European Journal of Cancer Care

WILEY

RESEARCH ARTICLE OPEN ACCESS

Retrospective Assessment of Neutrophil/Lymphocyte Ratio and CRP Value Correlation with Infections in Cancer Patients

Mehmet Ali Tüz[1] | Hande Aydemir[2] | Güven Çelebi[2] | Nihal Pişkin[2] | Hüseyin Engin[3] | Mustafa Çağatay Büyükuysal[4]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Balıkesir University, Balıkesir, Türkiye | [2]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Türkiye | [3]Department of Medical Oncology, Acıbadem Bakırköy Hospital, İstanbul, Türkiye | [4]Department of Biostatistics, Faculty of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Türkiye

Correspondence: Mehmet Ali Tüz (mehmetali.tuz@balikesir.edu.tr)

Received: 10 March 2025 | **Revised:** 13 January 2026 | **Accepted:** 27 January 2026

Academic Editor: Antonio Navarro-Ballester

Keywords: C-reactive protein | cancer | diagnostic accuracy | infection | neutrophil-to-lymphocyte ratio | prognosis

ABSTRACT

Recent studies have pointed out that CRP and NLR levels are important in determining the prognosis for cancer and diagnosis of infection, but there are few studies on cut-off levels in patients with solid tumours. In this study, the relationship between CRP cut-off levels with infection and NLR with infection has investigated in adult solid organ cancer patients receiving inpatient treatment. Patients with solid cancer hospitalised in ZBEU Oncology and Infectious Diseases between 2013 and 2018 were included to study retrospectively. Patients were separated into 2 groups: 240 patients with clinical and radiological or microbiological evidence of infection as group 1 and 240 patients with no signs of infection as group 2. Both groups were subdivided into patients with metastatic cancer and nonmetastatic cancer. The mean CRP at admission and 24th hour in the group 1 (170.0 and 157.5 mg/L, respectively) were found to be statistically higher than group 2 (51.0 and 47.5 mg/L, respectively) ($p < 0.001$ and $p < 0.001$). The best cut-off value of CRP at admission was found to be 108 mg/L with %72.08 sensitivity, %75.42 specificity ($p < 0.001$) and 88 mg/L 24th hour CRP ($p < 0.001$). Mean values of NLR on admission and 24th hour were significantly higher in group 1 than in group 2 ($p < 0.001$ and $p < 0.001$). The best NLR cut-off value was found to be 7.823 at admission ($p < 0.001$) and 8.4 at 24th hours ($p < 0.001$). Although both tests are used to detect infection in patients with solid cancer, it is important to know that the cut-off values are high. In patients with solid cancer who do not have clinical signs of infection, unnecessary antibiotherapy should not be performed because of high CRP or NLR.

1 | Introduction

C-reactive protein (CRP) is an acute phase reactant synthesised in the liver under the control of tumour necrosis factor-alpha (TNF) and interleukin 6 (IL 6). Serum levels of CRP can be elevated in many conditions, including infection, inflammation, malignancy and autoimmune disease [1, 2]. Chronic inflammation promotes growth, protection from apoptosis and angiogenesis in cancer cells [3, 4]. Proinflammatory cytokines induce chronic systemic inflammation and CRP synthesis in hepatocytes. CRP is elevated in most malignancies, especially in diffuse and metastatic cancers [1, 5].

Several studies have shown that cancer patients with CRP levels above normal limits have higher mortality rates, increased

tumour extent and stage, higher relapse rates and poorer response to chemotherapy, and that prognostic findings worsen with increasing CRP levels [5–8].

In recent years, the neutrophil/lymphocyte ratio (NLR) has also been used as an indicator of systemic inflammation. There are study results suggesting that NLR provides guidance in determining prognostic outcomes including mortality, response to treatment and development of complications in community-acquired pneumonia, ischaemic heart disease and cancer [9–13].

In cancer patients, CRP levels may be elevated due to both chronic inflammation associated with malignancy and infectious causes. Although there are many studies showing that CRP is elevated in inflammatory and infectious pathologies, there are a limited number of studies on what the cut-off level of CRP should be in patients with malignancy [14, 15]. The value of CRP both in the diagnosis of infection and in the monitoring of malignancy and determination of prognosis should be carefully considered. Studies evaluating the relationship between infection and CRP in patients with cancer have generally been performed in patients with neutropenic fever and have been found to have insufficient sensitivity and specificity in detecting infection [16, 17]. In particular, in non-neutropenic patients with solid tumours, the value of CRP in the diagnosis of infectious diseases has not been fully established, and there are very few studies on this subject [1].

Similarly, NLR may be elevated due to both underlying disease and infectious causes. There are not enough studies to show the diagnostic value of NLR in infections that develop in cancer patients. In addition, the confounding effect of infectious causes has not been adequately taken into account in most studies investigating the relationship between NLR and CRP and cancer prognosis [1, 5, 9].

This study, we aimed to investigate CRP cut-off levels and the relationship between infection and NLR in infections that developed in adult solid organ cancer patients who received inpatient treatment in the Oncology and Infectious Diseases wards of our hospital between October 2013 and November 2018. It was also planned to compare these parameters between cancer patients with metastases and cancer patients without metastases.

2 | Materials and Methods

2.1 | Study Design and Patients

The admission files of patients with solid organ cancer who were admitted to the Zonguldak Bülent Ecevit University (ZBEU) Oncology and Infectious Diseases Service between 25.10.2013 and 25.10.2018 were scanned, and the data of patients who met the inclusion criteria were recorded on a case report form and transferred to the computer environment [18]. These dates were chosen because the laboratory methods used in the study did not change over a 5-year period, and the clinicians involved worked at the hospital throughout this time. This study was conducted for the purpose of Turkish Infectious Diseases and Clinical Microbiology speciality thesis, with the approval of ZBEÜ Clinical Research Ethics Committee dated 23/01/2019 and protocol number 2018-220-07/11 [18]. The research adhered to the STARD guidelines for reporting on the diagnostic accuracy of studies [19].

Patients were divided into two groups: infected (group 1) and noninfected (group 2, control group). Patients who had symptoms and/or signs compatible with bacterial and/or fungal infection, and whose presence of bacterial/fungal infection was supported/proven by microbiological and/or radiological methods, were included in the 'infected' group. Routine bacteriological and fungal culture results were considered as microbiological evidence. Infections caused by viral and/or parasitic infectious agents were excluded from this study. Patients in group 1 and group 2 were further divided into two subgroups, 'with metastases' and 'without metastases'.

Patients who died or were discharged within the first 72 h after admission, patients under 18 years of age, patients with a diagnosis of haematological malignancy or lymphoma and patients whose complete blood count and CRP levels were not checked at the intervals and with the method specified below were excluded from the study.

2.2 | Control Group

Patients with solid organ malignancy who were evaluated with anamnesis, system questioning, physical examination, basic laboratory tests, routine bacteriological and mycological cultures and who had no symptoms and findings compatible with infectious diseases were included in the study as control group.

2.3 | Grouping of Patients

Patients enrolled in the study were divided into 4 study groups.

- I. Group 1a: Metastatic cancer patients with infection.
- II. Group 1b: Nonmetastatic cancer patients with infection.
- III. Group 2a: Metastatic cancer patients without infection.
- IV. Group 2b: Patients with cancer without infection and metastases.

