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Systemic inflammatory markers as predictors of survival and postoperative complications in patients with head and neck squamous cell carcinoma: a scoping review

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Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide, with a high mortality rate. It is often treated with primary surgery. There is a well-established relationship between the immune-inflammatory response and tumors. Currently, peripheral blood-based biomarkers are extensively studied as prognostic factors in HNSCC patients. Here, we reviewed the studies assessing the predictive role of preoperative neutrophil-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammatory index (SII), systemic inflammatory marker index (SIM), white blood cell count (neutrophils, lymphocytes, monocytes, platelet count), and albumin for overall survival (OS), disease-free survival (DFS), and postoperative complications. PubMed was searched for studies that assessed the role of these biomarkers in surgically treated HNSCC patients. The review included 32 studies. Higher NLR and SIM were most strongly associated with adverse OS and DFS, while a higher PLR was associated with adverse DFS. A lower lymphocyte count was associated with adverse OS. Only dNLR was significantly associated with the occurrence of postoperative complications. Other analyzed biomarkers did not show such a consistent pattern but did demonstrate some level of association with survival outcomes. Substantial heterogeneity and variability in cutoff values underscore the need for further standardized studies before clinical implementation.

INTRODUCTION

Head and neck cancer is the seventh most common malignancy worldwide, with squamous cell carcinoma accounting for approximately 90% of the cases (1). It comprises carcinomas arising from the epithelial lining of the oral cavity, pharynx, and larynx (1). The most important risk factors are alcohol consumption and tobacco exposure (2). Human papillomavirus (HPV) infection plays a crucial role in head and neck squamous cell carcinoma (HNSCC); therefore, HPV stratification has been added to the 8th edition of the cancer staging manual of the American Joint Committee on Cancer as HPV-related HNSCC has distinct risk factors, prognosis, and behavior (3). HNSCC is frequently diagnosed in an advanced stage and is associated with relatively high mortality rates, which underscores the need for improved prognostic tools (1).

The inter-relations between tumors and the immune system, specifically inflammation, have long been a subject of research (4). Malignant progression is influenced by inflammatory cytokines and chemokines produced by tumor cells and/or tumor-associated leucocytes and platelets, as well as by the systemic inflammatory response (4). Accumulating evidence suggests that inflammatory cells can promote tumor progression by enhancing angiogenesis, cancer cell proliferation, and invasiveness, through the production of growth factors, survival factors, enzymes, and other mediators (5).

The interplay between inflammatory and immune responses and tumor biology was leveraged for prognostic assessment, which led to the development of easy-to-use peripheral blood inflammatory markers. Hence, the roles of white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) were evaluated in various solid tumors (such as lung cancer, esophageal cancer, and melanoma) (6-8). More indices and markers have been developed since: systemic immune-inflammatory index (SII), systemic inflammatory marker index (SIM), derived NLR (dNLR), and C-reactive protein (CRP)/albumin ratio (CAR). There is a growing body of literature on these biomarkers in HNSCC, with many differing findings and varying treatment modalities. However, no single review comprehensively synthetized all these biomarkers with a focus on surgically treated patients. Therefore, we aimed to review the studies on the prognostic role of NLR, dNLR, PLR, LMR, SII, SIM, neutrophils, lymphocytes, monocytes, platelet count, and albumin levels on survival and postoperative complications. Surgery is often the primary treatment modality in these tumors, so we restricted our analysis to patients undergoing primary surgical treatment.

MATERIALS AND METHODS

PubMed was searched for articles that assessed the predictive role of NLR, dNLR, PLR, LMR, SII, SIM, neutrophils, lymphocytes, monocytes, platelet count, and albumin levels on survival and postoperative complications in surgically treated HNSCC patients. The initial search yielded 218 results (Table 1). The results were then limited to articles published in the last 10 years to ensure the most up-to-date findings, yielding 206 results. When the search was limited to articles published in English, it resulted in 201 articles. Finally, the results were filtered to include only studies with human subjects, leaving 147 articles in the final analysis. The final search was performed on November 29, 2025 at 6:15 pm.

The PICO framework, inclusion, and exclusion criteria are shown in in Table 2.

The screening process is illustrated in Figure 1. In the initial screening of titles and abstracts, 96 studies were excluded based on the exclusion criteria; therefore, 51 papers were included in the full-text screening. Nine

TABLE 1. Terms and steps used in PubMed search*

Search steps	Search terms	Hits
1	(Head and neck squamous cell carcinoma OR HNSCC) AND (Systemic Inflammatory Marker OR SIM OR SII OR NLR OR dNLR OR PLR OR LMR) AND (prognosis OR overall survival OR disease-free survival) AND surgery	218
2	Filter: a time frame of the last 10 years	206
3	Filter: English language	201
4	Filter: Human subjects	147

* Abbreviations: **HNSCC** – head and neck squamous cell carcinoma, **NLR** – neutrophil-to-lymphocyte ratio, **LMR** – lymphocyte-to-monocyte ratio, **PLR** – platelet-to-lymphocyte, **SII** – systemic immune-inflammatory index, **SIM** – systemic inflammatory marker index, **dNLR** – derived NLR, **Neu** – neutrophils, **Lym** – lymphocytes, **Mono** – monocytes, **Plt** – platelet count.

TABLE 2. Inclusion and exclusion criteria used in the review*

Inclusion criteria	
Population	Subjects of any age, gender, or ethnicity with a head and neck squamous cell carcinoma (oral cavity, oropharynx, hypopharynx, larynx, cervical esophagus) that underwent surgery as the primary treatment modality without neo-adjuvant therapy
Intervention	Studies evaluating at least one blood-based biomarker of the following: NLR, dNLR, PLR, LMR, SII, SIM/SIRI, neutrophils, lymphocytes, monocytes, platelets, albumin, total proteins) measured preoperatively
Comparator	Comparison of specific cutoff values of the measured markers and indices
Outcomes	Overall survival, disease-free survival, postoperative complications
Study design	Retrospective and prospective cohort studies, case-control or cross-sectional studies, case series, case reports
Exclusion criteria	
	Explicitly focusing on p-16 positive HNSCC Enrolling subjects with hematologic diseases or acute inflammatory diseases Focusing on subjects with distant metastases or multiple primary tumors Focusing only on local inflammatory markers and indices rather than systemic (tumor microenvironment) Primary treatment modality other than surgery

* Abbreviations: **HNSCC** – head and neck squamous cell carcinoma, **NLR** – neutrophil-to-lymphocyte ratio, **LMR** – lymphocyte-to-monocyte ratio, **PLR** – platelet-to-lymphocyte, **SII** – systemic immune-inflammatory index, **SIM** – systemic inflammatory marker index, **dNLR** – derived NLR, Neu – neutrophils, **Lym** – lymphocytes, **Mono** – monocytes, **Plt** – platelet count

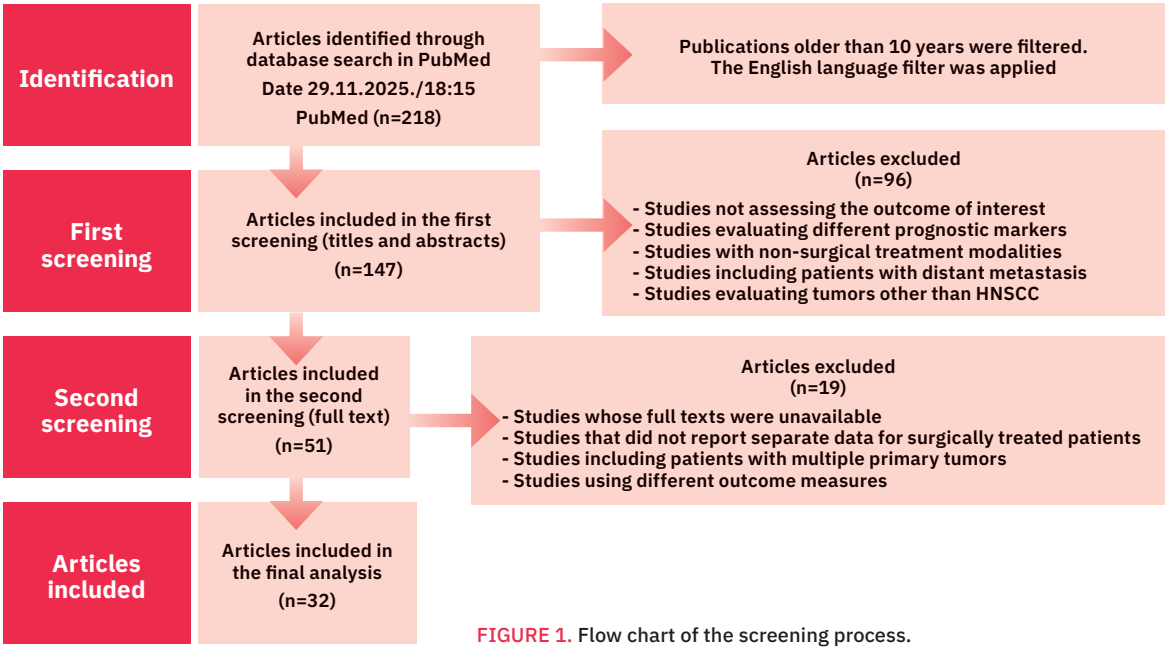

FIGURE 1. Flow chart of the screening process.

articles for which the complete text was unavailable were excluded from further analysis. The other papers were analyzed in full, and 10 articles were excluded, which left 32 articles in the final analysis (Figure 1). The screening process was done twice by the same author.

The ratios and indices used as biomarkers in the analysis are shown in Table 3. Four studies used the systemic inflammatory response index (SIRI) (9-12), which is equivalent to the systemic inflammation marker (SIM); therefore, it is referred to as SIM throughout this review (Table 3).

The outcome measures used in the analysis were overall survival (OS) (the time from surgery to death of any cause) (13), disease-free survival (DFS) (the time from surgery to tumor recurrence or death from non-tumor-related causes), and postoperative complications

TABLE 3. The ratios and indices used as biomarkers in the analysis

Ratios		Definition
Neutrophil-lymphocyte ratio (NLR)		Baseline absolute neutrophil count/baseline absolute lymphocyte count
Derived NLR		Baseline absolute neutrophil count/(baseline absolute leucocyte count – baseline absolute neutrophil count)
Platelet-lymphocyte ratio		Baseline absolute platelet count/baseline absolute lymphocyte count
Lymphocyte-monocyte ratio		Baseline absolute lymphocyte count/baseline absolute monocyte count
Indices	Systemic immune-inflammatory index	Baseline absolute neutrophil count × baseline absolute platelet count/baseline absolute lymphocyte count
	Systemic inflammatory marker index	Baseline absolute neutrophil count × baseline absolute monocyte count/baseline absolute lymphocyte count

(11, 12). One study (14) used event-free survival, which is equivalent to DFS; hence, it is referred to as DFS in this review. Postoperative complications were defined as the appearance of a fistula, free-flap necrosis, stasis of the flap blood supply, and complications at the donor site or the operative region in 14 days following surgery (15).

