5579 gastric cancer patients, elevated GPS was significantly associated with high TNM stage (odds ratio 3.09; 95% CI = 2.11–4.53) as reported by Zhang et al. [106].

5.2.5. Manifestations of invasive growth

In a homogeneous group of 88 gastric cancer patients undergoing only surgical treatment, increasing GPS was associated with presence of venous invasion [96]. In a recent meta-analysis including 14 studies and 5579 gastric cancer patients, high GPS was significantly associated with lymphatic (OR 3.04; 95% CI = 2.00–4.62) and venous (OR 3.56; 95% CI = 1.81–6.99) invasion [106]. In a meta-analysis devoted to the modified Glasgow prognostic score, higher rates of lymphatic (OR 2.51; 95% CI = 1.80–3.51) and venous (OR 2.63; 95% CI = 1.35–5.11) invasion were found in patients in whom the score was at least 1 [109].

5.3. Meta-analyses of Glasgow prognostic score and its modifications in gastric cancer

Recently, a meta-analysis was carried including 14 studies and 5579 gastric cancer patients. High GPS was significantly associated with poor overall survival (hazard ratio 1.51; 95% CI 1.37–1.66), and disease-free survival (HR 1.45; 95% CI = 1.26–1.68) as well as with high TNM stage (odds ratio 3.09; 95% CI = 2.11–4.53), N+ (OR 4.60; 95% CI = 3.23–6.56), lymphatic (OR 3.04; 95% CI = 2.00–4.62) and venous (OR 3.56; 95% CI = 1.81–6.99) invasion [106].

In a meta-analysis devoted to the modified Glasgow prognostic score, worse overall survival (odds ratio OR 2.54; 95% CI = 1.62–3.98 for mGPS = 1 and OR 12.02; 95% CI 6.79–21.28 for mGPS = 2), higher rates of lymphatic (OR 2.51; 95% CI = 1.80–3.51) and venous (OR 2.63; 95% CI = 1.35–5.11) invasion were found in patients in whom the score was not zero [109].

6. Fibrinogen in gastric cancer evaluation

The association between malignant solid tumours and disturbances of blood clotting is well-known. In addition, fibrinogen is an acute phase reactant glycoprotein [110]. Consequently, the presence of hyperfibrinogenaemia in gastric cancer patients can be almost expected. Indeed, increased levels of fibrinogen have been identified and explored regarding the prognostic value or the association with tumour parameters. The studies range from historical to up-to-dated and cover aspects of patient's survival, tumour progression, diagnostic value, estimates of tumour burden and insights into novel treatment options.

Elevated concentration of fibrinogen in the serum of gastric carcinoma patients has negative prognostic value regarding several aspects of survival—overall and cancer-free survival. The independent prognostic value of increased fibrinogen level has been demonstrated in 351 surgically treated gastric cancer patients. The hazard ratio was 2.61 (95% CI = 1.18–5.76) as reported by Suzuki et al. [111]. The independent prognostic role was confirmed in another large surgically treated cohort of 1196 gastric cancer patients [112]. Applying ROC-identified cut-off (3.9 g/L), high fibrinogen level was significantly associated with overall survival in multivariate analysis [113]. In patients who underwent curative gastrectomy, hyperfibrinogenaemia (reaching or exceeding 350 mg/dL) was associated not only with overall but also cancer-free survival. By multivariate analysis, fibrinogen level again was an independent prognostic factor along with pTN [33].

Classic studies have explored the diagnostic meaning of hyperfibrinogenaemia resulting in conclusion that fibrinogen level is significantly elevated in gastric cancer patients but not in individuals having gastric or duodenal peptic ulcer. Such reports stem back as far as to 1975 [114]. Later, it was repeatedly confirmed that fibrinogen levels in gastric cancer are higher than in controls, even if the tumour was non-metastatic. The mean levels in cancer patients vs. control individuals were 505 vs. 336 mg/dL [115]. Nowadays, the ongoing research has identified fibrinogen fragments that could potentially serve as serum markers of gastric cancer. Fibrinogen fragments, e.g., carboxyl terminal fraction of fibrinogen alpha, have been tested as a serum marker of gastric cancer in comparison with healthy controls and individuals affected by chronic gastritis [116, 117].