2.4 | Clinical and Laboratory Evaluation

Parameters (complete blood count, CRP) routinely checked at the ZBEÜ Health Practice and Research Hospital were recorded on the case report forms using the computer system. Patients' age, sex, total number of days in hospital, number of days in intensive care unit for those in intensive care unit, type of cancer and distant organ metastases, whether they had received chemotherapy in the previous 6 months, antibiotic treatments used in the previous 3 months before and during hospitalisation, other concomitant diseases, CRP levels at the time of initial hospitalisation, 24 h later, between the 3rd and 7th day of hospitalisation and at the end of treatment or before discharge. CRP levels, complete blood count (white blood cells, platelets, neutrophils, lymphocytes, MPV) at the time of initial hospitalisation, 24 h later, between the 3rd and 7th day of hospitalisation and at the end of treatment or before discharge were recorded on the case report form. All culture results and radiology reports obtained up to discharge were recorded on the case report form.

Empirical antibiotic treatment was initiated in patients in whom an infectious focus was identified by the infectious disease specialist. Antibiotic treatment was re-evaluated and adjusted by the infectious disease specialist in patients with clinical deterioration and/or growth of microorganisms resistant to antibiotic treatment in cultures. The changes in treatment and the

microorganisms grown were recorded on the case report form. The growth of *Staphylococcus epidermidis* in at least two blood cultures was considered to be the causative organism. The case report form also recorded the study parameters of patients who were seen by the oncology specialist, but in whom no infectious focus could be detected by physical examination and laboratory tests during follow-up. Fever response was defined as the absence of fever recurrence in patients with fever until the end of antibiotic treatment or discharge. For patients with radiological findings, radiological response was defined as the absence of new radiological findings at the end of treatment and partial or complete resolution of existing findings. Patient data were analysed until death or discharge. Death in patients who did not have a clinical response to treatment for infection and who did not have resolution of biochemical findings of infection and/or microbiological eradication was accepted as infection-related death. Deaths that occurred despite clinical response to treatment, resolution of biochemical evidence of infection and/or microbiological eradication were considered to be death from malignancy and other causes.

Blood cultures were analysed using the BACTEC 9120 blood culture system (Becton Dickinson, USA). Microorganisms were isolated using conventional methods and confirmed using semi-automated API systems (bioMe'rieux, Marcyl'Etoile, France). Antibiotic susceptibility testing was performed using the Kirby–Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

White blood cell count, neutrophil count, lymphocyte count, platelet count and MPV were measured using a Beckman Coulter haematology analyser. CRP levels were measured nephelometrically. The normal range of the nephelometric CRP assay used was 0–8 mg/L.

2.5 | Statistical Analysis

Statistical analyses of the study were performed using the SPSS 19.0 package. Descriptive statistics of categorical variables were expressed as frequencies and percentages; continuous variables were expressed as medians with interquartile range. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to analyse the normality of continuous variables. Independent samples t-test or Mann–Whitney *U* tests were used for 2-group comparisons of continuous variables. The Pearson chi-squared test was used for between-group comparisons of categorical variables. In all statistical analyses in the study, results below a p value of 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve analysis was conducted to determine the cut-off values. In the ROC curve analysis, patients with infection were compared to the control group, metastatic patients with infection were compared to the metastatic control group, and non-neutropenic patients with infection were compared to the non-neutropenic control group. The cut-off values for CRP and NLR were determined as the values at which the Youden index was at its maximum. The discriminatory ability of the cut-off values determined by ROC analysis was assessed by calculating the sensitivity, specificity, positive predictive value, negative predictive value and the area under the curve (AUC) with their respective 95% confidence intervals (CIs). The DeLong test was used to perform a statistical comparison of the AUCs between admission and 24 h.

3 | Results

A total of 2415 patients diagnosed with solid organ cancer who were followed up and treated in the oncology and infectious diseases services during the specified time interval were identified. Figure 1 shows the flowchart for this study, which is based on the STARD guidelines. Among these patients, those who did not meet the study criteria were excluded, and 240 patients in the infection group (group 1) and 240 patients in the control group (group 2) who met the study criteria were identified.

In the study, 300 patients (62.5%) were male and 180 patients (37.5%) were female. The reasons for hospitalisation were infections in 27.1% (130 patients), noninfectious oncological emergencies in 18.3% (88 patients), palliative care in 43.8% (210 patients), chemotherapy in 9.4% (45 patients) and further investigation in 1.5% (7 patients); 87.5% (420 patients) had a planned and ongoing chemotherapy protocol, 12.5% (60 patients) had not received chemotherapy or had not planned a new chemotherapy protocol in the previous 6 months. Metastases in at least one distant organ were present in 375 patients (78.1%). The most common distant organs were bone (161/375, 42.9%), liver (147/375, 39.2%), lung (79/375, 21.0%), brain (66/375, 17.6%), and kidney (40/375, 10.7%).

In 35.8% of all patients (172 patients), there was a history of antibiotic and/or antifungal use in the 3 months prior to hospitalisation. Respiratory fluoroquinolones (levofloxacin, moxifloxacin) were used in 51 patients, 2nd- and 3rd-generation cephalosporins in 45 patients, aminopenicillin with beta-lactamase inhibitors in 26 patients, ciprofloxacin in 24 patients and carbapenems in 16 patients. The remaining 10 patients had no history of different antibiotic groups or antifungal use. Of all patients, 149 (31.0%) died during follow-up.

When comparing group 1 and group 2, there was no statistically significant difference between the groups in terms of age, gender, comorbidities and chemotherapy rate. There was a statistically significant difference when comparing group 1 and group 2 in terms of the distribution of the underlying cancer type, but no difference was observed when patients with gynaecological cancer were excluded. The difference may be due to gynaecological cancer ($p = 0.06$).

In the infection and metastasis groups, patients were compared with respect to age, sex, comorbidities, rate of chemotherapy and number of distant organ metastases (Table 1). The median age of patients in group 2b was statistically significantly ($p = 0.034$) older than the median age of patients in group 1b. The proportion of patients using antibiotics in the last 3 months prior to hospitalisation was statistically significantly higher in group 1a and group 1b, i.e. in patients diagnosed with infection, compared to the other subgroups ($p = 0.01$). As these were exploratory subgroup analyses, no additional adjustments were made between groups.

When comparing group 1 and group 2, median CRP ($p < 0.001$), median NLR ($p = 0.017$) and median CRP measured at 24 h ($p < 0.001$) and median NLR ($p = 0.001$) were statistically significantly higher in group 1 compared to those without infection (Table 2). The study subgroups were compared in terms of median CRP levels. No statistically significant difference was found between group 1a and group 1b in hospital admission and 24 h CRP levels ($p > 0.05$). The median CRP values on admission

