A novel inflammation and tumor marker-based prognostic score, neutrophil-lymphocyte ratio-C-reactive protein-Ca19-9, in metastatic gastric cancer

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Abstract. Metastatic gastric cancer is an aggressive malignancy characterized by poor survival rates and heterogeneous treatment outcomes. Reliable prognostic tools to identify patients who may benefit from systemic therapy remain limited. Therefore, there is a need for easily accessible and clinically applicable prognostic tools. The present single-center retrospective study included 70 patients with microsatellite-stable, HER2-negative metastatic gastric cancer who were treated with first-line fluoropyrimidine-based chemotherapy between 2020 and 2024. The present study aimed to develop and evaluate a novel composite prognostic score integrating systemic inflammation and tumor burden. The neutrophil-C-reactive protein (CRP)-CA19-9 (NCC) score was constructed based on baseline neutrophil-to-lymphocyte ratio (NLR ≥5), CRP >20 mg/l and CA19-9 levels (>90 U/ml). Patients were classified into low-risk (0-1) and high-risk (2-3) groups. Overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan-Meier and Cox regression methods, with internal validation performed by bootstrap resampling. The median OS for the entire cohort was 13.4 months. A high NCC score was associated with significantly shorter OS compared with a low NCC score (9.6 vs. 15.2 months; P=0.00065) and an increased risk of mortality (hazard ratio=2.59; 95% CI: 1.47-4.56). The median PFS was also shorter in the high-risk NCC group (9.2 vs. 10.1 months; P=0.04). The optimism-corrected C-index for OS was 0.60, indicating that the NCC score is a simple and practical prognostic tool for survival stratification with favorable discriminative performance compared with established prognostic indices in metastatic gastric cancer.

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Introduction

Gastric cancer remains one of the most common malignancies accounting for ~8.2% of all cancer-related deaths worldwide and continues to be a leading cause of cancer-related mortality despite advances in systemic treatment strategies (1). A marked proportion of patients are diagnosed at an advanced or metastatic stage, which is associated with aggressive disease and poor survival outcomes. In metastatic gastric cancer, the reported median overall survival (OS) rarely exceeds 1 year, even with contemporary chemotherapy regimens, highlighting the urgent need for improved prognostic stratification (2).

The clinical course of metastatic gastric cancer is highly heterogeneous. While a number of patients derive notable benefit from systemic therapies, others experience rapid disease progression despite receiving similar treatments. To the best of our knowledge, currently, no robust and universally accepted method exists to accurately predict survival outcomes or treatment benefits in the metastatic setting. This uncertainty complicates treatment planning and underscores the need for practical, prognostic tools that can be applied in routine clinical practice (3).

Systemic inflammation is recognized as a key contributor to cancer progression, influencing tumor growth, immune evasion and metastatic potential. In this context, inflammation-based biomarkers have garnered increasing attention as prognostic indicators in gastric cancer (4-6). The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between pro-tumor inflammatory activity and anti-tumor immune response and has been consistently associated with survival outcomes in gastric cancer across numerous disease stages (4). Similarly, C-reactive protein (CRP), an acute-phase reactant indicative of systemic inflammatory burden, has been shown to be associated with poor prognosis and has been incorporated into established inflammation-based prognostic scores, such as the Glasgow Prognostic Score (7,8).

In addition to inflammatory markers, tumor burden-associated biomarkers also offer prognostic information in advanced gastric cancer. CA19-9 is widely used in gastrointestinal malignancies and elevated baseline levels have been associated with advanced disease stage, treatment response and poorer survival outcomes in patients with gastric cancer (9).

Although these biomarkers have demonstrated individual prognostic relevance, their isolated use may not fully capture the complex interactions between tumor biology and the host inflammatory response in metastatic gastric cancer. Combining inflammatory markers and tumor burden indicators into a single composite score may therefore enhance prognostic discrimination. Based on this rationale, the present study aimed to develop a novel composite prognostic score incorporating NLR, CRP and CA19-9 levels and to evaluate its prognostic value in patients with metastatic gastric cancer receiving first-line systemic therapy.

Materials and methods

Study design and patient selection. As a single-center, retrospective study, the present study was conducted at Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Ankara, Turkey). Patients diagnosed with microsatellite-stable (MSS) HER2-negative metastatic gastric cancer between 2020 and 2024 were included. All patients received first-line fluoropyrimidine-based chemotherapy, including folinic acid, 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CAPEOX) or folinic acid, fluorouracil and irinotecan (FOLFIRI) regimens. Based on previous evidence suggesting comparable survival outcomes among these regimens in the first-line treatment of metastatic gastric cancer, patients receiving any of these treatments were included in the present analysis (10). Following ethical approval, patient data were accessed through the electronic medical record system of the hospital in December 2025. Data analyses were completed in January 2026.