When studies included multiple treatment modalities or evaluated additional markers or indices, only data pertaining to surgically treated patients and the markers defined in Table 3 were used in the analysis. As Yamagata et al (10) analyzed the surgical cohort separately from the entire cohort, only these analyses were included in the current review. Although the assessment of HPV-positive tumors was predefined as an exclusion criterion, several eligible studies did not determine HPV status. Excluding these studies would have resulted in an insufficient number of studies for analysis. Therefore, studies explicitly reporting HPV-positive tumors were excluded, while studies including HPV-negative tumors or those in which HPV status was not assessed were retained. No stratification or subgroup analysis based on HPV tumor status was performed. Additionally, when studies analyzed preoperative and postoperative laboratory findings, our analysis included only the preoperative measures. The results are stratified according to the analyzed biomarkers, but not according to precise tumor location, sex, or age. When data were available, forest plots were used to present results. They were constructed using dedicated software (MetaAnalysisOnline.com) based on reported hazard ratios (HR) and corresponding confidence intervals (CI), with all data derived exclusively from published aggregate results and no further formal analysis. These were created solely for descriptive purposes to illustrate the distribution, direction, and variability of reported effects, intended only to illustrate the overall direction of the results. The forest plots represented either categorized or continuous variables. HR were harmonized by inversion (1/HR). Additionally, conflicts of interest and funding of the studies were noted to assess possible bias.

RESULTS

Overview of the included studies

All the included studies were retrospective cohort studies (Table 4), except for one prospective cohort study (16). The studies enrolled a total of 11869 patients, 9242 of whom were male (77.8%). The patients' mean age ranged from 49.1 to 66 years, with a median from 50.8 to 71.3 years. All of the patients had HNSCC of the oral cavity, oropharynx, hypopharynx, larynx, or cervical esophagus, with no other primary tumors. And all were treated with surgery as the primary modality. Of the studies focusing on singular tumor locations, 6 focused on laryngeal SCC (12, 17-21), 9 on oral SCC (10, 11, 16, 22-27), and 2 on hypopharyngeal SCC (28, 29). The majority of the studies evaluated all clinical stages (9, 10, 14, 16, 19, 20, 23-27, 30-38), 7 focused on advanced stages (III, IV) (15, 18, 21, 22, 28, 29, 39, 40), 2 on stages II-IV (12, 13), and 2 provided only TNM staging (11, 17). The HPV status of the tumor was assessed in 9 papers, with 7 reporting a negative status (13, 15, 31, 34, 38-40) and 2 reporting both positive and negative status (14, 35).

Regarding biomarker ratios, 26 studies assessed NLR (9-11, 13-24, 26-28, 30, 32, 34-38), 5 assessed dNLR

(15, 19, 24, 28, 32), 18 assessed PLR (14-17, 19-22, 24, 26-29, 32-35, 37), and 12 assessed LMR (10, 14, 15, 19, 24, 26, 27, 32, 34, 36-38). Six studies assessed SII (10, 15, 25, 27, 32, 34) and 8 assessed SIM (9-12, 15, 31, 32, 34). Of the individual blood-based biomarkers, 7 studies assessed neutrophil count (9, 13, 15, 30, 31, 34, 37), 7 assessed lymphocyte count (9, 13, 15, 30, 31, 34, 37), 6 monocyte count (9, 13, 15, 31, 34, 37), 7 platelet count (13, 15, 17, 29, 34, 37), and 5 albumin (13, 21, 23, 31, 39). Table 4 shows only the analyzed biomarkers in individual studies that match our inclusion criteria.

OS was the outcome measure in all of the included studies, DFS in 9 studies (11, 12, 15, 29, 30, 32, 34, 39, 40), and postoperative complications in only 3 studies (15, 39, 40). Onan et al (21) used postoperative complications as an outcome measure, but not in the analysis of the biomarkers included in our review; hence, this article is not listed in Table 4. All univariate and multivariable analyses were performed using a Cox proportional hazards model, and all survival curves were generated by the Kaplan-Meier method.

TABLE 4. An overview of the included studies*

First author and year of publication	Study type	Tumor type and location	Tumor staging	HPV type	Number of patients (N)	Male (N)	Female (N)	Age (years)	Biomarkers analyzed	Outcome measures
Onan et al, 2025 (21)	Retrospective cohort study	LSCC	III, IV	NA	111	105	6	61.77 (average)	NLR, PLR, Albumin	OS
Mazzocco et al, 2025 (38)	Retrospective cohort study	SCC (oral cavity, oropharynx, hypopharynx, larynx)	I-IV	-	493	366	127	68 (median)	NLR, LMR	OS
Zhou et al, 2023 (37)	Retrospective cohort study	SCC (oral cavity, oropharynx, larynx, hypopharynx, other)	I-IV	NA	304	240	64	63 (median)	NLR, PLR, LMR, Neu, Lym, Mono, Plt	OS
Wang et al, 2023 (12)	Retrospective cohort study	LSCC	II-IV	NA	78	77	1	63,5 (median)	SIM	OS, DFS
Tomasoni et al, 2023 (13)	Retrospective cohort study	SCC (oral cavity, oropharynx, hypopharynx, larynx)	II-IVb	-	542	392	150	67 (median)	NLR, Plt, Neu,Mono, Lym, Albumin	OS
Hu et al, 2022 (36)	Retrospective cohort study	HNSCC (oral cavity, oropharynx, other)	I-IV	NA	599	395	204	≤59 (n=361), >59 (n=238)	NLR, LMR	OS
Wang et al, 2022 (35)	Retrospective cohort study	SCC (oral cavity, oropharynx, hypopharynx, larynx)	I-IV	- and + (5.2% p16 +)	155	145	10	53 (median)	NLR, PLR	OS
Ruiz-Ranz et al, 2022 (27)	Retrospective cohort study	OSCC	I-IV	NA	348	221	127	62 (median)	NLR, PLR, LMR, SII	OS
Mahajan et al, 2022 (40)	Response	SCC (oral cavity, oropharynx, hypopharynx, larynx, cervical esophagus)	IVa, IVb	-	90	69	21	61.15 (average)	None	OS, DFS, postoperative complications
Košec et al, 2022 (39)	Response								Albumin	
Košec et al, 2022 (15)	Retrospective cohort study								NLR, PLR, LMR, dNLR, SII, SIM, Neu, Lym, Mono, Plt,	
Song et al, 2022 (11)	Retrospective cohort study	OSCC	cT1-2N0	NA	235	128	107	53 (median)	NLR, SIM	OS, DFS
Zhuang et al, 2022 (16)	Prospective cohort study	OSCC	I-IV	NA	792	515	277	60 (median)	NLR, PLR	OS

TABLE 4. An overview of the included studies*

First author and year of publication	Study type	Tumor type and location	Tumor staging	HPV type	Number of patients (N)	Male (N)	Female (N)	Age (years)	Biomarkers analyzed	Outcome measures
Boscolo-Rizzo et al, 2022 (34)	Retrospective cohort study	SCC (oral cavity, oropharynx, larynx, hypopharynx)	I-IV	-	925	679	246	68 (median)	NLR, PLR, LMR, SII, SIM, Neu, Lym, Mono, Plt	OS, DFS
Zhou et al, 2021 (33)	Retrospective cohort study	SCC (larynx, hypopharynx)	I-IV	NA	181	181	0	63 (median)	PLR	OS
Yamagata et al, 2021 (10)	Retrospective cohort study	OSCC	I-IVc	NA	205	123	82	71.3 (median)	NLR, LMR, SII, SIM	OS
Wu et al, 2021 (26)	Retrospective cohort study	OSCC	I-IV	NA	890	828	62	50.8 (median)	NLR, PLR, LMR,	OS
Hung et al, 2021 (25)	Retrospective cohort study	OSCC	I-IV	NA	993	922	71	51 (median)	SII	OS
Xun et al, 2020 (20)	Retrospective cohort study	LSCC	I-IV	NA	151	147	4	65 (median)	NLR, PLR	OS
Zhou et al, 2020 (32)	Retrospective cohort study	SCC (oral cavity, oropharynx, larynx, hypopharynx, others)	I-IV	NA	367	257	110	60.33 (average)	NLR, dNLR, PLR, LMR, SII, SIM	OS, DFS
Lau et al, 2020 (29)	Retrospective cohort study	Hypopharyngeal SCC	III, IV	NA	247	242	5	59.2 (average)	PLR, Plt	OS, DFS
Valero et al, 2020 (9)	Retrospective cohort study	SCC (oral cavity, oropharynx, hypopharynx, larynx)	I-IV	NA	1369	770	599	61.9 (average)	NLR, SIM, Neu, Lym, Mono	OS
Chen et al, 2020 (19)	Retrospective cohort study	LSCC	I-IV	NA	473	456	17	63 (median)	NLR, dNLR, PLR, LMR	OS
Tham et al, 2019 (14)	Retrospective cohort study	SCC (oral cavity, oropharynx, larynx)	I-IV	+ and -	123	88	35	62.2 (average)	NLR, PLR, LMR	OS, DFS (EFS)
Jariod-Ferrer et al, 2019 (24)	Retrospective cohort study	OSCC	I-IV	NA	215	145	70	67,5 (median)	NLR, dNLR, PLR, LMR	OS
Gaudioso et al, 2021 (31)	Retrospective cohort study	SCC (oral cavity, oropharynx, hypopharynx, larynx)	I-IV	-	223	151	72	66 (median)	NLR, SIM, Neu, Lym, Mono, Albumin	OS
Chen et al, 2021 (28)	Retrospective cohort study	Hypopharyngeal SCC	III, IV	NA	89	86	3	66 (average)	NLR, dNLR, PLR	OS
Kao et al, 2018 (23)	Retrospective cohort study	OSCC	I-IV	NA	613	556	57	53,0 (average)	NLR, Albumin	OS
Muhaxheri et al, 2018 (30)	Retrospective cohort study	SCC (oral cavity, oropharynx)	I-IV	NA	182	156	26	60 (average)	NLR, Neu, Lym	OS, DFS
Sano et al, 2018 (22)	Retrospective cohort study	OSCC	III, IV	NA	94	66	28	67 (median)	NLR, PLR	OS
Fu et al, 2016 (18)	Retrospective cohort study	LSCC	III, IV	NA	420	413	7	60 (median)	NLR	OS
Zhong et al, 2018 (17)	Retrospective cohort study	LSCC	T3, T4	NA	362	323	39	49,1 (average)	NLR, PLR, Plt	OS

* Abbreviations: **NA** – not addressed; **SCC** – squamous cell carcinoma; **LSCC** – laryngeal squamous cell carcinoma; **OSCC** – oral squamous cell carcinoma, **NLR** – neutrophil-to-lymphocyte ratio, **LMR** – lymphocyte-to-monocyte ratio, **PLR** – platelet-to-lymphocyte, **SII** – systemic immune-inflammatory index, **SIM** – systemic inflammatory marker index, **dNLR** – derived NLR, **Neu** – neutrophils, **Lym** – lymphocytes, **Mono** – monocytes, **Plt** – platelet count; **OS** – overall survival, **DFS** – disease-free survival.