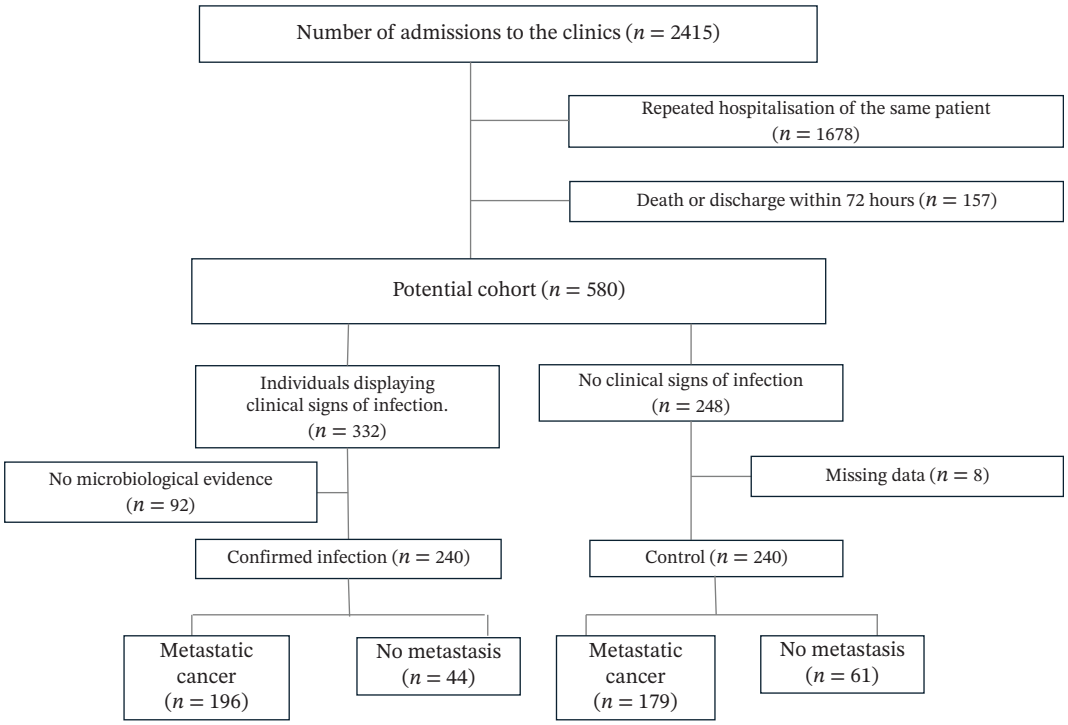

FIGURE 1 | Study flowchart.

and at 24 h were statistically significantly higher in group 1a and group 1b than in group 2a. The median CRP levels in group 2a were also statistically significantly higher than in group 2b ($p < 0.05$ for all comparisons). The median NLR in group 1a was statistically significantly higher than in group 1b and group 2a ($p < 0.05$ for all comparisons). The median 24 h NLR was statistically significantly higher in group 1a than in the other three groups ($p < 0.05$). The comparison of the median values of CRP and NLR on admission and at 24 h by group is shown in Table 2.

There were 61 patients with a neutrophil count of less than 500 per mm^3 on admission and who received 24 h and/or antibiotic treatment with a diagnosis of neutropenic fever. These patients were excluded from the study population and the NLR values were recalculated in groups. It was found that 186 of the remaining 419 patients were infected, and the median values for hospital admission ($p < 0.001$) and 24 h NLR ($p < 0.001$) were statistically significantly higher in the infected group compared to the non-infected group.

TABLE 1 | General characteristics of the study groups.

		Group				*p*
		1a (*n* = 196)	**1b (*n* = 44)**	**2a (*n* = 179)**	**2b (*n* = 61)**	
Age*	Median (IQR)	62.5 (54–69)	65.5 (57.25–73.5)	62 (54–69)	58 (51–65)	0.033
Gender	Woman *n* (%)	74 (%37.8)	18 (%40.9)	61 (%34.1)	27 (%44.3)	0.470
	Man *n* (%)	122 (%62.2)	26 (%59.1)	118 (%65.9)	34 (%55.7)	
Percentage of recipients of chemotherapy	*n* (%)	170 (%86.7)	39 (%88.6)	157 (%87.7)	54 (%88.5)	0.977
Comorbidities	HT *n* (%)	59 (%30.1)	17 (%38.6)	40 (%22.3)	17 (%27.9)	0.135
	DM *n* (%)	38 (%19.4)	6 (%13.6)	34 (%19)	13 (%21.3)	0.790
	HF *n* (%)	37 (%18.9)	10 (%22.7)	26 (%14.5)	12 (%19.7)	0.522
	COPD *n* (%)	22 (%11.2)	10 (%22.7)	14 (%7.8)	8 (%13.1)	0.690
	CKD *n* (%)	7 (%3.6)	1 (%2.3)	5 (%2.8)	2 (%3.3)	0.962
Number of distant organ metastases	1 *n* (%)	112 (%57.1)		105 (%58.7)		0.382
	2 *n* (%)	59 (%30.1)		61 (%34.1)		
	3 *n* (%)	21 (%10.7)		11 (%6.1)		
	> 3 *n* (%)	4 (%2.0)		2 (%1.1)		
Use of antibiotics**	*n* (%)	85 (%43.4)	18 (%40.9)	55 (%30.7)	14 (%23)	0.010
Mortality	*n* (%)	111 (%56.6)	17 (%38.6)	18 (%10.1)	3 (%4.9)	< 0.001

*The median age of patients in group 1b was statistically significantly older than that of patients in group 2b ($p = 0.034$). There was no statistically significant difference in median age in other comparisons between groups ($p > 0.05$).
**Patients with a history of antibiotic use in the previous 3 months.

TABLE 2 | Evaluation of CRP and NLR in the study groups.

		CRP on admission	CRP 24th hour	NLR on admission	NLR 24th hour
Group 1 ($n = 240$)	Median (IQR)	170.0 (94.5–264)	157.5 (106.0–240.5)	7.05 (2.64–15.92)	8.80 (2.86–17.92)
Group 2 ($n = 240$)	Median (IQR)	51.0 (13.25–107.75)	47.5 (14.25–108)	4.84 (2.63–9.18)	5.38 (2.67–9.58)
p		< 0.001	< 0.001	0.017	0.001
Group 1a $n = 196$	Median (IQR)	174.5 (104.75–264)	158.0 (108.25–238.5)	8.2 (3.0–18.15)	9.5 (3.69–19.44)
Group 1b $n = 44$	Median (IQR)	132.5 (66.5–259)	143.0 (70.25–278.75)	3.92 (0.54–8.04)	4.25 (0.84–13.93)
Group 2a $n = 179$	Median (IQR)	72.0 (25–125)	74.0 (31–116)	5.5 (2.95–10.4)	6.5 (3.07–11.25)
Group 2b $n = 61$	Median (IQR)	11.0 (4.5–28)	12.0 (5.5–27)	3.7 (2.30–6.79)	4.0 (2.21–6.19)
p		< 0.001	< 0.001	< 0.001	< 0.001

In the ROC curve analysis performed to determine the best CRP cut-off value to differentiate infection in all cancer patients in our study, the best CRP cut-off value at hospital admission was 108 mg/L with 72% sensitivity and 75% specificity ($p < 0.001$), and the best CRP cut-off value at 24 h was 88 mg/L with 83% sensitivity and 67% specificity ($p < 0.001$). When only patients with a diagnosis of metastatic malignancy were considered, the best CRP cut-off value at admission was 118 mg/L with 70% sensitivity and 74.9% specificity ($p < 0.001$), and the best CRP cut-off value at 24 h was 121 mg/L with 70% sensitivity and 77.5% specificity ($p < 0.001$) (Table 3). The ROC curve analysing all patients is shown in Figure 2(a), and the ROC curve analysing metastatic patients only is shown in Figure 2(b). The best cut-off values for the NLR ROC curve analysis to determine infection and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and AUC of the test based on these values are shown in Table 3. In the analysis performed by excluding patients with a neutrophil count of less than 500 per mm^3, the best cut-off value for NLR at admission was 7.823 ($p < 0.001$) with a sensitivity of 59.7% and a specificity of 69.5%, and the best cut-off value for NLR at 24 h was 8.4 ($p < 0.001$) with a sensitivity of 63.9% and a specificity of 70% (Table 3). The ROC curve analysis after excluding neutropenic patients is shown in Figure 2(c). No statistically significant difference was found when comparing the AUC values for CRP and NLR during hospital admission and 24 h later (Table 4).