Inclusion criteria were as follows: i) Aged ≥18 years at diagnosis; ii) histologically determined gastric adenocarcinoma; iii) presence of metastatic disease at diagnosis or during follow-up; iv) MSS and HER2-negative tumor status; v) receipt of first-line 5-FU-based combination chemotherapy (FOLFOX, CAPEOX or FOLFIRI); and vi) availability of complete baseline clinical, laboratory and follow-up data.

Exclusion criteria included: i) Microsatellite instability-high (MSI-H) or deficient mismatch repair tumors; ii) HER2-positive disease; iii) prior systemic therapy for metastatic disease before the initiation of first-line treatment at our center; iv) concomitant malignancies or a history of another malignancy requiring active treatment; v) receipt of immune checkpoint inhibitors or targeted agents in the first-line setting; and vi) incomplete clinical records or missing survival data.

Neutrophil-CRP-CA19-9 (NCC) score. Baseline inflammatory and tumor-related biomarkers were evaluated, including the NLR, CRP and CA19-9. Based on these parameters, a novel composite scoring system termed the NCC score was developed. The NCC score comprises three components: i) NLR ≥5; ii) CRP >20 mg/l; and iii) CA19-9 >90 U/ml. Each criterion was assigned 1 point, resulting in a total NCC score ranging from 0-3. Patients were further categorized into two risk groups based on their NCC scores: A low-risk NCC score group (0-1 points) and a high-risk group (2-3 points).

The cut-off value for CA19-9 was determined using a data-driven approach based on the log-rank test to identify the threshold that best discriminated PFS. Given the exploratory nature of the present study, this threshold was subsequently evaluated through multivariable analyses and internal validation procedures. For the NLR, a cut-off value reported in the literature was adopted (4). Reported cut-off values for CRP vary widely in the literature, ranging from 3.5-70 mg/l, with heterogeneous thresholds applied across different studies (7,11,12). In the present study, a CRP cut-off value of >20 mg/l was selected to enhance the prognostic performance of the scoring system and to more specifically reflect pronounced systemic inflammation in the metastatic disease setting.

Statistical analysis. Statistical analyses were conducted using R software (R 4.4.1) (R Foundation for Statistical Computing) and SPSS (version 27.0; IBM Corp). Categorical variables were compared using the χ^2 test or Fisher's exact test, and presented as frequencies and percentages, as appropriate. Survival analyses were carried out using the Kaplan-Meier method and differences between groups were evaluated with the log-rank test.

The prognostic impact of the NCC score on OS and PFS was evaluated using Cox proportional hazards regression models, with results reported as hazard ratios (HRs) and 95% CIs. Internal validation of the model was conducted using bootstrap resampling with 1,000 iterations and model discrimination was assessed using the optimism-corrected concordance index (C-index). For comparative purposes, the discriminative performance of the NCC score was further evaluated against established inflammation- and nutrition-based prognostic indices, including the modified Glasgow Prognostic Score (mGPS), Prognostic Inflammatory Value (PIV), Systemic Immune-Inflammation Index (SII) and Prognostic Nutritional Index (PNI), using Harrell's C-index derived from univariate Cox models (13-16). In addition, time-dependent receiver operating characteristic (ROC) curve analysis and calibration plots were generated to evaluate the predictive performance of the NCC score for 12-month OS. The primary endpoint was OS, defined as the time from the diagnosis of metastatic disease to mortality from any cause or the date of the last follow-up. The secondary endpoint was progression-free survival (PFS), defined as the time from the initiation of first-line systemic therapy to radiological or clinical disease progression, mortality or the date of the last follow-up.

All statistical tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 70 patients were included in the present study. The mean age was 58.9±14.0 years. Of the patients, 27.1% (n=19) were female and 72.9% (n=51) were male. Baseline clinicopathological and demographic characteristics according to NCC risk groups are summarized in Table I. Age distribution and sex were comparable between the

Table I. Clinicopathological and demographic characteristics of the study population.