Neutrophil-lymphocyte ratio

NLR was assessed in 26 studies (9-11, 13-24, 26-28, 30-32, 34-38) (Table 5). All of the studies evaluated its impact on OS, 6 on DFS (11, 14, 15, 30, 32, 34), and 1 on postoperative complications (15). The effect of an increased NLR on OS and DFS (categorized values in multivariate Cox regression analysis) is demonstrated in forest plots (Figures 2 and 3). The hazard ratio reported by Wu et al (26) (harmonized HR: NLR>2.9, HR=1.26, 95% CI: 1.04-1.52) and by Gaudioso et al (31) (harmonized HR: NLR>3.7, HR=1.96, 95% CI: 1.04-3.57) were harmonized to reflect the effect of a higher NLR on OS.

Preoperative NLR was not an independent prognostic factor for OS in 8 of the 26 studies (11, 15, 17, 19, 21, 24, 28, 32). In 18 studies, a higher preoperative NLR was associated with worse OS (Table 5). The cutoff values for NLR ranged from 1.94 to 5.7. When studies compared the survival rates of low-NLR and high-NLR groups (the cutoff points varied between studies), they confirmed the finding. The pooled HR (Figure 2) suggested a significant association of NLR with adverse OS.

NLR was an independent prognostic factor for DFS in 2 studies (11, 30), while the other 4 studies (14, 15, 32, 34) found a higher NLR to be negatively associated with DFS. The cutoff values of DFS ranged from 1.8 to 13.2 (Table 5). The pooled HR (Figure 3) suggested a significant association with adverse DFS.

The only study assessing the prognostic value of preoperative NLR for postoperative complications found no significant results (15).

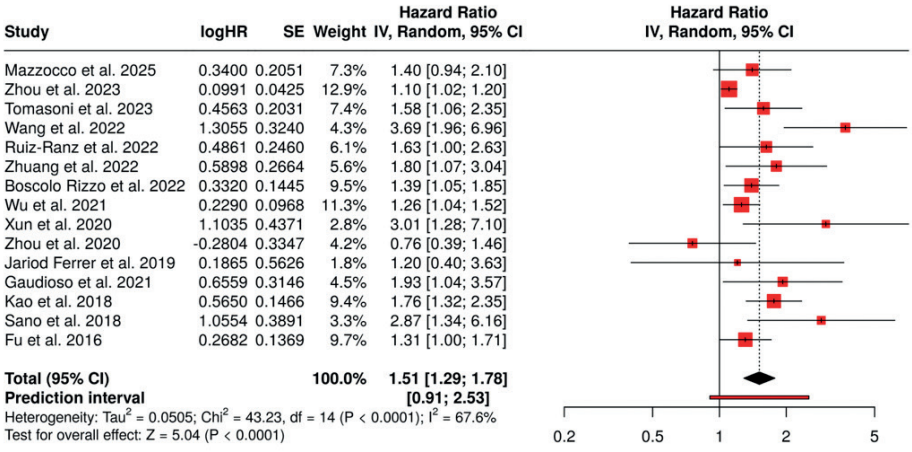

FIGURE 2. The effect of a higher neutrophil-lymphocyte ratio (categorized value) on overall survival (OS) in multivariate Cox regression analysis. Individual study hazard ratios (HR) and confidence intervals (CI) are presented, together with pooled estimates generated for descriptive purposes only, in this case pointing towards an association with adverse OS.

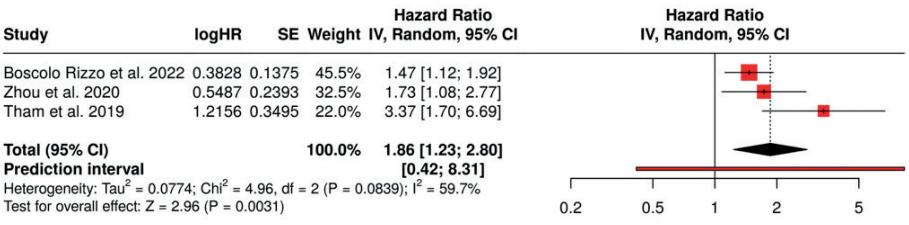

FIGURE 3. The effect of a higher neutrophil-lymphocyte ratio (categorized value) on disease-free survival (DFS) in multivariate Cox regression analysis. Individual study hazard ratios (HR) and confidence intervals (CI) are presented, together with pooled estimates generated for descriptive purposes only, in this case pointing towards an association with adverse DFS.

TABLE 5. Studies assessing the prognostic value of neutrophil-lymphocyte ratio (NLR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (p=0.09)	■ Rising NLR (>13.2) was negatively associated with DFS (p=0.031, multivariate Cox regression analysis) ■ Low NLR (<13.2) 80% vs high NLR (>13.2) 74% 2-year OS rate	NS (p=0.650)
Onan et al, 2025 (21)	NS (p=0.348)	NA	NA
Mazzocco et al, 2025 (38)	NS (multivariate Cox regression analysis, NLR ≥ 3.76 [ref. <2.10] HR=1.4, 95% CI: 0.94-2.10)	NA	NA
Zhou et al, 2023 (37)	■ Preoperative NLR was an independent prognostic factor for OS (< 1.94/≥1.94 HR=1.104, 95% CI: 1.016-1.200, p=0.019; multivariate Cox regression analysis ■ Low NLR group (<1.94) had significantly higher OS rates that the high NLR group (p<0.001) ■ Low NLR group (<1.94) had a significantly higher 3-year survival rate than the high group (p<0.001)	NA	NA
Tomasoni et al, 2023 (13)	■ NLR >4.2 was associated with worse OS (HR=1.58, 95% CI: 1.06-2.35, p=0.024; multivariable Cox regression analysis)	NA	NA
Hu et al, 2022 (36)	■ NLR was associated with OS (HR=1.096, 95% CI: 1.011-1.189, p=0.025; multivariable Cox regression analysis) ■ Patients with a low-NLR <2.47 had better survival (p<0.0001)	NA	NA
Wang et al, 2022 (35)	■ High NLR (≥2.46) was associated with worse OS (HR=3.690, 95% CI: 1.955-6.963, p<0.001; multivariable Cox regression analysis)	NA	NA
Ruiz-Ranz et al, 2022 (27)	■ High NLR (>4.08) was associated with worse OS (HR=1.626, 95% CI: 1.004- 2.633, p=0.04; multivariate Cox regression analysis	NA	NA
Song et al, 2022 (11)	NS on univariate analysis (<1.8 vs ≥1.8, HR=1.62, 95% CI: 0.90-2.93, p=0.111)	NS in univariate analysis (<1.8 vs ≥1.8, HR=1.63, 95% CI: 0.89-2.99, p=0.114)	NA
Zhuang et al, 2022 (16)	■ NLR was an independent prognostic indicator for worse OS (>1.3; HR=1.80, 95% CI: 1.07-3.04, p<0.05; multivariate Cox regression analysis)	NA	NA
Boscolo Rizzo et al, 2022 (34)	■ NLR ≥ 3.76 was associated with worse OS ([ref. <2.10], HR=1.39, 95% CI: 1.05-1.85, p=0.0231; multivariate Cox regression analysis)	■ NLR ≥ 3.76 had worse DFS (ref. <2.10, HR=1.47, 95% CI: 1.12-1.92, p=0.0048; multivariate Cox regression analysis)	NA
Yamagata et al, 2021 (10)	Significantly associated with OS in univariate analysis for the surgical cohort (≥ 3.59 vs. < 3.59, HR=2.181, 95% CI: 1.021-4.662, p=0.044)	NA	NA
Wu et al, 2021 (26)	■ NLR < 2.9 was independently associated with better OS (HR=0.794, 95% CI: 0.656-0.961, p=0.018; multivariate Cox regression analysis)	NA	NA
Xun et al, 2020 (20)	■ High NLR ≥ 2.2 was associated with significantly poor survival outcome (5-year OS 57.7% vs 83.5%, p<0.001) (KM) ■ High NLR ≥ 2.2 was associated with adverse 5-year OS (HR=3.02, 95% CI: 1.28-7.10, p=0.01; multivariate Cox regression analysis)	NA	NA
Valero et al, 2020 (9)	■ High NLR (≥5.7) groups had worse 5-year OS than the intermediate (2.9-5.7) and low NLR groups (≤2.9) – 35.6% vs 61.9% vs 69.5% (p<0.001) ■ This persisted in multivariate analysis.	NA	NA
Zhou et al, 2020 (32)	NS on multivariate analysis (>2.81, HR=0.692, 95% CI: 0.329-1.456, p=0.332; multivariate Cox regression analysis)	■ High NLR (>2.81) was an independent prognostic factor for DFS (HR=1.731, 95% CI: 1.083-2.767, p=0.022; multivariate Cox regression analysis)	NA

TABLE 5. Studies assessing the prognostic value of neutrophil-lymphocyte ratio (NLR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Chen et al, 2020 (19)	NS (univariate and multivariate analysis)	NA	NA
Tham et al, 2019 (14)	■ NS on multivariate analysis (>2.87, p=0.243) ■ NLR had the second highest c-index on multivariate analysis when compared with PLR and LMR (c=0.761)	■ High NLR (>2.69) was significantly associated with DFS on multivariate analysis (HR=3.37, 95% CI: 1.7-6.69, p<0.001)	NA
Jariod-Ferrer et al, 2019 (24)	NS with 5-year OS on multivariate analysis (>3, HR=1.21, 95% CI: 0.40-3.63, p=0.735; multivariate Cox regression analysis)	NA	NA
Gaudioso et al, 2021 (31)	■ NLR <3.7 was associated with better OS (HR=0.51, 95% CI: 0.28-0.96; multivariate Cox regression model)	NA	NA
Chen et al, 2021 (28)	NS (univariate and multivariate analysis)	NA	NA
Kao et al, 2018 (23)	■ NLR ≤2.28 had better 5-year OS (75.2%) than NLR >2.28 (60.7%) (p<0.0001) ■ NLR >2.28, HR=1.759, 95% CI: 1.320-2.345, p=0.0001; multivariate Cox regression analysis	NA	NA
Muhaxheri et al, 2018 (30)	■ NLR increased the risk of death by 38% per unit change (HR=1.375, 95% CI: 1.128-1.676, p=0.002; multivariate Cox regression analysis)	NS	NA
Sano et al, 2018 (22)	■ NLR <2.36 predicted a significantly longer OS (p=0.04) ■ NLR ≥ 2.36 was associated with worse OS (HR=2.88, 95% CI: 1.34-6.16, p=0.006; multivariate Cox regression analysis)	NA	NA
Fu et al, 2016 (18)	■ 5-year OS rates were significantly lower in the high NLR group ≥2.59 (52.8% vs 63%, p=0.032) ■ NLR ≥2.59 was associated with worse OS (HR=1.31, 95% CI: 1.00-1.71, p=0.046; multivariate Cox regression analysis)	■ NLR ≥ 3.76 had worse DFS (ref. <2.10, HR=1.47, 95% CI: 1.12-1.92, p=0.0048; multivariate Cox regression analysis)	NA
Zhong et al, 2018 (17)	NS on univariate analysis (p=0.592)	NA	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **HR** – hazard ratio, **CI** – confidence interval.