Microbiological evidence was present in all patients in the infection group, while radiological evidence was present in 53.3%. 124 patients were treated with a diagnosis of pneumonia, 91 with urinary tract infection, 13 with skin and soft tissue infection, 12 with peritonitis, 7 with fungemia and 4 with acute gastroenteritis. Fifty-four patients were treated for neutropenic fever. Out of 240 patients, only 6 had no obvious focus of infection and were treated for neutropenic fever. The most frequently isolated microorganisms were *E. coli* (101/240, 44.2%) and *Klebsiella* spp. (45/240, 18.75%). Among the cultures obtained from group 1 patients, 23.75% of the cultures grew extended-spectrum beta-lactamase (ESBL)-positive members of *Enterobacteriaceae*, 17.1% grew *Acinetobacter* spp, 12.9% grew *Pseudomonas aeruginosa* and 11.25% grew *Enterococcus* spp. When Gram-positive organisms were analysed, methicillin-sensitive *Staphylococcus aureus* (MSSA) was found in only 15 patients (6.25%) and methicillin-resistant *Staphylococcus aureus* (MRSA) in 1 patient.

There was no statistically significant difference between group 1a and group 1b in terms of clinical ($p = 0.803$), radiological ($p = 0.745$) and microbiological ($p = 0.958$) response (Table 5). The mortality rate was statistically significantly higher in group 1a than in group 1b ($p = 0.031$), while the mortality rate due to infection alone was similar in groups 1a and 1b, but not statistically significant ($p = 0.054$).

The median CRP and NLR values at admission and at 24 h were statistically significantly higher in patients who died than in those who were discharged ($p < 0.001$ for all comparisons). The median CRP at 24 h was statistically significantly higher in patients who died in group 2 ($p = 0.014$). Although the median CRP on admission was higher in these patients than in discharged patients, it was not statistically significant ($p = 0.15$) (Table 6).

4 | Discussion

In recent years, many studies have shown that CRP and NLR can be prognostic indicators in cancer patients [5–8, 20–22]. When these studies are reviewed, it is clear that there are not enough studies considering the effect of possible infections in cancer patients with CRP and NLR. In our study, patients with microbiological evidence in addition to clinical findings suggestive of infection were defined as infected patients. Patients with no clinical, microbiological and radiological evidence of infection during hospitalisation were included in the control group. All 240 patients with infection had microbiological evidence, and 129 patients had radiological evidence in addition to microbiological evidence. Our study also grouped cancer patients with and without metastases and investigated the best cut-off values for CRP and NLR in infected patients.

Although there are studies investigating the role of CRP and NLR in determining infection in cancer patients, most of these studies have evaluated patients with haematological malignancies or patients diagnosed with neutropenic fever [14–16, 23]. The value of these markers in determining infection in patients with non-neutropenic solid cancers has not been sufficiently investigated [1]. In our study, only 12.7% of all patients were neutropenic (neutrophil count < 500/mm^3) and/or receiving treatment with a diagnosis of neutropenic fever. In addition, the analyses performed in our study for mean NLR and NLR cut-off were re-examined by excluding these neutropenic patients.

In our study, hospital admission and 24-h CRP levels were statistically significantly higher in cancer patients with infection compared with those without infection. The median CRP hospitalisation value in the group of patients with infection was 170

TABLE 3 | Best cut-off values of CRP and NLR to determine infection.

	*	Cut-off (mg/L)	Sensitivity (%95 CI)	Specificity (%95 CI)	PPV (%95 CI)	NPV (%95 CI)	AUC (%95 CI)	*p*
All patients ($n = 480$)	CRP1	108	%72.08 (65.9–77.7)	%75.42 (69.5–80.7)	%74.57 (69–81)	%72.98 (66–78)	0.819 (0.781–0.852)	< 0.001
	CRP2	88	%83.75 (78.5–88.2)	%67.08 (60.7–7)	%71.79 (66–77)	%80.50 (74–86)	0.836 (0.800–0.868)	< 0.001
	NLR1	7.823	%47.50 (41.0–54.0)	%70.42 (64.2–76.1)	%61.62 (54–68)	%57.29 (51–63)	0.563 (0.517–0.608)	0.019
	NLR2	12.57	%40.00 (33.8–46.5)	%82.92 (77.5–87.5)	%70.07 (61–77)	%58.02 (52–63)	0.587 (0.542–0.632)	0.001
Metastatic patients only ($n = 375$)	CRP1	118	%70.4 (63.1–76.4)	%74.9 (67.7–80.9)	%75.27 (68–81)	%69.43 (63–77)	0.797 (0.753–0.837)	< 0.001
	CRP2	121	%70.05 (63.1–76.4)	%77.53 (70.7–83.4)	%77.40 (71–84)	%70.20 (64–77)	0.815 (0.772–0.853)	< 0.001
	NLR1	12.6	%36.04 (29.3–43.2)	%83.71 (77.4–88.8)	%71.00 (61–80)	%54.55 (48–61)	0.579 (0.527–0.629)	0.010
	NLR2	9.2	%51.27 (44.1–58.4)	%70.79 (63.5–77.3)	%65.79 (58–73)	%56.95 (50–64)	0.598 (0.546–0.648)	0.001
Non-neutropenic ($n = 419$)	NLR1	7.823	%59.68 (52.3–66.8)	%69.53 (63.2–75.4)	%60.99 (52–67)	%68.35 (63–75)	0.685 (0.638–0.730)	< 0.001
	NLR2	8.4	%63.98 (56.6–70.9)	%69.96 (63.6–75.8)	%62.96 (57–71)	%70.87 (64–76)	0.698 (0.651–0.741)	< 0.001

*CRP1: CRP on admission CRP2: CRP 24th hour NLR1: NLR on admission NLR2: NLR 24th hour.

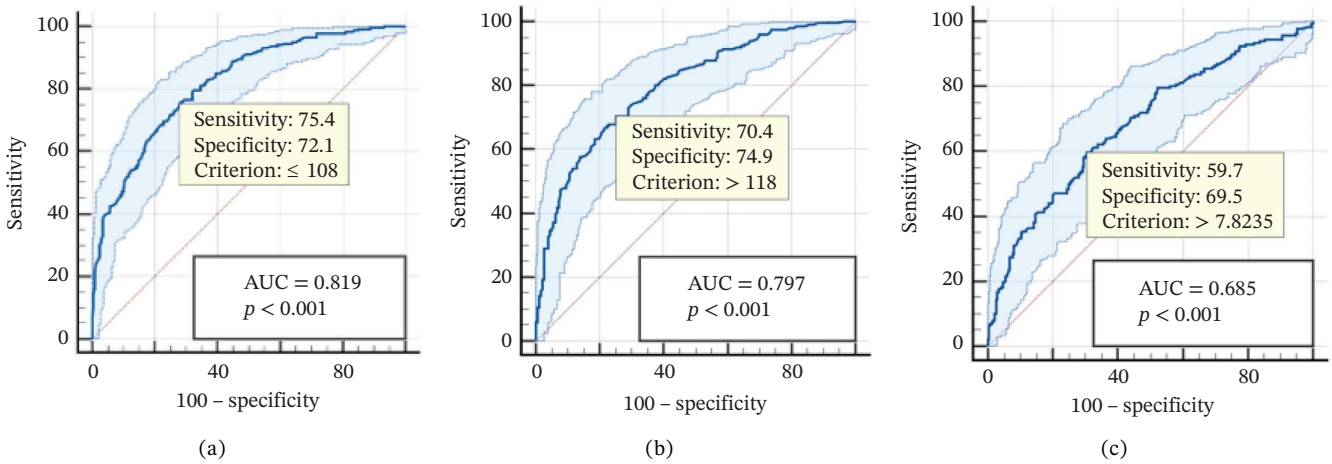

FIGURE 2 | (a) ROC curve showing the relationship between admission CRP and infection in all patients. (b) ROC curve showing the relationship between admission CRP and infection in patients with metastatic malignancy. (c) ROC curve showing the relationship between admission NLR and infection in non-neutropenic patients.

versus 51 mg/L in the control group, while the 24-h CRP value was 157.5 versus 47.5 mg/L, respectively. In a 2017 study conducted in paediatric cancer patients, the median hospital CRP level was found to be statistically significantly higher in the blood culture–positive group in patients hospitalised with suspected sepsis than in the culture-negative group [14].