Item	Total	NCC low risk	NCC high risk	P-value
Age, years				0.600
<65	38 (54.3)	26 (56.5)	12 (50.0)	
≥65	32 (45.7)	20 (43.5)	12 (50.0)	
Sex				0.770
Female	19 (27.1)	13 (28.3)	6 (25.0)	
Male	51 (72.9)	33 (71.7)	18 (75.0)	
Subtype				0.561
Non-SRCC	44 (62.9)	29 (63.0)	15 (62.5)	
SRCC	19 (27.1)	14 (30.4)	5 (20.8)	
Other	7 (10.0)	3 (6.5)	4 (16.7)	
Stage at time of diagnosis				0.004
Early/locally advanced	13 (18.6)	13 (28.3)	0 (0.0)	
Metastatic	57 (81.4)	33 (71.7)	24 (100)	
Second-line treatment				0.630
No	41 (58.6)	26 (56.5)	15 (62.5)	
Yes	29 (41.4)	20 (43.5)	9 (37.5)	
First-line treatment type				0.701
FOLFOX	59 (84.2)	36 (78.2)	23 (95.8)	
CAPEOX	5 (7.2)	5 (10.9)	0 (0.0)	
FOLFIRI	6 (8.6)	5 (10.9)	1 (4.2)	
Neoadjuvant treatment				0.060
No	64 (91.4)	40 (87.0)	24 (100)	
Yes	6 (8.6)	6 (13.0)	0 (0.0)	

All patients had an ECOG performance status of 0-1. Values are expressed as n (%). Comparisons reflect baseline characteristics and are not intended to imply causality. SRCC, signet ring cell carcinoma; NCC, neutrophil-C-reactive protein-CA19-9; FOLFOX, folinic acid, fluorouracil and oxaliplatin; CAPEOX, capecitabine and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan.

NCC low- and high-risk groups, with no statistically significant differences observed (P=0.60 and P=0.77, respectively). Histological subtypes were similarly distributed across risk groups. At diagnosis, metastatic disease was significantly more frequent in the NCC high-risk group compared with the low-risk group (100 vs. 71.7%; P=0.004). Rates of second-line treatment and neoadjuvant therapy did not differ significantly between groups, although neoadjuvant treatment tended to be less frequent in the high-risk group (P=0.06), which was not statistically significant. Overall, except for disease stage at diagnosis, baseline characteristics were well balanced between NCC risk groups.

Survival analysis. In the overall study population, the median OS was 13.4 months. Patients in the high-NCC group had a significantly shorter OS than those in the low NCC group (9.6 vs. 15.2 months, respectively; P=0.00065; Fig. 1).

The NCC score was analyzed both as a continuous and a categorical variable. When evaluated as a continuous variable, each 1-point increase in the NCC score was associated with a significant increase in the risk of mortality. In the categorical analysis, patients in the high-risk NCC group exhibited an ~2.6-fold higher risk of mortality compared with those in the low NCC group (HR=2.59; 95% CI: 1.47-4.56; P<0.001).

In the overall study population, the median PFS (mPFS) was 9.8 months. Patients in the high-risk NCC group exhibited a significantly shorter mPFS compared with those in the low-risk NCC group (9.2 vs. 10.1 months, respectively; P=0.04; Fig. 2).

The discriminative ability of the NCC score for OS was evaluated using a Cox regression model. The apparent C-index of the model was 0.60. Internal validation, performed using bootstrap resampling with 1,000 iterations, yielded an optimism-corrected C-index of 0.60, indicating stable model performance. In a time-dependent ROC curve analysis, the NCC score demonstrated moderate discriminative ability for predicting 12-month OS, with an area under the curve of 0.64 (Fig. 3). Calibration plots for 12-month OS exhibited good agreement between predicted and observed survival probabilities (Fig. 4).

Model performance and validation. Among the evaluated prognostic indices, the NCC score demonstrated the highest discriminative ability for OS (C-index: 0.600; standard error: 0.031). In comparison, mGPS and PIV exhibited moderate and comparable discrimination (C-index: 0.583 and 0.581, respectively), whereas SII and PNI exhibited lower discriminative performance (C-index: 0.560). These findings suggested