A 15-amino acid peptide of the fibrinogen alpha chain, fibrinostatin, has anti-angiogenic properties; thus therapeutic applications have been hypothesised [118].

Regarding the local events within the tumour, fibrinogen has been identified in tumour stroma as early as 1984 [119, 120] while fibrin and D-dimers are found in the invasive front [120].

Fibrinogen level parallels the tumour burden, correlates with advanced TNM stage [112] and is associated with adjacent organ involvement [121]. In a recent considerable cohort of 1090 gastric cancer patients treated by gastrectomy, high fibrinogen level (exceeding the ROC-identified cut-off at 3.9 g/L) was significantly associated with tumour size, T, N and TNM stage [113]. Fibrinogen shows statistically significant associations with the invasion depth of gastric cancer confirmed by several other studies focusing on T [122–124]. Several studies have identified meaningful association with presence of metastasis in lymph nodes [122–124]. The association with tumour spread has also been confirmed, regarding the presence of distant metastases [122].

The logical next step is incorporation of fibrinogen measurements into combined scores that could be used to assess the prognosis or tumour spread. A complex score comprising evaluation of hyperfibrinogenemia (exceeding 400 mg/dL) and elevated NLR (exceeding 3.0) was associated with shorter survival. The combined score showed significantly different results in patients developing progressive disease despite chemotherapy or chemoradiotherapy [103]. Similar score comprising evaluation of hyperfibrinogenemia (reaching or exceeding 305 mg/dL) and elevated NLR (reaching or exceeding 2.34) was significantly associated with invasion depth, lymph node metastasis, lymphovascular invasion and stage [110]. Coagulation score based on

the assessment of fibrinogen and D-dimer levels, was significantly associated with overall and cancer-free survival as well as with recurrence and development of liver metastases [125].

Other blood clotting parameters show similar associations with patient's prognosis and tumour burden. Thus, D-dimers [126, 127] and thrombocytosis [128] have prognostic role in gastric cancer. In turn, D-dimers and prothrombin time are associated with lymph node involvement [129].

7. Application of SIR in complex scoring systems for gastric cancer

SIR parameters have been incorporated in diverse complex scores that allow reaching higher diagnostic value (see also **Tables 6–7**).

A complex score, based on fibrinogen (cut-off 400 mg/dL) and NLR (cut-off 3.0) levels, was applied to predict the effect of chemotherapy or chemoradiotherapy in advanced gastric cancer. The created score indeed was significantly higher in patients having cancer progression during treatment; it also was an independent prognostic factor by multivariate analysis [103]. The same authors have elaborated similar combined score, based on the same parameters which by different cut-off levels are adjusted for another research target. The fibrinogen-NLR score at cut-off 305 mg/dL and 2.34, respectively, was significantly associated with depth of tumour invasion, lymph node metastasis, lymphatic and venous invasion and tumour stage. The 5-year survival rates by score categories 0 vs. 1 vs. 2 were 92.9, 84.1 and 66.5%; the differences being statistically significant [110].

The coagulation score, recently proposed by Kanda et al., distinguished high-risk patients having low overall and cancer-free survival. High coagulation score was also an independent prognostic factor for recurrence and was associated with liver metastasis as the initial recurrence [125]. It is in accordance with the observation that D-dimer is associated with metastatic tumour spread both in murine gastric carcinoma models and in patients having visceral metastasis [130].

The score developed by Ishizuka et al. was based on platelet count and NLR to predict post-operative survival. The score classified patients into 3 groups: 0 vs. 1 vs. 2 had post-operative survival of 1676 vs. 1310 vs. 1050 days. The differences were statistically significant. The cancer-specific survival also was significantly different by the score levels. The sensitivity and accuracy of the presented score in regard to survival was higher than the informativity of clinical and pathological parameters—carcinoembryonic antigen CEA, CA19-9, venous and lymphatic invasion and lymph node metastasis [29].