In a study conducted by Li et al. in 2019 in patients with paediatric solid malignancies, comparing 34 infected patients with a control group of 144 patients, it was reported that the median CRP hospitalisation value was 97.0 versus 1.99 mg/L, respectively [24]. In this study, the patient groups were divided into two subgroups according to the progression and stability of the underlying disease. While no statistically significant difference was found between the CRP levels in the group with infection and the subgroups, the mean CRP level in the control group was found to be statistically significantly higher in patients with progressive disease than in patients with stable disease. In the control group, the median CRP value was reported to be 12.99 mg/L in the subgroup with progressive disease and 0.94 mg/L in the group with stable disease [24]. In our study, similar to this study, the infection and control groups were divided into subgroups with respect to metastases. There was no statistically significant difference in median CRP between those with metastases in the infection group (group 1a) and those without metastases (group 1b). In these groups (groups 1a and 1b), the median CRP level was significantly higher than in the group with metastatic cancer without infection (group 2a). Median CRP levels at hospital admission were also higher in the group without infection and metastatic cancer (group 2a) than in the group with infection and metastatic cancer (group 2b). The main difference between our study and this study is that our patient group was adult and the number of patients was high.

When analysing the data in the literature, the limited number of studies evaluating the adequacy of CRP in differentiating infection in patients with solid cancers give variable results. In particular, there are not enough studies in non-neutropenic patients with solid cancers. In one study conducted in patients with solid cancers, the clinical value of CRP in differentiating malignant fever from fever due to infection was investigated, and it was found that CRP levels were similar in both groups, but unlike the group with infection, CRP levels in the malignant fever group did not decrease significantly during follow-up [25]. In another study of 37 febrile episodes in patients with urological cancer, it was concluded that CRP may not be sufficient to differentiate infectious fever from malignant fever [26]. In a case series of 15 patients who had fever as a side effect of the

TABLE 4 | Comparison of AUC values for CRP and NLR during hospital admission and at 24 h using the DeLong test.

	*	AUC	%95 CI	Difference between areas	95% CI of difference	*p*
All patients ($n = 480$)	CRP1	0.819	0.781–0.852	0.0176	−0.00341–0.0386	0.101
	CRP2	0.836	0.800–0.868			
	NLR1	0.563	0.517–0.608	0.0241	−0.00741–0.0556	0.134
	NLR2	0.587	0.542–0.632			
Metastatic patients only ($n = 375$)	CRP1	0.797	0.753–0.837	0.0182	−0.00870–0.0451	0.184
	CRP2	0.815	0.772–0.853			
	NLR1	0.579	0.527–0.629	0.0188	−0,0170–0.0546	0.304
	NLR2	0.598	0.546–0.648			
Non-neutropenic ($n = 419$)	NLR1	0.685	0.638–0.730	0.0124	−0.022–0.047	0.480
	NLR2	0.698	0.651–0.741			

*CRP1: CRP on admission CRP2: CRP 24th hour NLR1: NLR on admission NLR2: NLR 24th hour.

TABLE 5 | Evaluation of response to treatment in infected patients.

		Group 1a ($n = 196$)	Group 1b ($n = 44$)	All patient ($n = 240$)	p
Clinic response	n (%)	133 (%67.9)	29 (%65.9)	162 (%67.5)	0.803
Fever response*	n (%)	108 (%78.3)	24 (%80.0)	134 (%78.8)	0.745
	Median (day) (IQR)	4 (2–7.75)	5 (2–9.75)	4 (2–8)	
Radiologic response**	n (%)	43 (%41)	8 (%33.3)	51 (%39.5)	0.491
Microbiological eradication	n (%)	130 (%66.3)	29 (%65.9)	159 (%66.3)	0.958
Microbiological eradication provided sample	Blood n (%)	49 (%25)	11 (%25)	60 (%25)	0.469
	Sputum n (%)	53 (%27)	13 (%29.6)	66 (%27.5)	
	Urine n (%)	68 (%34.7)	16 (%36.4)	84 (%35)	
	Tracheal Aspirat n (%)	25 (%12.8)	7 (%15.9)	32 (%13.3)	
Discharged	n (%)	85 (%43.4)	27 (%61.4)	112 (%46.7)	0.031
Death***	Total n (%)	111 (%56.6)	17 (%38.6)	128 (%53.3)	0.031
	Infection-related n (%)	64 (%57.7)	14 (%82.4)	78 (%60.9)	0.054
	Due to malignancy n(%)	47 (%42.3)	3 (%17.6)	50 (%39.1)	0.054

*There were 138 patients with fever in group 1a and 30 patients in group 1b. Fever response indicates the proportion of patients with fever response among patients with fever.

**Radiological response indicates the proportion of patients with radiological improvement among patients with radiological evidence. (The number of patients with radiological evidence was 105 patients in group 1a, 24 patients in group 1b and 129 patients in total).

***Mortality rates due to infection and malignancy; refers to the proportion of patients who died due to infection or malignancy among patients who died.

TABLE 6 | Comparison of CRP and NLR levels in deceased and discharged patients.

			CRP on admission	CRP 24th hour	*	NLR on admission*	NLR 24th hour*
All patients ($n = 480$)	Deceased ($n = 149$)	Median (IQR)	170 (90.5–262.5)	163 (101.5–232)	($n = 126$)	10.06 (5.63–10.07)	12.73 (6.54–24.6)
	Discharge ($n = 331$)	Median (IQR)	76 (22–152)	79 (24–138)	($n = 293$)	5.4 (3.0–11.06)	6.22 (3.29–12.4)
	p		< 0.001	< 0.001		< 0.001	< 0.001
Control group ($n = 240$)	Deceased ($n = 21$)	Median (IQR)	70 (47.5–120)	87 (57–130.5)	($n = 21$)	7.07 (4.18–10.75)	6.57 (2.85–12.0)
	Discharge ($n = 219$)	Median (IQR)	46 (13–107)	42 (13–107)	($n = 212$)	4.85 (2.77–9.18)	5.48 0.2–86 (2.84–9.72)
	p		0.15	0.014		0.280	0.649

*NLR in patients with a neutrophil count > 500 mm^3 on admission and 24th hour who have not received treatment for neutropenic fever.

combination of dabrafenib and trametinib for the treatment of advanced malignant melanoma and who had no signs of infection, the mean CRP was 65.1 mg/L during the febrile period and 47.1 mg/L after the fever subsided, and it was shown that the neutrophil count and percentage were higher in the febrile period [27]. In contrast to these studies, in our study, only 2 patients in the control group had a single episode of fever and there was no recurrence of fever during follow-up.