Derived neutrophil-lymphocyte ratio

Derived NLR was assessed as a prognostic factor for OS, DFS, and postoperative complications in 5 studies (15, 19, 24, 28, 32) (Table 6). All of the studies analyzed its effect on OS, 2 on DFS (15, 32), and 1 on postoperative complications (15). The studies for which data were available are included in the forest plot (Figure 4). None of the analyzed studies found dNLR to be an adequate prognostic factor for OS or DFS (Table 6). An increased dNLR (>2.3) was a predictor of postoperative complications (15). The cutoff values of dNLR ranged from 1.455 to 2.3.

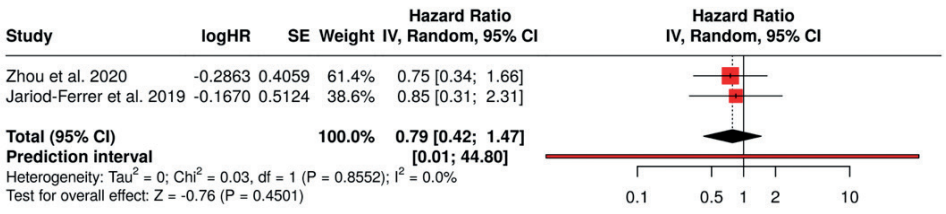

FIGURE 4. The effect of a higher derived neutrophil-lymphocyte ratio (categorized value) on overall survival in multivariate Cox regression analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

TABLE 6. Studies assessing the effect of derived neutrophil-lymphocyte ratio (dNLR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (p=0.058)	NS (p=0.06)	■ Increased dNLR (>2.3) tested as a predictor for postoperative complications (p=0.013)
Zhou et al, 2020 (32)	NS (>1.46) (HR=0.751, 95% CI: 0.339-1.664, p=0.481; multivariate Cox regression analysis)	NS on multivariate analysis (>1.46, HR=1.300, 95% CI: 0.799-2.115, p=0.29)	NA
Chen et al, 2020 (19)	NS (1.7 cutoff value) (univariate and multivariate Cox regression analysis)	NA	NA
Jariod-Ferrer et al, 2019 (24)	NS with 5-year OS (dNLR >1.9, HR=0.845, 95% CI: 0.31-2.31, p=0.743; multivariate Cox regression analysis)	NA	NA
Chen et al, 2021 (28)	NS (1.455 cutoff value) (univariate analysis)	NA	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **HR** – hazard ratio, **CI** – confidence interval.

Platelet-to-lymphocyte ratio

PLR was assessed as a prognostic factor in 18 studies (14-17, 19-22, 24, 26-29, 32-35, 37) (Table 7). All of the studies analyzed its impact on OS, 5 on DFS (14, 15, 29, 32, 34), and 1 on postoperative complications (15). The effect of an increased PLR (as a categorized value in multivariate Cox regression analysis) on OS and DFS is presented in forest plots (Figures 5 and 6).

Five studies (20, 24, 29, 33, 34) found higher levels of PLR to be associated with adverse OS. In one study, a higher PLR (≥ 106) was associated with worse 5-year OS, but in multivariate analysis, a higher PLR was associated with better OS (20) (Table 7). The cutoff values between the low and high-PLR groups ranged from 66 to 218.97. The pooled HR (Figure 5) did not indicate a statistically significant association.

Three studies (14, 29, 34) found high PLR to be associated with adverse OS, while the other 2 studies did not find a significant association (Table 7). The cutoff values ranged from 140.22 to 171.4. The pooled HR (Figure 6) indicated a significant association between higher PLR values and adverse DFS.

PLR was not significantly associated with postoperative complications (15).

TABLE 7. Studies assessing the prognostic value of platelet-to-lymphocyte ratio (PLR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (p=0.27)	NS (p=0.71)	NS (p=0.969)
Onan et al, 2025 (21)	NS (p=0.185)	NA	NA
Zhou et al, 2023 (37)	NS (107.8 cutoff value) (univariate analysis, HR=1.002, 95% CI: 1.000-1.005, p=0.073)	NA	NA
Wang et al, 2022 (35)	NS (≥151.45, HR=1.132, 95% CI: 0.673-2.984, p=0.641; multivariable Cox regression analysis)	NA	NA
Ruiz-Ranz et al, 2022 (27)	NS on univariate analysis (>205, HR=1.465, 95% CI: 0.908-2.363, p=0.11))	NA	NA
Zhuang et al, 2022 (16)	NS (>218.97, HR=1.08, 95% CI: 0.72-1.62; multivariate Cox regression analysis)	NA	NA
Boscolo Rizzo et al, 2022 (34)	■ PLR ≥ 162.8 was associated with worse OS ([ref. <127.7] HR=1.30, 95% CI: 1.01-1.68, p=0.0413; multivariable Cox regression analysis)	■ PLR ≥ 162.8 was associated with worse DFS ([ref. <127.7] HR=1.35, 95% CI: 1.07-1.71, p=0.0111; multivariable Cox regression analysis)	NA

TABLE 7. Studies assessing the prognostic value of platelet-to-lymphocyte ratio (PLR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Zhou et al, 2021 (33)	■ PLR >112.5 group had a decreased OS (p=0.027) ■ PLR >112.5 vs. >112.5 HR= 0.480, 95% CI: 0.246-0.936, p=0.028; univariate Cox regression analysis	NA	NA
Yamagata et al, 2021 (10)	NS	NA	NA
Xun et al, 2020 (20)	■ High PLR ≥ 106 had poor survival (5-year OS 56.9% vs 90.2%, p<0.001) ■ High PLR was associated with better OS (HR=0.33, 95% CI: 0.14-0.78, p=0.011; multivariate Cox regression analysis)	NA	NA
Zhou et al, 2020 (32)	NS (>140.22, HR=1.003, 95% CI: 0.499-2.015, p=0.993; multivariate Cox regression analysis)	NS (HR=1.247, 95% CI: 0.820-1.896, p=0.302; multivariate Cox regression analysis)	NA
Lau et al, 2020 (29)	■ The low PLR group (≤ 171.4) exhibited better 3-year OS than the high PLR group (58.3% vs 23.3%, p<0.001) ■ High PLR (>171.4) was an independent prognostic factor for OS (HR=2.141, 95% CI: 1.358-3.375, p=0.001; multivariate Cox regression analysis)	■ The low PLR group (≤ 171.4) exhibited better 3-year DFS than the high PLR group (47.5% vs. 18.6%, p<0.001) ■ High PLR (>171.4) was an independent prognostic factor for DFS (HR=1.621, 95% CI: 1.062-2.474, p=0.025; multivariate Cox regression analysis)	NA
Chen et al, 2020 (19)	NS (>218.97, HR=1.08, 95% CI: 0.72-1.62; multivariate Cox regression analysis)	NA	NA
Tham et al, 2019 (14)	NS on multivariate Cox regression analysis (>194, p=0.1593) PLR had the lowest c-index in multivariate analysis when compared with NLR and LMR (c=0.739)	■ High PLR (>164.8) was significantly associated with DFS on multivariate analysis (HR=2.68, 95% CI: 1.42-5.09, p=0.003)	NA
Jariod-Ferrer et al, 2019 (24)	■ Not significant, but marginally, high PLR (>66) association with 5-year OS (HR=4.06, 95% CI: 0.95-17.42, p=0.059; multivariate Cox regression analysis)	NA	NA
Chen et al, 2021 (28)	NS PLR≥98.815 had a higher death rate (70.3%) than a low PLR >98.815 (36.0%)	NA	NA
Sano et al, 2018 (22)	PLR <138.47 had significantly longer OS (p=0.01) NS (≥138.47, HR=1.56, 95% CI: 0.58-4.19 p=0.38; multivariate Cox regression analysis)	NA	NA
Zhong et al, 2018 (17)	NS	NA	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **HR** – hazard ratio, **CI** – confidence interval.

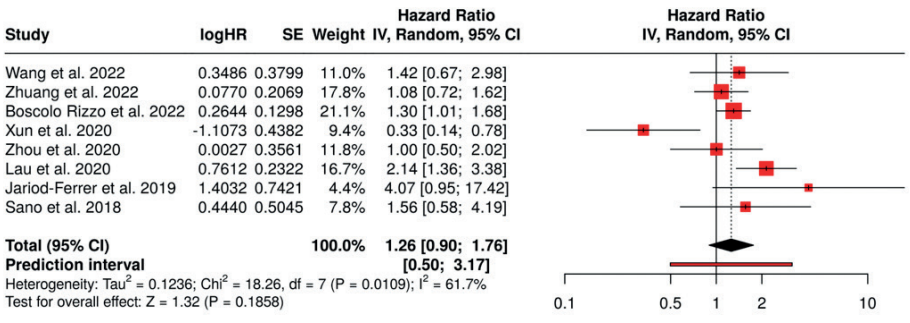

FIGURE 5. The effect of an increased platelet-to-lymphocyte ratio (categorized value) on overall survival in multivariate Cox regression analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

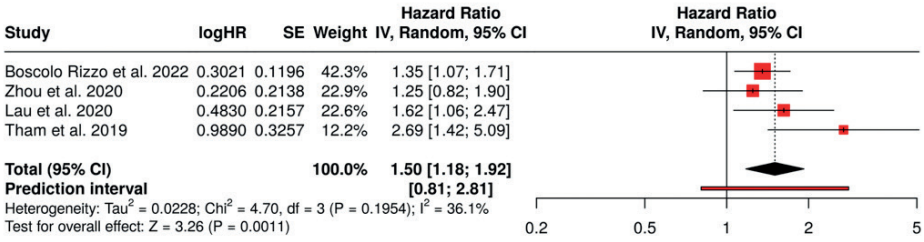

FIGURE 6. **The effect of an increased platelet-to-lymphocyte ratio (categorized value) on disease-free survival in multivariate Cox regression analysis.** Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Lymphocyte-monocyte ratio

LMR was assessed as a prognostic factor in 12 studies (10, 14, 15, 19, 24, 26, 27, 32, 34, 36-38) (Table 8). All of the studies evaluated its prognostic value for OS, 4 for DFS (14, 15, 32, 34), and 1 for postoperative complications (15). The effect of a lower LMR (categorized value) on OS and DFS in multivariate Cox regression analysis is presented in forest plots (Figures 7 and 8). The hazard ratio reported by Zhou et al (32) was harmonized to reflect the effect of a lower LMR value on OS (harmonized HR=1.43, 95% CI: 0.64-3.16). The same was done for DFS (harmonized HR=0.73, 95% CI: 0.41-1.16).