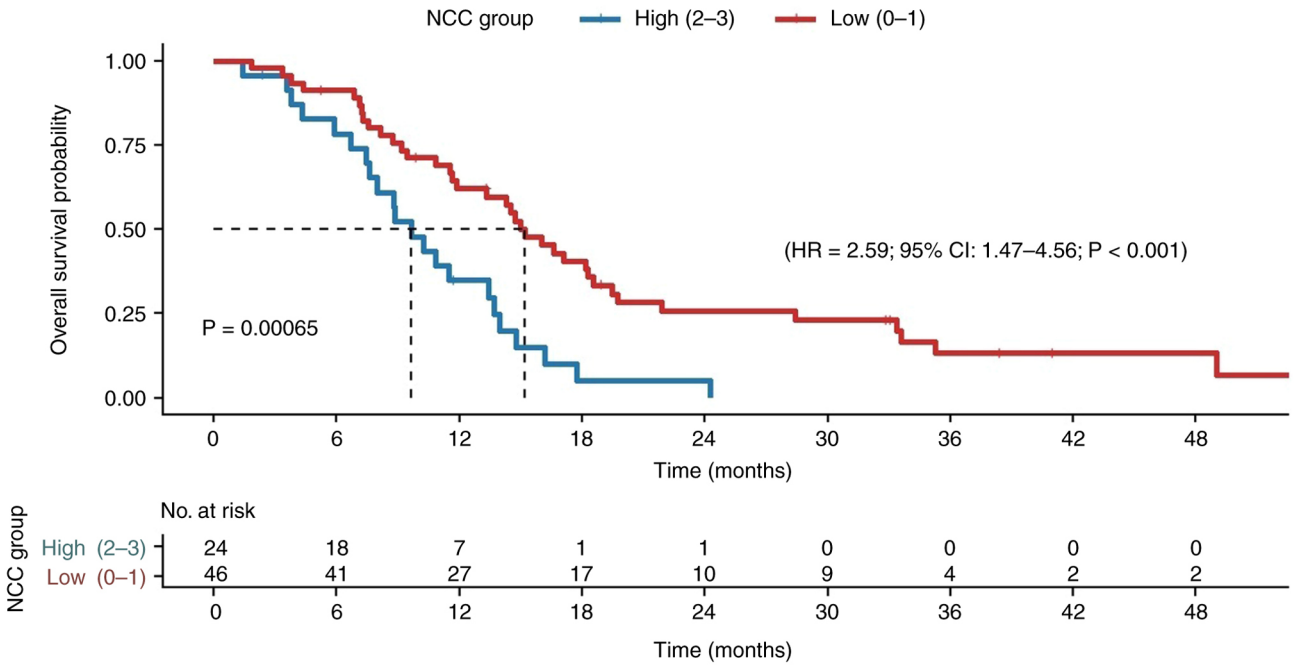

Figure 1. Kaplan-Meier curve for overall survival according to NCC score. NCC, neutrophil-C-reactive protein-CA19-9.