Studies evaluating the clinical value of CRP in patients with neutropenic fever and haematological cancer have shown mixed results. A study comparing bacteremic and nonbacteremic neutropenic fever episodes in adult patients with leukaemia reported no statistically significant difference in CRP levels between the two groups at the time of application [28]. As clinical findings of infection in neutropenic patients may be subtle, fever may sometimes be the only finding of bacterial infection, but fever may also develop due to underlying disease and other causes. In a study comparing CRP and other markers (IL-6 and procalcitonin) in patients followed up with a diagnosis of neutropenic fever who remained febrile for more than 3 days, no statistically significant difference in median CRP levels was found between the group with infection-related complications and the group without complications [23]. In another study investigating the value of CRP in predicting bacteraemia in patients aged 16 years and older with a diagnosis of neutropenic fever, the median CRP on admission was 56 mg/L in the nonbactaeremia group and 159 mg/L in the bacteraemia group. The difference between the two groups was reported to be statistically significant ($p < 0.01$) [15]. In this retrospective study in which 239 out of 286 patients were diagnosed with solid cancer and 38 patients had bacteraemia, CRP ROC curve analysis showed an AUC of 0.655 in differentiating bacteraemia, sensitivity of 57.6% and specificity of 67.3% when the CRP cut-off value was 100 mg/L, while sensitivity was lower at 36.8% and specificity was higher at 88.3% when the cut-off value was 200 mg/L [15]. In another study of paediatric cancer patients followed up for suspected sepsis, CRP ROC curve analysis showed an AUC of 0.638 in predicting bacteraemia. In this study, when the cut-off value was 84 mg/L, the sensitivity was 53.49%, the specificity was 70.04%, the positive predictive value (PPV) was 23% and the negative predictive value (NPV) was 90%, and when the cut-off value was 53 mg/L, the sensitivity was 72.09%, the specificity was 51.36%, the PPV was 19.87% and the NPV was 91.67% [14].

In the study by Li et al. in paediatric patients, AUC 0.935, the best cut-off value was 28 mg/L with 88.2% sensitivity and 87.3% specificity in CRP ROC curve analysis for detection of infection. In addition, this study found CRP to be an important indicator for predicting tumour progression alone and in combination with other markers [24].

In our study, in the ROC curve analysis of CRP in determining infection in adult patients with solid cancers, the best cut-off value was found to be 108 mg/L with an AUC of 0.819, 72.08% sensitivity, 75.42% specificity, 74.57% PPV and 72.98% NPV. In the ROC analysis for 24th-hour CRP, the AUC was 0.836 and the best cut-off was 88 mg/L with a sensitivity of 83.75%, specificity of 67.08%, PPV of 71.79% and NPV of 80.5%. When these results are evaluated in the light of literature data, they show that CRP is an important marker for the detection of infection in solid cancer patients with relatively good sensitivity, specificity, PPV and NPV.

It is known that CRP and NLR is lower in the early period of infection and increases more in the 24–48 h of follow-up [3, 4, 23]. In our study, no statistically significant difference was found between the CRP level at admission and the CRP level at 24 h of clinical follow-up in patients with infection. No statistically significant difference was found when the AUCs at admission and after 24 h were compared for both CRP and NLR. We believe that this may be related to the time from symptom onset to hospital admission.

There are many studies showing that NLR is a useful parameter in predicting the prognosis of sepsis, complications such as acute kidney injury and the detection of bacteraemia [10–13]. In the study by Loonen et al. comparing biochemical markers in predicting bacteraemia, the mean NLR was 23.0 in bacteremic patients and 12.2 in patients with clinical infection without bacteraemia [11].

There are very few studies investigating the value of NLR in the diagnosis of infection in cancer patients. In the study by Odagiri et al. comparing the findings of cancer patients with malignant fever and fever due to infection, it was found that there was no statistically significant difference between the two groups in terms of the NLR value examined in the last 1 month before the onset of fever, but it was reported that the NLR increased statistically significantly more in the infected group with high fever [29]. In our study, when neutropenic patients were excluded, the median NLR at admission was 5,08 and the median NLR at 24 h was 5.67 in the group without infection, whereas the median NLR at admission was 9.34 and the median NLR at 24 h was 12.51 in the patients with infection, which was statistically significantly higher. When NLR was analysed according to subgroups, it was found to be statistically significantly higher in the infected metastatic group than in the other groups. In metastatic patients without infection, the median NLR at 24 h was statistically significantly higher than in nonmetastatic patients.

In the ROC curve analysis performed to investigate the performance of NLR in detecting infection in cancer patients, the AUC for NLR at admission was 0.685, the best cut-off value was 7.823 with a sensitivity of 59.68%, specificity of 69.53%, PPV of 60.99% and NPV of 68.35%. In the 24-h NLR ROC curve analysis, the AUC was 0.698, the best cut-off was 8.4 with a sensitivity of 63.98%, specificity of 69.96%, PPV of 62.96% and NPV of 70.87%. We believe that NLR is a test that can be used to support the diagnosis of infection because it is statistically significantly higher in cancer patients with infection than in those without, and it is an easily calculable and cost-effective test.

Over the past few years, most studies evaluating prognosis in patients with solid tumours have used indices combining CRP with parameters such as albumin and lymphocyte count to assess systemic inflammation, rather than CRP alone [30]. A 2023 meta-analysis evaluating prospective studies in patients diagnosed with prostate cancer demonstrated that high CRP levels are associated with a poor prognosis. Following analyses aimed at reducing heterogeneity, it was found that elevated CRP levels were associated with poorer survival outcomes according to the stage of malignancy [31]. Studies investigating the relationship between indices indicating systemic inflammation and prognosis

have also found that the results of these indices affected by elevated CRP are associated with poor prognosis [30, 32–34]. A 2025 study evaluating 209 patients with non-small-cell lung cancer assessed the lymphocyte–CRP ratio (LCR), NLR and other indices that could indicate systemic inflammation. The study demonstrated that the LCR was significantly associated with disease stage and could be used as a prognostic marker [30]. Furthermore, the LCR was found to have a higher AUC than other systemic inflammation markers and was superior as a prognostic marker [30]. In a study evaluating 2424 patients diagnosed with stage 4 cancer, LCR was shown to have higher AUC and C-index values than the other 15 scoring systems that could be used as prognostic markers [32]. While these studies provide evidence that various systemic inflammation markers, including CRP and NLR, may be prognostic indicators, the confounding effect of infection has not been sufficiently considered and adequate study designs to exclude infection have not been specified.

Studies comparing prognostic markers have demonstrated that both CRP alone and CRP-incorporating scoring systems are superior to NLR and have higher AUCs [30, 32]. Similarly, numerous studies have shown that CRP is better than NLR at detecting infection in patients with malignancy [29]. In our study, CRP demonstrated superior performance to NLR in detecting infection. This may be because NLR is more affected by noninfectious conditions, such as chemotherapeutic drugs and malignancy-related complications, than CRP is [9, 35]. Additionally, lymphocytes are directly involved in antitumour activity, and a decrease in lymphocytes and a marked increase in neutrophil count and NLR has been observed in advanced-stage patients [22, 30, 35]. In our study, patients with a variety of tumour types, most of whom were in the advanced stage of the disease, may have limited NLR's ability to determine infection.

It has been demonstrated that some solid tumours can express CRP. Furthermore, changes in CRP and NLR may occur at varying rates in different tumour types at advanced stages of the disease [5–7]. Evaluating patients with many different tumour types in our study may have affected the role of CRP and NLR in detecting infection and determining cancer prognosis. However, some studies involving different tumour types have shown that CRP and NLR are important in determining cancer prognosis independently of tumour type [9, 34].

Many studies have shown that CRP and NLR can be a prognostic marker in cancer patients [5–8, 20–22]. It is known that the prognosis of metastatic patients is worse than that of nonmetastatic patients [20, 36]. The mortality rate was statistically significantly higher in the group of patients with metastases and no infection than in the group of patients without infection and metastases. As in the control group, the mortality rate was statistically significantly higher in patients with infection compared to those without metastases. Although malignancy-related mortality was higher in the group with infection and metastases, it was not statistically significant. On the other hand, median CRP and NLR levels on admission and at 24 h were statistically significantly higher in patients who died compared with those who were discharged. Our study data support the finding that CRP and NLR levels were higher in the metastatic group, similar to recent studies. However, as mortality could only be followed up during hospitalisation in our study, we believe that prospective studies with longer follow-up are needed to evaluate the relationship between CRP and mortality and prognosis more accurately.