Eleven studies did not find LMR to be an independent prognostic factor for OS, while Boscolo Rizzo et al (34) found lower LMR values to be associated with worse OS. The cutoff values ranged from 2.6 to 5.08. The pooled HR suggests a significant association between lower LMR values and adverse OS (Figure 7).

Boscolo Rizzo et al (34) also found LMR to be an independent prognostic factor for DFS, with values below 2.92 being associated with worse DFS. A similar finding was reported by Tham et al (14). They additionally found LMR to have a higher prognostic value than NLR and PLR (c=0.762). The cutoff values ranged from 2.8 to 3.76. The pooled HR suggested no significant association between a lower LMR and DFS (Figure 8).

LMR was not significantly associated with postoperative complications (15).

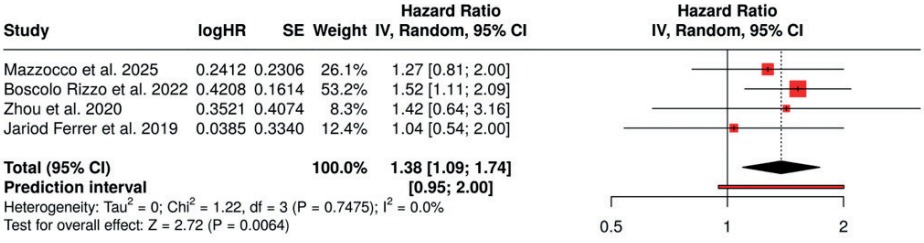

FIGURE 7. **The effect of a lower lymphocyte-monocyte ratio (categorized value) on overall survival in multivariate Cox regression analysis.** Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

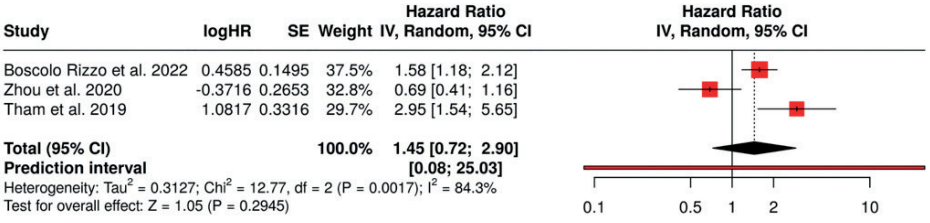

FIGURE 8. **The effect of a lower lymphocyte-monocyte ratio (categorized value) on disease-free survival in multivariate Cox regression analysis.** Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

TABLE 8. Studies assessing the prognostic value of lymphocyte-monocyte ratio (LMR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (p=0.230)	NS (p=0.300)	NS (p=0.180)
Mazzocco et al, 2025 (38)	Preoperative LMR <2.92 was NS ([ref. ≥4.28] HR=1.27, 95% CI: 0.81-2.00; multivariable Cox regression analysis)	NA	NA
Zhou et al, 2023 (37)	NS (univariate analysis, <5.08/≥5.08, HR=0.930, 95% CI: 0.815-1.062, p=0.285)	NA	NA
Hu et al, 2022 (36)	NS in multivariate analysis (univariable analysis, HR=0.781, 95% CI: 0.703-0.866, p= 0.00)	NA	NA
Ruiz-Ranz et al, 2022 (27)	NS in multivariate analysis (univariate analysis, >4.58 HR=0.668, 95% CI: 0.466-0.957, p=0.02)	NA	NA
Boscolo Rizzo et al, 2022 (34)	■ LMR ≥ 3.76 indicated 10-year OS 60.4%, LMR < 2.92 40.5%, c=0.568 ■ LMR <2.92 was associated with worse OS ([ref. ≥ 4.28] HR=1.52, 95% CI: 1.11-2.09, p=0.0098; multivariable Cox regression analysis)	■ LMR ≥ 3.76 had a 10-year DFS 55.2%, LMR<2.92 33.6%, c=567 ■ LMR <2.92 was associated with worse DFS ([ref. ≥ 4.28] HR=1.58, 95% CI: 1.18-2.12, p=0.0021; multivariable Cox regression analysis)	NA
Yamagata et al, 2021 (10)	NS (univariate analysis, HR=0.567, 95% CI: 0.275-1.168, p=0.124)	NA	NA
Wu et al, 2021 (26)	NS (≥4.21, univariate analysis HR=0.838, 95% CI: 0.696-1.008)	NA	NA
Zhou et al, 2020 (32)	NS (>3.08, HR=0.701, 95% CI: 0.316-1.556, p=0.382; multivariate Cox regression analysis)	NS (>3.08, HR=1.380, 95% CI: 0.861-2.414, p=0.181; multivariate Cox regression analysis)	NA
Chen et al, 2020 (19)	NS	NA	NA
Tham et al, 2019 (14)	NS on multivariate Cox regression analysis (<2.8 cutoff value) (p=0.0552) (univariate analysis, LMR < 2.8, HR=3.07, 95% CI: 1.13-8.35, p=0.028)	■ Low LMR (<2.8) was significantly associated with DFS (HR=2.95, 95% CI: 1.54-5.65, p=0.001; multivariate Cox regression analysis) ■ LMR had a higher multivariate c-index than NLR and PLR (c=0.762)	NA
Jariod-Ferrer et al, 2019 (24)	NS for 5-year OS (LMR <2.6, HR=1.04, 95% CI: 0.54-2.00, p=0.905; multivariate Cox regression analysis)	NA	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **HR** – hazard ratio, **CI** – confidence interval.

Systemic immune-inflammatory index

SII was assessed as a prognostic factor in 6 studies (10, 15, 25, 27, 32, 34) (Table 9). All of the studies evaluated its prognostic value on OS, 3 studies on DFS (15, 32, 34), and 1 on postoperative complications (15). The effect of an increased SII on OS and DFS is shown in Figures 9 and 10.

In 3 of the 6 studies (15, 25, 34), higher SII values were significantly associated with adverse OS. Yamagata et al (10) reported its prognostic significance only in a univariate analysis in patients treated primarily with surgery. The cutoff values of SII ranged from 531.93 to 1137. The pooled HR suggested a significant association with adverse OS (Figure 9).

Only one study reported higher SII values to be significantly associated with adverse DFS (34). The cutoff values of SII ranged from 531.93 to 754. The pooled HR indicated no significant association (Figure 10).

No significant association was found between SII and postoperative complications (15).

TABLE 9. Studies assessing the prognostic value of lymphocyte-monocyte ratio (LMR) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	■ Increased SII (multivariate Cox regression model, p=0.022) was associated with adverse OS (1005.3 cutoff value) ■ Low SII (≤1005.3) 91% vs. high SII (>1005.3) 64% 2-year OS rate	NS (multivariate Cox regression model, p=0.726)	NS (multivariate Cox regression model, p=0.698)
Ruiz-Ranz et al, 2022 (27)	NS in multivariate analysis (SII>1137 univariate analysis, HR=1.979, 95% CI: 1.260-3.108, p=0.003)	NA	NA
Boscolo Rizzo et al, 2022 (34)	■ SII ≥ 754 was associated with worse OS (HR=1.32, 95% CI: 1.05-1.66, p=0.00171; multivariate Cox regression analysis)	■ SII ≥ 754 was associated with worse DFS (HR=1.37, 95% CI: 1.11-1.70, p=0.0034; multivariate Cox regression analysis)	NA
Yamagata et al, 2021 (10)	SII ≥ 823.1 vs. <823.1 was associated with worse OS in univariate analysis (HR=2.623, 95% CI: 1.262-5.449, p=0.010)	NA	NA
Hung et al, 2021 (25)	■ High SII (>810.6) was associated with adverse OS (HR=1.466, 95% CI: 1.225-1.755, p<0.001) ■ Median OS in patients with high SII (>810.6) was significantly shorter than with a low SII (4.9 y vs. 9.4 y, p<0.001)	NA	NA
Zhou et al, 2020 (32))	NS (>531.93; HR=1.148, 95% CI: 0.541-2.433, p=0.719; multivariate Cox regression analysis)	NS (>531.93; HR=1.003, 95% CI: 0.629-1.599, p=0.991; multivariate Cox regression analysis)	NA

* Abbreviations: **OS** – overall survival, **DFS** – disease-free survival, **CI** – confidence interval, **HR** – hazard ratio, **NA** – not addressed, **NS** – not significant.

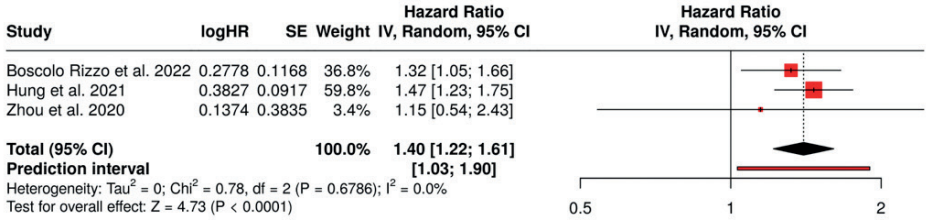

FIGURE 9. The effect of an increased systemic immune-inflammatory index (categorized value) on overall survival in multivariate Cox regression analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

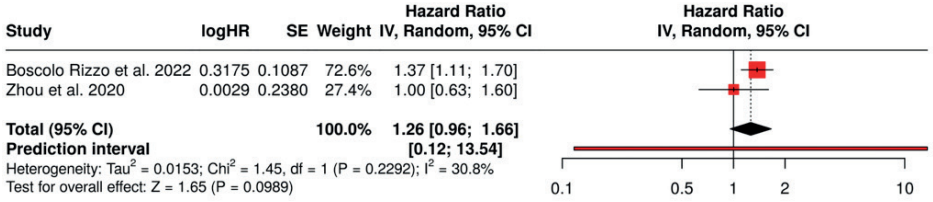

FIGURE 10. The effect of an increased systemic immune-inflammatory index (categorized value) on disease-free survival in multivariate Cox regression analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Systemic inflammatory marker

The prognostic value of SIM was assessed in 8 studies (9-12, 15, 31, 32, 34) (Table 10). All studies evaluated its effect on OS, 5 studies on DFS (11, 12, 15, 32, 34), and 1 study on postoperative complications (15). The effect of an increased SIM on OS and DFS is presented in Figures 11 and 12.