NLR-PLR score can be used to assess overall survival in gastric cancer patients diagnosed at stage I–II. This score was an independent prognostic factor while mGPS, the prognostic nutritional index and combination of platelet count and NLR were not. The score had the highest area under ROC curve in comparison with the listed other scores. The hazard ratio associated with NLR-PLR score was 1.51 (95% CI = 1.02–2.24). Interestingly, there was a trend to shorter mean OS in stage I patients having NLR-PLR score of 2 than in stage II patients scored 0: 89 months vs. 127 months. The score retained prognostic value in stage I and II [31].

Target	Score description	References
Lymph node metastases in early gastric cancer	PLR (cut-off 106, based on ROC analysis), age, grade, depth of invasion and tumour size	[72]
Survival of early gastric cancer patients	NLR (cut-off 2.1), PLR (cut-off 120)	[31]
Lymph node metastases	Independent predictive factors (for lymph node metastasis) that can be determined preoperatively: NLR (cut-off 1.59), PLR (cut-off 155.67), T/ depth of invasion, macroscopic type (Bormann), tumour size	[55]
Overall survival	Albumin (cut-off 35 g/L), NLR (cut-off 2.3)	[30]
Cancer-specific survival (CSS) and cancer-free survival (CFS)	Nomogram including independent predicting factors: (1) for CSS: NLR, age, tumour stage, presence of lymph node metastases, presence of distant metastases; (2) for CFS: NLR, tumour stage, presence of distant metastases, family history of gastric cancer; CA 19-9 level.	[47]
Overall survival and chemotherapy response	NLR (cut-off 3.0) and fibrinogen (cut-off 400 mg/dL)	[103]
Prognosis and cancer characteristics	NLR (cut-off 2.34) and fibrinogen (cut-off 305 mg/dL)	[110]
Overall survival	Canton score: [1]prognostic nutritional index (PNI; cut-off 48), platelet count (cut-off 3×10^{11}/L) and NLR (cut-off 1.83)	[45]
Overall and cancer-specific survival	Platelet count and NLR	[29]
Overall and cancer-free survival Recurrence Metachronous liver metastases	Coagulation score: increased level of fibrinogen and D-dimers	[125]
Overall survival	NLR, mGPS and patient-generated subjective global assessment score	[26]

Abbreviations: PLR, platelet to lymphocyte ratio; ROC, receiver operating characteristic curve; NLR, neutrophil to lymphocyte ratio; T, local spread of primary gastric cancer by tumour-nodes-metastasis (TNM) classification; CSS, cancer-specific survival; CFS, cancer-free survival; mGPS, modified Glasgow prognostic score.

[1]PNI = albumin (g/L) + 5 × total lymphocyte count ($\times 10^9$/L).

Table 6. Application of SIR in complex scoring systems for gastric cancer.

The score based on albumin and NLR was elaborated to improve the evaluation of overall survival. The resulting score was independently associated with overall survival. It had higher diagnostic value than NLR, PLR and GPS, as shown by higher area under ROC curve. The overall survival by score values 0 vs. 1 vs. 2 was 44.9% vs. 29.8% vs. 20.3%, respectively [30].