Strengths of our study include the fact that it is one of the few studies to investigate the cut-off levels of CRP and NLR in detecting infection in adult solid tumour patients, the fact that it included a total of 480 cancer patients with 240 infected and 240 noninfected patients, which is higher than the number of patients in studies in the literature, and the exclusion of the neutropenic group from the study patients when evaluating the NLR ratio. The study had several limitations. First, it was retrospective, so only hospitalisation records could be obtained. Second, confounders were not adjusted for, and there was potential bias from prior antibiotic exposure. It was found that patients with infections had a higher rate of antibiotic use in their medical history. A recent history of infection and antibiotic use may have created potential bias among clinicians.

5 | Conclusion

In the ROC curve analysis for CRP cut-off in determining infection in patients with solid cancers, the best cut-off value was found to be 108 mg/L, while this value was 88 mg/L for the 24 h CRP value. In patients with metastatic malignancies, the best admission cut-off for CRP in determining infection was 118 mg/L and the 24 h cut-off was 121 mg/L. The median admission and 24 h NLR values were found to be statistically significantly higher in patients with infection and non-neutropenic patients compared to the group without infection and neutropenia.

Although both tests are used to detect infection in cancer patients, it is important to be aware of the high cut-off values. Unnecessary antibiotherapy should not be planned for cancer patients without clinical signs of infection based on elevated CRP or NLR alone. These levels were also found to be higher in metastatic patients than in nonmetastatic patients. At the same time, median CRP levels were found to be higher in patients who died. We believe that prospective studies are needed to determine the relationship between CRP and NLR with mortality and prognosis.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mehmet Ali Tüz, Mustafa Çağatay Büyükuysal and Hande Aydemir. The first draft of the manuscript was written by Mehmet Ali Tüz, and all authors commented on previous versions of the manuscript.

Acknowledgements

We thank the other doctors of Infectious Diseases and Clinical Microbiology (Hande İdil Tüz, Meral Çeker) working at Zonguldak Bulent Ecevit University during the study period.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Disclosure

All authors read and approved the final manuscript. This article is based on a revised version of the Turkish Infectious Diseases and Clinical

Microbiology speciality thesis "In cancer patients retrospective assessment of neutrophil/lymphocyte ratio and CRP value correlation with infections" that has been submitted to the Faculty of Medicine at the Zonguldak Bulent Ecevit University in 2019. The thesis has been prepared by Mehmet Ali Tüz under the supervision of Hande Aydemir.

Ethics Statement

This study was conducted with the approval of the Zonguldak Bülent Ecevit University Clinical Research Ethics Committee dated 23/01/2019 and protocol number 2018–220-07/11.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analysed during this study are available online in Supporting information labelled as SPSS data file.

References

1. F. A. Mahmoud and N. I. Rivera, "The Role of C-reactive Protein as a Prognostic Indicator in Advanced Cancer," *Current Oncology Reports* 4, no. 3 (2002): 250–255, https://doi.org/10.1007/s11912-002-0023-1.

2. S. Black, I. Kushner, and D. Samols, "C-reactive Protein," *Journal of Biological Chemistry* 279, no. 47 (2004): 48487–48490, https://doi.org/10.1074/jbc.R400025200.

3. A. Mantovani, C. Garlanda, and P. Allavena, "Molecular Pathways and Targets in cancer-related Inflammation," *Annals of Medicine* 42, no. 3 (2010): 161–170, https://doi.org/10.3109/07853890903405753.

4. F. Colotta, P. Allavena, A. Sica, C. Garlanda, and A. Mantovani, "Cancer-Related Inflammation, the Seventh Hallmark of Cancer: Links to Genetic Instability," *Carcinogenesis* 30, no. 7 (2009): 1073–1081, https://doi.org/10.1093/carcin/bgp127.

5. K. Amano, I. Maeda, T. Morita, et al., "Clinical Implications of C-Reactive Protein as a Prognostic Marker in Advanced Cancer Patients in Palliative Care Settings," *Journal of Pain Symptoms Management* 51, no. 5 (2016): 860–867, https://doi.org/10.1016/j.jpainsymman.2015.11.025.

6. T. Nakatsu, S. Motoyama, K. Maruyama, et al., "Tumoral CRP Expression in Thoracic Esophageal Squamous Cell Cancers is Associated with Poor Outcomes," *Surgery Today* 42, no. 7 (2012): 652–658, https://doi.org/10.1007/s00595-012-0147-3.

7. C. Can, M. F. Acikalin, A. Ozen, and E. Dundar, "Prognostic Impact of Intratumoral C-reactive Protein Expression in Patients with Clear Cell Renal Cell Carcinoma," *Urology International* 92, no. 3 (2014): 270–275, https://doi.org/10.1159/000353401.

8. B. S. Oh, J. W. Jang, J. H. Kwon, et al., "Prognostic Value of C-reactive Protein and neutrophil-to-lymphocyte Ratio in Patients with Hepatocellular Carcinoma," *BMC Cancer* 13, no. 1 (2013): 78, https://doi.org/10.1186/1471-2407-13-78.

9. Y. A. Vano, S. Oudard, M. A. By, et al., "Optimal cut-off for neutrophil-to-lymphocyte Ratio: Fact or Fantasy? A Prospective Cohort Study in Metastatic Cancer Patients," *PLoS One* 13, no. 4 (2018): e0195042, https://doi.org/10.1371/journal.pone.0195042.

10. H. Yilmaz, M. Cakmak, O. Inan, T. Darcin, and A. Akcay, "Can neutrophil-lymphocyte Ratio be Independent Risk Factor for Predicting Acute Kidney Injury in Patients with Severe Sepsis?" *Renal Failure* 37, no. 2 (2015): 225–229, https://doi.org/10.3109/0886022X.2014.982477.

11. A. J. Loonen, C. P. de Jager, J. Tosserams, et al., "Biomarkers and Molecular Analysis to Improve Bloodstream Infection Diagnostics in an Emergency Care Unit," *PLoS One* 9, no. 1 (2014): e87315, https://doi.org/10.1371/journal.pone.0087315.

12. C. P. de Jager, P. T. van Wijk, R. B. Mathoera, J. de Jongh-Leuvenink, T. van der Poll, and P. C. Wever, "Lymphocytopenia and neutrophil-lymphocyte Count Ratio Predict Bacteremia Better than Conventional Infection Markers in an Emergency Care Unit," *Critical Care* 14, no. 5 (2010): R192, https://doi.org/10.1186/cc9309.

13. R. Terradas, S. Grau, J. Blanch, et al., "Eosinophil Count and neutrophil-lymphocyte Count Ratio as Prognostic Markers in Patients with Bacteremia: a Retrospective Cohort Study," *PLoS One* 7, no. 8 (2012): e42860, https://doi.org/10.1371/journal.pone.0042860.

14. S. Nath, S. Jayapalan, H. Nair, et al., "Comparative Diagnostic Test Evaluation of Serum Procalcitonin and C-reactive Protein in Suspected Bloodstream Infections in Children with Cancer," *Journal of Medical Microbiology* 66, no. 5 (2017): 622–627, https://doi.org/10.1099/jmm.0.000478.

15. D. Y. Kim, Y. S. Lee, S. Ahn, Y. H. Chun, and K. S. Lim, "The Usefulness of Procalcitonin and C-reactive Protein as Early Diagnostic Markers of Bacteremia in Cancer Patients with Febrile Neutropenia," *Cancer Research and Treatment* 43, no. 3 (2011): 176–180, https://doi.org/10.4143/crt.2011.43.3.176.