Six studies reported higher values of SIM as a significant prognostic factor for adverse OS (9, 11, 15, 31, 32,

34). Wang et al (12) did not find a significant difference in HRs between lower and higher values of SIM. The cutoff values ranged from 1.19 to 4.05. The pooled HR suggested a significant association between higher SIM values and adverse OS (Figure 11).

Higher SIM values were a significant prognostic factor for adverse DFS in 4 studies (12, 15, 32, 34). Of all of the studies evaluating its predictive value for DFS, only Song et al (11) did not find a significant effect (Table 10). The cutoff values ranged from 1.2 to 4.05. The forest plot seems to indicate a significant association between a higher SIM and adverse DFS (Figure 12).

SIM was not found to be an independent prognostic factor for postoperative complications (15).

TABLE 10. Studies assessing the prognostic value of systemic inflammatory marker (SIM) on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	■ Rising SIM (p = 0.0001) was associated with adverse OS (SIM >4.05 cutoff value) ■ Low SIM 88% vs high SIM 57% 2-year OS rate	■ Rising SIM was negatively associated with DFS (p = 0.042) (SIM >4.05 cutoff value) ■ Low SIM (<4.05) 85% vs high SIM (>4.05) 47% 2-year OS rate	NS (p=0.992)
Wang et al, 2023 (12)	High SIM (1.2) had poorer 5-year OS (p=0.014) NS (low vs high SIM, HR=1.217, 95% CI: 0.554-2.67, p=0.625; multivariate Cox regression analysis)	■ High SIM (≥ 1.2) group had poorer 5-year DFS (p=0.012) ■ High SIM (≥ 1.2) was associated with worse DFS (multivariate Cox proportional hazard mode analysis, HR: 2.539, 95% CI: 1.188-5.427, p=0.046)	NA
Song et al, 2022 (11)	■ High SIM ≥ 2.3 was associated with worse OS in multivariate Cox regression analysis (HR=2.87, 95% CI: 1.35-6.1, p=0.006) ■ SIM ≥1.3 was associated with significantly reduced OS compared with SIM < 1.3 (p=0.001) ■ High SIM was associated with adverse 1-year (HR=6.60, 95% CI: 1.58-27.63, p=0.003), 3-year (HR=2.98, 95% CI: 1.58-5.65, p<0.001) and 5-year OS (HR=2.59, 95% CI: 1.41-4.76, p=0.001)	SIM was not a useful indicator for DFS, with no difference between high SIM and low SIM groups (p=0.594)	NA
Boscolo Rizzo et al, 2022 (34)	■ SIM<1.4 had a 53.2% 10-year OS, SIM ≥ 2.46 40.9% – c=0.569 ■ SIM ≥ 2.46 was associated with worse OS with a multivariate Cox proportional hazard model analysis ■ (HR=1.43, 95% CI: 1.09-1.89, p=0.0099)	■ SIM <1.4 had a 48.8% 10-year DFS, SIM ≥ 2.46 – 29.8%, c=0.563 ■ SIM ≥ 2.46 was associated with worse DFS in a multivariate Cox proportional hazard model analysis (HR=1.48, 95% CI: 1.15-1.91, p=0.0024)	NA
Yamagata et al, 2021 (10)	NS (≥ 1.19 vs. < 1.19 on univariate Cox regression analysis, HR=1.981, 95% CI: 0.941-4.168, p=0.072) (surgical group	NA	NA
Zhou et al, 2020 (32)	■ High SIM (>1.34) had lower 2-year OS rate than the low SIM group (67.2% vs 87.4%, p<0.001) ■ SIM (>1.34) was an independent prognostic factor for OS (multivariate Cox proportional hazards mode analysis, HR=2.878, 95% CI: 1.801-4.598, p<0.001)	■ High SIM (>1.34) group had lower 2-year DFS rate than the low SIM group (24.1% vs 68.7%, p<0.001) ■ SIM (>1.34) was an independent prognostic factor for DFS (multivariate Cox proportional hazards mode analysis, HR=2.083, 95% CI: 1.228-3.533, p=0.007)	NA
Gaudioso et al, 2021 (31)	■ SIM ≥2.5 was associated with OS (multivariate Cox proportional hazards mode analysis, HR=2.60, 95% CI: 1.19-5.67)	NA	NA
Valero et al, 2020 (9)	■ High SIM (≥ 1.9) had worse 5-year OS 44.5%, than the intermediate group (1.0-1.9) 62.2% and the low group (≤ 1.0) 72.5% (p<0.001) ■ SIM was associated with worse OS in multivariate Cox proportional hazards mode analysis – SIM ≥ 1.9 (HR=2.485, 95% CI: 2.017-3.061, p<0.001)	NS (>531.93; HR=1.003, 95% CI: 0.629-1.599, p=0.991; multivariate Cox regression analysis)	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **CI** – confidence interval, **HR** – hazard ratio.

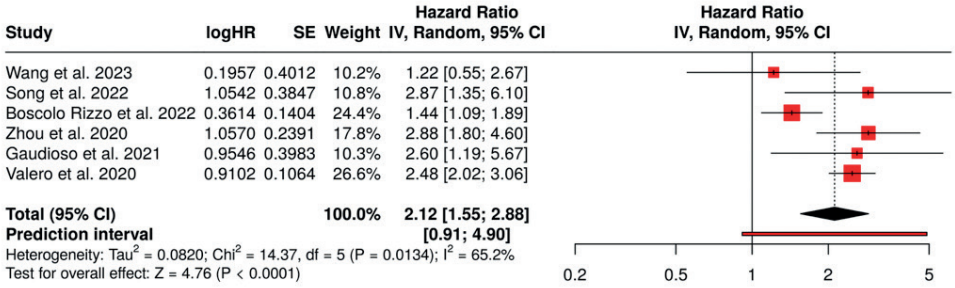

FIGURE 11. **The effect of an increased systemic inflammatory marker (categorized value) on overall survival in multivariate Cox regression analysis.** Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

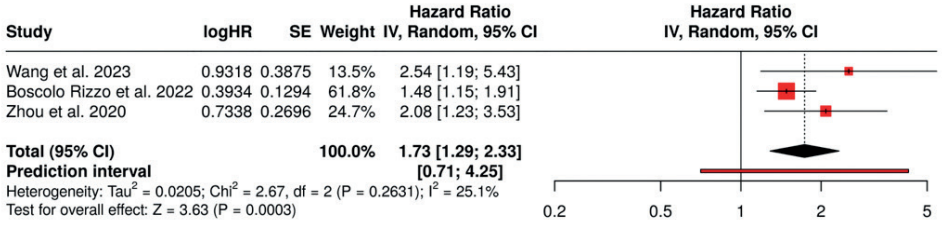

FIGURE 12. **The effect of an increased systemic inflammatory marker (categorized value) on disease-free survival in multivariate Cox regression analysis.** Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Neutrophils

Pre-operative neutrophil count was assessed as a prognostic factor in 7 studies (9, 13, 15, 30, 31, 34, 37) (Table 11). All of the studies evaluated its prognostic value on OS, 3 on DFS (15, 30, 34), and 1 on postoperative complications (15). Only 3 studies provided adequate data for a forest plot (multivariate analysis of categorized values) (Figure 13).

A higher preoperative neutrophil count was reported as a prognostic factor for adverse OS in 3 studies (9, 30, 37). The other 4 studies did not find preoperative neutrophil count to be a significant prognostic factor for OS (13, 15, 31, 34). The pooled HR indicated a significant association between a higher neutrophil count and adverse OS (Figure 13).

Of the 3 studies evaluating the prognostic value of preoperative neutrophil count on DFS (15, 30, 34) only Muhaxheri et al (30) reported preoperative neutrophil count to be associated with better DFS. The other studies found no statistically significant association (Table 5).

Neutrophil count was not found to be an independent prognostic factor for postoperative complications (15).

TABLE 11. **Studies assessing the prognostic value of neutrophil count for overall survival (OS), disease-free survival (DFS), and postoperative complications***

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (multivariate Cox regression model, p=0.114)	NS (multivariate Cox regression model, p=0.140)	NS (multivariate Cox regression model, p=0.127)
Zhou et al, 2023 (37)	■ Preoperative neutrophil count was an independent prognostic factor for OS (Neu < 4.57/4.57 × 109/L, multivariate analysis Cox regression model), HR= 1.234, 95% CI: 1.107-1.375, p=0.000)	NA	NA

TABLE 11. Studies assessing the prognostic value of neutrophil count for overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Muhaxeri et al, 2018 (30)	■ Preoperative neutrophil count lowered the risk of death by 16% per each 1×109/L (p=0.03) (multivariate Cox proportional hazard model analysis, HR=0.844, 95% CI: 0.724-0.984, p=0.03)	■ Preoperative neutrophil count was associated with better DFS (multivariate Cox proportional hazard model analysis, HR=0.866, 95% CI: 0.750-0.999, p=0.049)	NA
Valero et al, 2020 (9)	■ High neutrophil (≥ 9.1 × 10^9/L) groups had worse 5-year OS than the intermediate, (4.8-9.1 × 10^9/L) and low neutrophil groups (≤ 4.8 × 10^9/L) – 31.5% vs 59.4% vs 69.7% (p < 0.001) ■ This was sustained in multivariate Cox's proportional hazard regression analysis (not reported)	NS (multivariate Cox regression model, p=0.140)	NS (multivariate Cox regression model, p=0.127)
Gaudioso et al, 2021 (31)	■ NS (≥ 5.8 × 10^3/μL, multivariate Cox proportional hazard model analysis, HR=1.05, 95% CI: 0.48-2.28)	NA	NA
Tomasoni et al, 2023 (13)	NS (multivariate Cox proportional hazard model analysis, HR=1.05, 95% CI: 0.97-1.14, p=0.229)	NA	NA
Boscolo Rizzo et al, 2022 (34)	NS (Cox proportional hazard model, ≥5.54×103/μL, [ref. <4.28], HR=1.04, 95% CI: 0.80-1.36)	NS (Cox proportional hazard model, ≥5.54×103/μL [ref. <4.28], HR=1.06, 95% CI: 0.83-1.35)	NA

* Abbreviations: **NA** – not addressed, **NS** – not significant, **CI** – confidence interval, **HR** – hazard ratio.