Modified Glasgow prognostic score [31]	
0	CRP ≤ 10 mg/L irrespectively of albumin level
1	Albumin ≥ 35 g/L AND CRP > 10 mg/L
2	Albumin < 35 g/L AND CRP > 10 mg/L
Albumin—NLR score [30]	
0	Albumin ≥ 35 g/L AND NLR < 2.3
1	Albumin ≥ 35 g/L AND NLR ≥ 2.3 OR Albumin < 35 g/L AND NLR < 2.3
2	Albumin < 35 g/L AND NLR ≥ 2.3
NLR—PLR score [31]	
0	Both values are low: NLR < 2.1 AND PLR < 120
1	Only one elevated value: NLR ≥ 2.1 AND PLR < 120 OR NLR < 2.1 AND PLR ≥ 120
2	Both values are elevated: NLR ≥ 2.1 AND PLR ≥ 120
Inflammation and nutrition based score [26]	
0–2	Favourable group
3–4	Intermediate risk
5–6	High risk
	Definitions of the score components: NLR > 3 equals 1, otherwise scored 0 mGPS > 1 equals 3, otherwise scored 0 Patient-Generated Subjective Global Assessment C equals 2, otherwise (A or B) scored 0
Hyperfibrinogenemia—NLR score [103]	
0	NLR ≤ 3.0 AND fibrinogen ≤ 400 mg/dL
1	NLR >3.0 OR fibrinogen > 400 mg/dL
2	NLR >3.0 AND fibrinogen > 400 mg/dL
Hyperfibrinogenemia—NLR score II [110]	
0	NLR < 2.34 AND fibrinogen > 305 mg/dL
1	NLR ≥ 2.34 OR fibrinogen ≥ 305 mg/dL
2	NLR ≥ 2.34 AND fibrinogen ≥ 305 mg/dL
Combined score to predict lymph node metastases [55]	
0–155	Low risk
>156	High risk
	Definitions of the score components: Tumour size ≥ 3 cm scored 39, otherwise scored 0 Macroscopic type: early vs. Borrmann I–II vs. Borrmann III–IV scored 0 vs. 32 vs. 59 PLR > 155.67 scored 28, otherwise scored 0 NLR > 1.59 scored 28, otherwise scored 0 Depth of invasion: T3—4 scored 60, otherwise scored 0
Combined score to predict lymph node metastases [72]	
0–11	Low risk

12–20	High risk
	Definitions of the score components: Age ≥ 65 scored 3, otherwise scored 0 Tumour size ≥ 1.8 cm scored 4, otherwise scored 0 Grade: G3 scored 5, otherwise scored 0 Depth of invasion: submucosa scored 3, while mucosa scored 0 PLR > 106 scored 3, otherwise scored 0
Canton score [45]	
0	No high-risk parameters: [1]PNI ≥ 48 AND NLR ≤ 1.83 AND PLT ≤ 3×10^{11}/L
1	One high-risk parameter: PNI < 48 AND NLR ≤ 1.83 AND PLT ≤ 3×10^{11}/L PNI ≥ 48 AND NLR > 1.83 AND PLT ≤ 3×10^{11}/L PNI ≥ 48 AND NLR ≤ 1.83 AND PLT > 3×10^{11}/L
2	Two high-risk parameters: PNI < 48 AND NLR > 1.83 AND PLT ≤ 3×10^{11}/L PNI < 48 AND NLR ≤ 1.83 AND PLT > 3×10^{11}/L PNI ≥ 48 AND NLR > 1.83 AND PLT > 3×10^{11}/L
3	Three high-risk parameters: PNI < 48 AND NLR > 1.83 AND PLT > 3×10^{11}/L
Platelet count and NLR score [29]	
0	No elevated parameters: PLT ≤ 300×10^{3}/mkL AND NLR ≤ 3
1	One elevated parameter: PLT > 300×10^{3}/mkL OR NLR >3
2	Two elevated parameters: PLT > 300×10^{3}/mkL AND NLR >3
Coagulation score [125]	
0	Normal level of D-dimer AND fibrinogen
1	Increased level of either D-dimer OR fibrinogen
2	Increased level of both D-dimer AND fibrinogen

Abbreviations: CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; mGPS, modified Glasgow prognostic score; T, local spread of primary gastric cancer by tumour-nodes-metastasis (TNM classification), G, grade; PNI, prognostic nutritional index; PLT, platelet count.

[1]PNI = albumin (g/L) + 5 × total lymphocyte count ($\times 10^{9}$/L).

Table 7. The definitions of complex scores.

The inflammation and nutrition-based score was elaborated to predict overall survival in patients diagnosed with metastatic gastric cancer. According to this score, patients were classified into favourable, intermediate and high-risk groups exhibiting the median overall survival of 27.6 vs. 13.2 vs. 8.2 months. The respective two-year survival rates were 52% vs. 16% vs. 3%. The ROC curve analysis confirmed that the novel score has higher informativity than any of its components [26].