16. K. G. Miedema, E. S. de Bont, R. F. Elferink, et al., "The Diagnostic Value of CRP, IL-8, PCT, and sTREM-1 in the Detection of Bacterial Infections in Pediatric Oncology Patients with Febrile Neutropenia," *Supportive Care in Cancer* 19, no. 10 (2011): 1593–1600, https://doi.org/10.1007/s00520-010-0987-6.

17. A. G. Freifeld, E. J. Bow, K. A. Sepkowitz, et al., "Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America," *Clinical Infectious Diseases* 52, no. 4 (2011): e56–e93, https://doi.org/10.1093/cid/cir073.

18. M. A. Tüz, *In Cancer Patients Retrospective Assessment of Neutrophil/Lymphocyte Ratio and CRP Value Correlation With Infections* (2019), https://acikbilim.yok.gov.tr/bitstream/handle/20.500.12812/252756/yokAcikBilim_10334108.pdf?isAllowed=y%26sequence=-1.

19. P. M. Bossuyt, J. B. Reitsma, D. E. Bruns, et al., "STARD 2015: an Updated List of Essential Items for Reporting Diagnostic Accuracy Studies," *BMJ* 351 (2015): h5527, https://doi.org/10.1136/bmj.h5527.

20. S. Wang, Z. Zhang, F. Fang, X. Gao, W. Sun, and H. Liu, "The neutrophil/lymphocyte Ratio is an Independent Prognostic Indicator in Patients with Bone Metastasis," *Oncology Letters* 2, no. 4 (2011): 735–740, https://doi.org/10.3892/ol.2011.304.

21. G. J. K. Guthrie, K. A. Charles, C. S. D. Roxburgh, P. G. Horgan, D. C. McMillan, and S. J. Clarke, "The Systemic Inflammation-based neutrophil–lymphocyte Ratio: Experience in Patients with Cancer," *Critical Reviews in Oncology* 88, no. 1 (2013): 218–230, https://doi.org/10.1016/j.critrevonc.2013.03.010.

22. N. Dirican, Y. A. Karakaya, S. Gunes, F. T. Daloglu, and A. Dirican, "Association of Intra-tumoral tumour-infiltrating Lymphocytes and neutrophil-to-lymphocyte Ratio is an Independent Prognostic Factor in Non-small Cell Lung Cancer," *Clinical Respiratory Journal* 11, no. 6 (2017): 789–796, https://doi.org/10.1111/crj.12417.

23. L. Persson, B. Soderquist, P. Engervall, T. Vikerfors, L. O. Hansson, and U. Tidefelt, "Assessment of Systemic Inflammation Markers to Differentiate a Stable from a Deteriorating Clinical Course in Patients with Febrile Neutropenia," *European Journal of Haematology* 74, no. 4 (2005): 297–303, https://doi.org/10.1111/j.1600-0609.2004.00387.x.

24. F. Li, W. Zhang, H. Hu, Y. Zhang, and D. Huang, "Diagnostic Value of Procalcitonin, C-reactive Protein and Lactate Dehydrogenase in Paediatric Malignant Solid Tumour Concurrent with Infection and Tumour Progression," *Scientific Reports* 9, no. 1 (2019): 5903, https://doi.org/10.1038/s41598-019-42264-0.

25. R. Kallio, A. Bloigu, H. M. Surcel, and H. Syrjala, "C-reactive Protein and Erythrocyte Sedimentation Rate in Differential Diagnosis Between Infections and Neoplastic Fever in Patients with Solid Tumours and Lymphomas," *Supportive Care in Cancer* 9, no. 2 (2001): 124–128, https://doi.org/10.1007/s005200000181.

26. H. Yaegashi, K. Izumi, Y. Kitagawa, et al., "Differential Diagnosis Between Bacterial Infection and Neoplastic Fever in Patients with Advanced Urological Cancer: the Role of Procalcitonin," *International Journal of Urology* 21, no. 1 (2014): 104–106, https://doi.org/10.1111/iju.12178.

27. T. Maeda, K. Yoshino, C. Yamashita, et al., "Dynamics of Neutrophil and C-reactive Protein Reflect the Clinical Course of Pyrexia During Combination Therapy with Dabrafenib and Trametinib," *The Journal of Dermatology* 46, no. 8 (2019): 716–719, https://doi.org/10.1111/1346-8138.14949.

28. R. Shilpakar, B. D. Paudel, P. Neupane, et al., "Procalcitonin and C-Reactive Protein as Markers of Bacteremia in Patients with Febrile Neutropenia Who Receive Chemotherapy for Acute Leukemia: a Prospective Study from Nepal," *Journal of Global Oncology* 5 (2019): 1–6, https://doi.org/10.1200/JGO.19.00147.

29. T. Odagiri, T. Morita, H. Sakurai, et al., "A Multicenter Cohort Study to Explore Differentiating Factors Between Tumor Fever and Infection Among Advanced Cancer Patients," *Journal of Palliative Medicine* 22, no. 11 (2019): 1331–1336, https://doi.org/10.1089/jpm.2018.0594.

30. Y. Xu, J. Li, X. Ji, Q. Chen, Z. Liu, and S. Ji, "Lymphocyte-to-C-reactive Protein Ratio Predicts Prognosis in Unresectable Locally Advanced Non-small Cell Lung Cancer Patients," *Annals of Medicine* 57, no. 1 (2025): 2487629, https://doi.org/10.1080/07853890.2025.2487629.

31. K. Zhou, C. Li, T. Chen, X. Zhang, and B. Ma, "C-reactive Protein Levels Could Be a Prognosis Predictor of Prostate Cancer: a meta-analysis," *Frontiers in Endocrinology* 14 (2023): 1111277, https://doi.org/10.3389/fendo.2023.1111277.

32. H. Y. Zhang, H. L. Xie, G. T. Ruan, et al., "Lymphocyte to C-reactive Protein Ratio Could Better Predict the Prognosis of Patients with Stage IV Cancer," *BMC Cancer* 22, no. 1 (2022): 1080, https://doi.org/10.1186/s12885-022-10145-x.

33. T. Araki, K. Tateishi, M. Komatsu, et al., "Predictive Value of Post-treatment C-reactive protein-to-albumin Ratio in Locally Advanced Non-small Cell Lung Cancer Patients Receiving Durvalumab After Chemoradiotherapy," *Thoracic Cancer* 13, no. 14 (2022): 2031–2040, https://doi.org/10.1111/1759-7714.14484.

34. D. Zhu, Y. D. Lin, Y. Z. Yao, X. J. Qi, K. Qian, and L. Z. Lin, "Negative Association of C-reactive protein-albumin-lymphocyte Index (CALLY Index) with all-cause and Cause-specific Mortality in Patients with Cancer: Results from NHANES 1999-2018," *BMC Cancer* 24, no. 1 (2024): 1499, https://doi.org/10.1186/s12885-024-13261-y.

35. A. Misiewicz and V. Dymicka-Piekarska, "Fashionable, but what is Their Real Clinical Usefulness? NLR, LMR, and PLR as a Promising Indicator in Colorectal Cancer Prognosis: a Systematic Review," *Journal of Inflammation Research* 16 (2023): 69–81, https://doi.org/10.2147/jir.s391932.

36. G. R. Mundy, "Metastasis to Bone: Causes, Consequences and Therapeutic Opportunities," *Nature Reviews Cancer* 2, no. 8 (2002): 584–593, https://doi.org/10.1038/nrc867.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

Supporting file.xlsx: SPSS data file containing the anonymised dataset used for all statistical analyses presented in this manuscript.