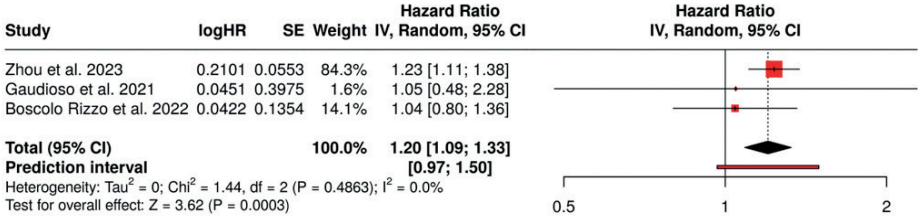

FIGURE 13. The effect of an increased neutrophil count (categorized values) on overall survival in multivariate analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Lymphocytes

The prognostic value of lymphocytes was assessed in 7 studies (9, 13, 15, 30, 31, 34, 37) (Table 12). The prognostic value on OS was evaluated in all of the studies, on DFS in 3 studies (15, 30, 34), and on postoperative complications in 1 study (15). A forest plot demonstrating the effect of a lower lymphocyte count on OS is shown in Figure 14. The HR reported by Gaudioso et al (31) was harmonized to reflect the effect of lower lymphocyte count on OS (harmonized HR: ≥2.1×10^3/μL HR=1.25, 95% CI: 0.57-2.78).

A lower lymphocyte count was shown to be an independent prognostic factor for adverse OS in 3 studies (9, 13, 34). Muhaxheri et al (30) reported a marginal non-significant association. Zhou et al (37) reported this effect only in univariate analysis. The cutoff values for low lymphocyte count ranged from 0.8 to 1.97. The other 2 studies (15, 31) did not find a significant association. The pooled HR suggested this effect to be statistically significant (Figure 14).

Muhaxheri et al (30) reported that preoperative lymphocyte count as a continuous variable was associated with worse DFS (Table 12). Boscolo Rizzo et al (34) reported that a lower preoperative lymphocyte count was associated with a reduced DFS, while Košec et al (15) did not find a significant association.

Preoperative lymphocyte count was not found to be a prognostic factor for postoperative complications (15).

TABLE 12. Studies assessing the prognostic value of lymphocyte count on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (multivariate Cox regression model, p=0.151)	NS (multivariate Cox regression model, p=0.151)	NS (multivariate Cox regression model, p=0.969)
Tomasoni et al, 2023 (13)	■ Low preoperative lymphocyte count ≤ 1.08×10³/µL was associated with worse OS (multivariable Cox proportional hazards model, HR = 1.85, 95% CI: 1.13-3.01, p=0.014)	NA	NA
Muhaxheri et al, 2018 (30)	Preoperative Lym count was marginally associated with worse OS (multivariate Cox proportional hazards model, HR=1.	■ Preoperative Lym count was associated with worse DFS (multivariate Cox proportional hazards model, HR=1.534, 95% CI: 1.053-2.235, p=0.026)	NA
Valero et al, 2020 (9)	■ High preoperative Lym group (> 0.8) had a better 5-year OS than the low preoperative Lym (≤ 0.8) group (65.3% vs 41.4%, p<0.001) ■ This was sustained in multivariable analysis	NA	NA
Boscolo Rizzo et al, 2022 (34)	■ Lymphocyte count < 1.97 × 10³/µL was associated with a reduction in OS (< 1.97 [ref. ≥ 1.97], HR=1.33, 95% CI: 1.02-1.73, multivariate Cox proportional hazard model)	■ Lymphocyte count < 1.97 × 10³/µL was associated with a reduced DFS (ref. ≥1.97, HR=1.34, 95% CI: 1.05-1.72, Cox proportional hazard model)	NA
Gaudioso et al, 2021 (31)	NS on multivariable analysis (≥2.1 × 10³/µL [ref. < 1.6] HR=0.80, 95% CI: 0.36-1.74; 1.6-2.0 × 10³/µL [ref. <1,6], HR=0.83, 95% CI: 0.42-1.63)	NA	NA
Zhou et al, 2023 (37)	NS on multivariate analysis (< 2.44/≥ 2.44 × 10⁹/L on univariate analysis, HR=0.684, 95% CI: 0.462-1.014, p=0.059)	NA	NA

* Abbreviations: **CI** – confidence interval, **HR** – hazard ratio, **NA** – not addressed, **NS** – not significant.

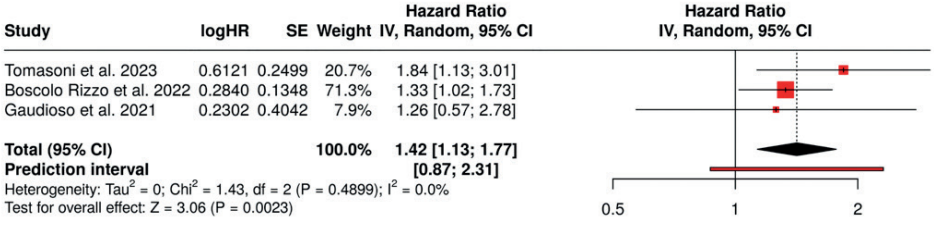

FIGURE 14. The effect of a lower lymphocyte count (categorized values) on overall survival in multivariate analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Monocytes

The prognostic value of preoperative monocyte count was assessed in 6 studies (9, 13, 15, 31, 34, 37) (Table 13). OS was used as an outcome measure in all the included studies, DFS in 2 studies (15, 34), and postoperative complications in 1 (15). Only 2 studies had adequate data for representation in a forest plot (31, 34) (Figure 15).

Only 1 study (9) found a higher monocyte count to be an independent prognostic factor for adverse OS. The other 6 studies did not find a significant association. A pooled HR did not indicate a significant association (Figure 15). None of the studies found monocyte count to be a prognostic factor for DFS or postoperative complications (Table 13).

TABLE 13. Studies assessing the prognostic value of monocyte count on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS (p=0.171)	NS (p=0.070)	NS (p=0.258)
Valero et al, 2020 (9)	■ Preoperative high monocyte group (>0.3) had worse 5-year OS than the low monocyte group (<-0.3) (58.6% vs 71.3%, HR=1.473, 95% CI: 1.240-1.749, p<0.001) ■ This was sustained in multivariate analysis.	NA	NA
Gaudioso et al, 2021 (31)	NS on multivariate Cox proportional hazard model analysis (≥ 0.72 × 10^3/μL [ref. < 0.51], HR=1.66, 95% CI: 0.78-3.50)	NA	NA
Tomasoni et al, 2023 (13)	NS (multivariable Cox proportional hazard model analysis, HR=1.27, 95% CI: 0.68-2.35, p=0.453)	NA	NA
Zhou et al, 2023 (37)	NS (univariate analysis, < 0.48/ ≥ 0.48 × 10^9/L, HR=2.220, 95% CI: 0.816-6.039, p=0.118)	NA	NA
Boscolo Rizzo et al, 2022 (34)	NS (≥ 0.78 [ref. < 0.59], HR=1.06, 95% CI: 0.81-1.38; multivariate Cox regression hazard model)	NS (≥ 0.78 [ref. < 0.59], HR=1.14, 95% CI: 0.90-1.46; multivariate Cox regression hazard model)	NA

* Abbreviations: **CI** – confidence interval, **HR** – hazard ratio, **NA** – not addressed, **NS** – not significant.

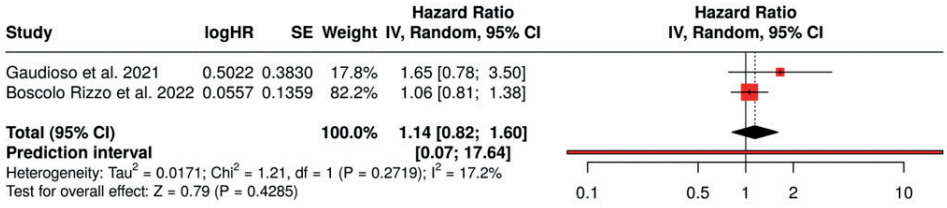

FIGURE 15. The effect of a higher monocyte count (categorized values) on overall survival in multivariate analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Platelets

The prognostic value of platelets was assessed in 6 studies (13, 15, 17, 29, 34, 37) (Table 14). OS was assessed in all of the studies, DFS in 3 (15, 29, 34), and postoperative complications in 1 study (15). The effect of a higher platelet count on OS is shown in Figure 16. The HR reported by Tomasoni et al (13) was harmonized to reflect the effect of a higher platelet count on OS (harmonized HR: >168, HR=0.76, 95% CI: 0.498-1.18). The effect of a higher platelet count on DFS is shown in Figure 17.

Only Košec et al (15) found platelet count to be a prognostic factor for OS. In their study, a low platelet count (<194) was associated with adverse OS. A pooled HR did not indicate a significant association of a higher platelet count with OS (Figure 16).

Košec et al (15) also found a low platelet count to be negatively associated with DFS, while the other two studies did not find a significant effect (Table 14). A pooled HR appears to indicate a significant association of a higher platelet count with adverse DFS (Figure 17).

Platelet count was not found to be a prognostic factor for postoperative complications (15).

TABLE 14. Studies assessing the prognostic value of platelet count on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	■ Low preoperative platelet count (< 194) was associated with adverse OS (multivariate Cox regression model, p=0.036) ■ Low-risk group (> 194) 95% vs. High-risk group (< 194) 78% 2-year OS rate (KM)	■ Low preoperative platelet count (< 244) was negatively associated with DFS (multivariate Cox regression model, VV p=0.006), ■ Low risk group (> 244) 90% vs. high risk group (< 244) 74% 2-year OS rate (KM)	NS (p=0.389)
Lau et al, 2020 (29)	NS (multivariate Cox regression model; High > 260 × 10⁹/L [ref. ≤ 260], HR=1.046, 95% CI: 0.486-2.251, p=0.909)	NS (multivariate Cox regression model; High > 260 × 10⁹/L [ref. ≤ 260], HR=1.564, 95% CI: 0.807-3.031, p=0.185)	NA
Zhou et al, 2023 (37)	NS (multivariate Cox regression model, Plt (< 246.5/≥246.5/L) HR=1.002, 95% CI: 0.998-1.005, p= 0.327)	NA	NA
Tomasoni et al, 2023 (13)	NS (multivariable Cox regression analysis, Plt ≤ 168 × 10³/uL, HR=1.31, 95% CI: 0.85-2.01, p=0.216)	NA	NA
Zhong et al, 2018 (17)	NS (univariate analysis, p=0.509)	NA	NA
Boscolo Rizzo et al, 2022 (34)	NS (≥ 236 [ref. 160 to < 236], HR=1.23, 95% CI: 0.98-1.54; Cox regression hazard model)	NS (≥ 236 [ref. 160 to < 236], HR=1.24, 95% CI: 1.01-1.53; < 160, HR=1.33, 95% CI: 0.98-1.79, Cox regression hazard model)	NA

* Abbreviations: **CI** – confidence interval, **HR** – hazard ratio, **NA** – not addressed, **NS** – not significant.