Deng et al. elaborated complex nomograms to predict cancer-specific and cancer-free survival in surgically treated gastric cancer patients [47].

Pang et al. developed complex system to predict lymph node metastases based on those tumour and systemic parameters that were independently associated with N+ and could be detected preoperatively. The point system was based on hazard ratios detected by logistic regression analysis. Youden Index was applied to detect the cut-off of the novel combined system. Finally, the developed score had specifity of 72.4%, sensitivity 82.7%, positive predictive value 88.7% and negative predictive value 61.5%. Besides the informative value of the score itself, the mathematical model of score design is flawless [55].

Lou et al. developed score to predict lymph node metastases in early gastric cancer. The scoring system reached reasonable accuracy of 0.817 when evaluating prospective cases [72].

The Canton score was created to predict overall survival after gastrectomy. The novel score possessed higher AUC than the classic parameters. The HR for Canton score values 1 vs. 2 vs. 3 (in comparison to 0) were 1.08 (95% CI = 0.80–1.45) vs. 1.55 (95% CI = 1.15–2.10) vs. 1.64 (95% CI = 1.14–2.36) as reported by Sun et al. [45].

8. Conclusions

Gastric cancer induces systemic inflammatory reaction. The biological background is complex, involving bone marrow activation, development of immune-suppressing immature myeloid cells, generation of pre-metastatic niches and neutrophil extracellular trap formation from externalised DNA network in bidirectional association with platelet activation. These mechanisms have been demonstrated in general studies of carcinogenesis as well as in animal models and human studies of gastric cancer.

Systemic inflammatory reaction can be easily evaluated by simple, patient friendly and economically non-demanding blood tests practically lacking complications. These tests could be broadly classified as cellular and protein-based. Among cellular tests, neutrophil to lymphocyte ratio is the most widely explored followed by platelet to lymphocyte ratio. Glasgow prognostic score is the prototype of protein-based test.

Although controversies still exist, most researchers have recognised the independent prognostic value of NLR, encompassing overall, cancer-specific, cancer-free or progression-free survival both in early and advanced gastric cancer. NLR can bring significant prognostic information in surgically treated individuals, in case of combined treatment and in patients receiving only chemotherapy.

NLR shows associations with TNM parameters. Thus, it can be incorporated in patient's evaluation for tumour burden. The possibility to predict serosal invasion, peritoneal and/or metastatic spread can be an adjunct to avoid inappropriate attempts of technically impossible gastrectomy. Lymph node status can be predicted as well.

PLR and GPS also possess diagnostic and prognostic information in gastric cancer patients, as well as show correlations with tumour parameters.

The cut-offs for NLR and PLR show significant variability. Mostly, the cut-off levels are identified either based on ROC analysis and Youden Index, or the median is selected for cut-off. Less frequently, the 75th percentile is applied.

Combined scores appear, based on SIR data in complex with patient's characteristics as well as tumour features. The informativity of such scores is generally higher than that of separate components; therefore, wider testing of these scores in different populations should be necessary to bring the promising novel scores to clinical application.

Abbreviations

AUC	Area under curve
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CI	Confidence interval
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
G	Grade
GPS	Glasgow prognostic score
HR	Hazard ratio
IL	Interleukin
LMR	Lymphocyte to monocyte ratio
LWR	Lymphocyte to white cell ratio
M	Presence or absence of distant metastases in accordance with TNM classification
mGPS	Modified Glasgow prognostic score
MWR	Monocyte to white cell ratio
N	Status of regional lymph nodes regarding metastases in accordance with TNM classification
NLR	Neutrophil to lymphocyte ratio
OR	Odds ratio
PLR	Platelet to lymphocyte ratio

R	Resection line status regarding presence or absence of tumour
ROC	Receiver operating characteristics
SIR	Systemic inflammatory reaction
T	Local tumour spread in accordance with TNM classification
TNF	Tumour necrosis factor
TNM	Tumour-node-metastasis classification to reflect the extent of tumour growth and spread
USA	The United States of America
vs.	versus

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