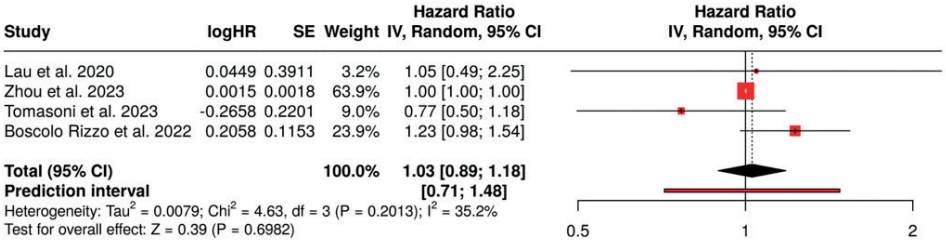

FIGURE 16. The effect of a higher platelet count (categorized values) on overall survival in multivariate analysiss. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

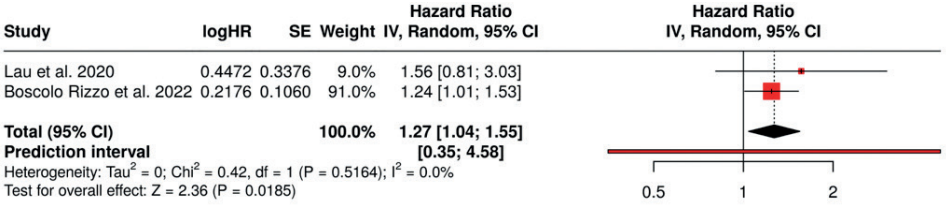

FIGURE 17. The effect of a higher platelet count (categorized values) on disease-free survival in multivariate analysis. Abbreviations: **HR** – hazard ratio, **CI** – confidence interval, **SE** – standard error.

Albumin

The prognostic value of albumin was assessed in 5 studies (13, 21, 23, 31, 39) (Table 15). OS was evaluated in all studies, while DFS and postoperative complications were evaluated in only 1 study (39). There was not enough data to represent the results in a forest plot.

Two studies (13, 23) found higher albumin levels to be associated with longer OS (Table 15). The other studies, however, did not find a significant effect of albumin levels (21, 31, 39).

The 1 study that assessed the effect of albumin on DFS and postoperative complications did not find a significant association (39) (Table 15).

TABLE 15. Studies assessing the prognostic value of albumin levels on overall survival (OS), disease-free survival (DFS), and postoperative complications*

First author and year of publication	OS	DFS	Postoperative complications
Košec et al, 2022 (15)	NS	NS	NA
Onan et al, 2025 (21)	NS (p=0.3)	NA	NA
Tomasoni et al, 2023 (13)	■ Higher albumin levels were associated with better OS (multivariable Cox regression analysis, HR = 0.57, 95% CI: 0.38-0.85, p=0.006)	NA	NA
Kao et al, 2018 (23)	■ 5-year OS was longer in patients with albumin ≥ 4.5 g/L (77.6% vs 58%, p < 0.0001) (univariate analysis, HR=2.109, 95% CI: 1.575-2.825, p < 0.0001)	NA	NA
Gaudioso et al, 2021 (31)	NS (multivariable Cox regression analysis; ≥ 4.4 [ref. < 4.0], HR=0.53, 95% CI: 0.25-1.09; 4.0-4.3, HR=0.59, 95% CI: 0.29-1.22)	NA	NA

* Abbreviations: **CI** – confidence interval, **HR** – hazard ratio, **NA** – not addressed, **NS** – not significant.

The characteristics of the included studies

All the included studies were cohort studies. The vast majority were retrospective studies and only one was a prospective study (16) (Table 4). None of the included studies received any private funding. The funding reported as not conflicting included that from public sources. Only one study (1) reported a potential conflict of interest (Table 16).

TABLE 16. The financial and conflict of interest statements of the included studies

First author and Year of Publication	Funding	Conflict of interest
Onan et al, 2025 (21)	None	None
Mazzocco et al, 2025 (38)	No conflicting funding	None
Zhou et al, 2023 (37)	No conflicting funding	None
Wang et al, 2023 (12)	No conflicting funding	None
Tomasoni et al, 2023 (13)	No conflicting funding	None
Hu et al, 2022 (36)	No conflicting funding	None
Wang et al, 2022 (35)	N/R	None
Ruiz-Ranz et al, 2022 (27)	No conflicting funding	None
Košec et al, 2022 (15)	None	None
Song et al, 2022 (11)	No conflicting funding	None
Zhuang et al, 2022 (16)	No conflicting funding	None
Boscolo-Rizzo et al, 2022 (34)	No conflicting funding	None
Zhou et al, 2021 (33)	No conflicting funding	None
Yamagata et al, 2021 (10)	N/R	None
Wu et al, 2021 (26)	No conflicting funding	None
Hung et al, 2021 (25)	None	None
Xun et al, 2020 (20)	No conflicting funding	None
Zhou et al, 2020 (32)	No conflicting funding	None
Lau et al, 2020 (29)	No conflicting funding	None
Valero et al, 2020 (9)	No conflicting funding	None
Chen et al, 2020 (19)	No conflicting funding	None
Tham et al, 2019 (14)	N/R	None
Jariod-Ferrer et al, 2019 (24)	N/R	None
Gaudioso et al, 2021 (31)	No conflicting funding	None
Chen et al, 2021 (28)	No conflicting funding	None
Kao et al, 2018 (23)	N/R	None
Muhaxheri et al, 2018 (30)	No conflicting funding	None
Sano et al, 2018 (22)	No conflicting funding	Masashi Sugasawa, Omo Pharmacy research grant.
Fu et al, 2016 (18)	No conflicting funding	None
Zhong et al, 2018 (17)	No conflicting funding	None

DISCUSSION

Our study reviewed the prognostic value of peripheral blood biomarkers (NLR, dNLR, PLR, LMR, SII, SIM, Neu, Lym, Mono, Plt, Alb) on OS, DFS, and postoperative complications in patients with HNSCC treated with primary surgery.

The investigated biomarkers increased in complexity, starting from individual WBCs (Neu, Lym, Mono, Plt), through derived ratios (NLR, dNLR, PLR, LMR), to composite indices (SII and SIM). Among WBC biomarkers, only a lower lymphocyte count was shown to be a prognostic factor for OS in most of the analyzed studies, as well as demonstrated by the pooled HR of the forest plot, indicating the highest association. The effect of a higher neutrophil count on OS and of a higher platelet count on DFS were found to be significant in the forest plots, but not when individual studies were analyzed.

Of the derived ratios, NLR was the most frequently studied, with 26 articles included in this review. A higher NLR was strongly associated with OS and DFS, both in the analysis of individual studies and in the forest plot analysis. This effect was confirmed in three meta-analyses (41-43). Mariani et al (43) emphasized the high heterogeneity of the literature. Of the other ratios, only an increased PLR was strongly associated with DFS. Russo et al did, however, report an increased PLR to be associated with adverse OS, although in our analysis, most of the included studies did not find a significant association (44). Russo et al also stated that the association between PLR and DFS may be a false positive, leaving room for further analysis (44). Huang et al also reported the prognostic role of PLR on OS and DFS (45). In our study, a lower LMR was associated with adverse DFS in the forest plot, but not when individual studies were analyzed.

Of composite indices, an increased SII was associated with adverse OS in the forest plot, while only half of the individual studies reported this association. A higher SIM, however, was significantly associated with OS and DFS, both in the individual studies and in forest plots, which demonstrated a strong association.

As nutritional status is an important factor of survival in cancer patients, albumin was also analyzed as a prognostic factor, but no significant association was found. We also contemplated assessing the effect of total protein count on survival, but as only one included study analyzed this effect, we decided not to evaluate it (39). As for the nutritional status, other markers were developed, such as the prognostic nutritional index, the Glasgow Prognostic Score, the fibrinogen/albumin ratio index, the C-reactive protein/albumin ratio, and the albumin/NLR score (10, 13, 21, 23, 35). The prognostic value of these markers should be evaluated.

Only one study in our analysis used postoperative complications as an outcome measure (15). Košec et al reported only dNLR to be associated with the occurrence of postoperative complications. As dNLR was not significantly associated with survival, its utility in clinical practice remains questionable. However, since this was only reported by one study in our analysis, the results should be interpreted with caution. A significant gap in the literature regarding the occurrence of postoperative complications highlights the need for future studies.

Both the systemic inflammatory response and tumor microenvironment play a crucial role in the biology of tumors (4). Several of the included studies found associations between the systemic and local inflammatory responses, mostly focusing on tumor-infiltrating lymphocytes but also on local COX expression (12, 22, 27, 36). These associations further emphasize the potential use of systemic markers as prognostic tools, as they are accessible in clinical practice and related to tumors.

To enable the use of these biomarkers in clinical practice, standardized cutoff values must be determined. The cutoff values differ significantly between various studies. They ranged from 1.94 to 5.7 for NLR, from 140.22 to 171.4 for the effect of PLR on DFS, and from 1.2 to 4.05 for SIM. Cho et al found that pretreatment NLR values below 2 and above 6 implied a better and worse prognosis for HNSCC, respectively (46). Further studies are needed to provide standardized cutoff values.

This review has some limitations. We did not stratify our analysis based on specific tumor locations or stages, as some of the included studies focused specifically on certain tumor locations or stages, leaving room for possible differences in the prognostic value of the biomarkers. This observation may serve as a basis for further, more detailed analyses. Another important limitation is HPV status. We excluded articles focusing specifically on HPV-positive HNSCC, but included those addressing HPV-negative tumors and those that did not assess HPV status or that included both types of cancers. This decision prevented us from stratifying our

findings based on HPV status. Therefore, the results should be interpreted with caution, as the potential modifying effect of HPV status on the observed associations could not be assessed. Justesen et al reported an increased NLR to be a prognostic factor for a worse outcome independent of HPV status in oropharyngeal SCC (47). As literature data are limited, the effect of HPV status on these biomarkers should be evaluated. Forest plots and pooled estimates were used in the current study for descriptive purposes only and do not represent results of a formal meta-analysis. In the absence of a predefined statistical model, study weighting, and formal assessment of heterogeneity, publication bias, or sensitivity analyses, the pooled estimates should not be interpreted as precise summary effect sizes, but rather as indicative of the general direction and variability of findings across studies.

Further studies are needed to determine optimal cutoff values and the impact of tumor location, stage, and HPV status on the prognostic value of the investigated biomarkers. Overall, this review highlights the growing interest in the studied biomarkers as preoperative prognostic tools and invites further research on this topic to provide more standardized values for potential inclusion in clinical practice.

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Ethical approval
Not required

Declaration of authorship
AK, ED conceived and designed the study; AK, ED acquired the data; GG, DV, DS, AP analyzed and interpreted the data; AK, ED drafted the manuscript; GG, DV, DS, AP critically reviewed the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests
All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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