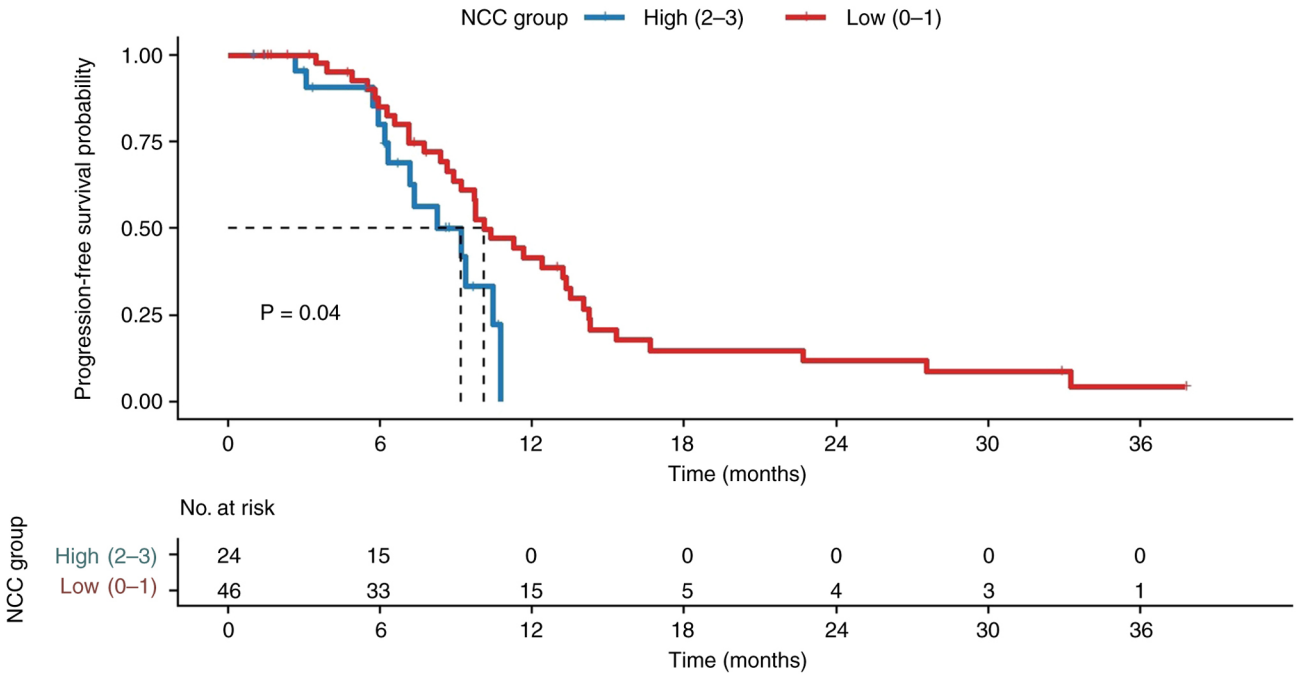

Figure 2. Kaplan-Meier curve for progression-free survival according to NCC score. NCC, neutrophil-C-reactive protein-CA19-9.

that the NCC score offered improved prognostic discrimination compared with commonly used inflammation- and nutrition-based indices in the present cohort (Table II).

Discussion

In the present study, a novel composite prognostic score that integrates systemic inflammation and tumor burden was developed, demonstrating its prognostic value in MSS, HER2-negative metastatic gastric cancer treated with first-line 5-FU-based chemotherapy. The NCC score effectively stratified both OS and PFS, with patients in the high-risk group experiencing significantly poorer outcomes compared with those in the low-risk group. Notably, the prognostic performance of the NCC score was consistent across multiple analyses and exhibited improved discriminative ability compared with commonly used inflammation- and nutrition-based prognostic indices. The association between the NCC score and PFS further supports its capacity to capture early disease aggressiveness. These findings suggest that the NCC score reflects

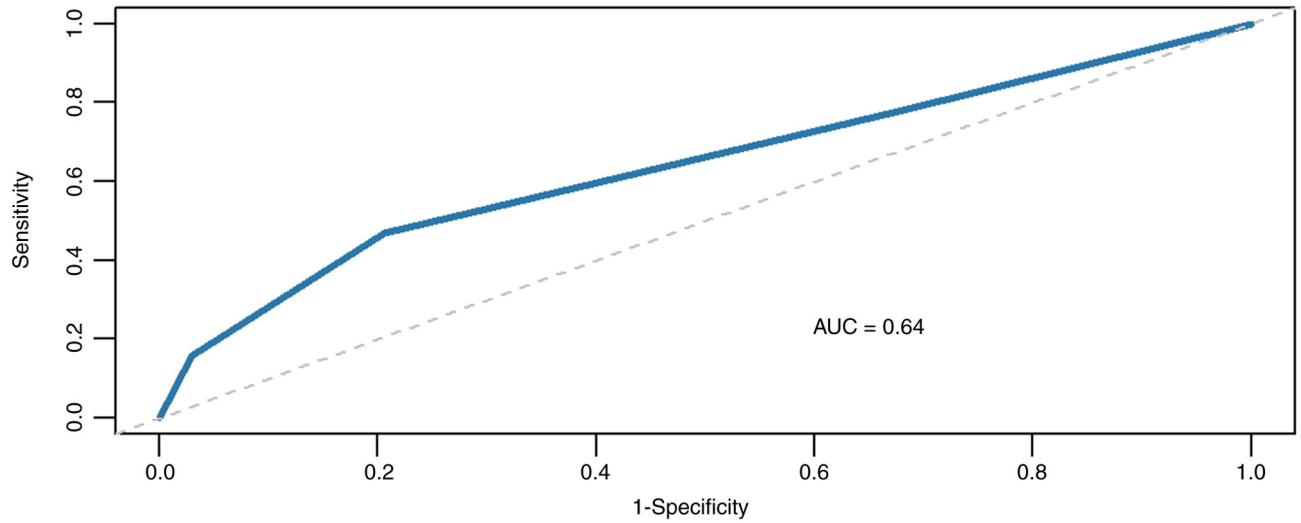

Figure 3. Time-dependent receiver operating characteristic curve for 12-month overall survival according to the NCC score. NCC, neutrophil-C-reactive protein-CA19-9; AUC, area under the curve.

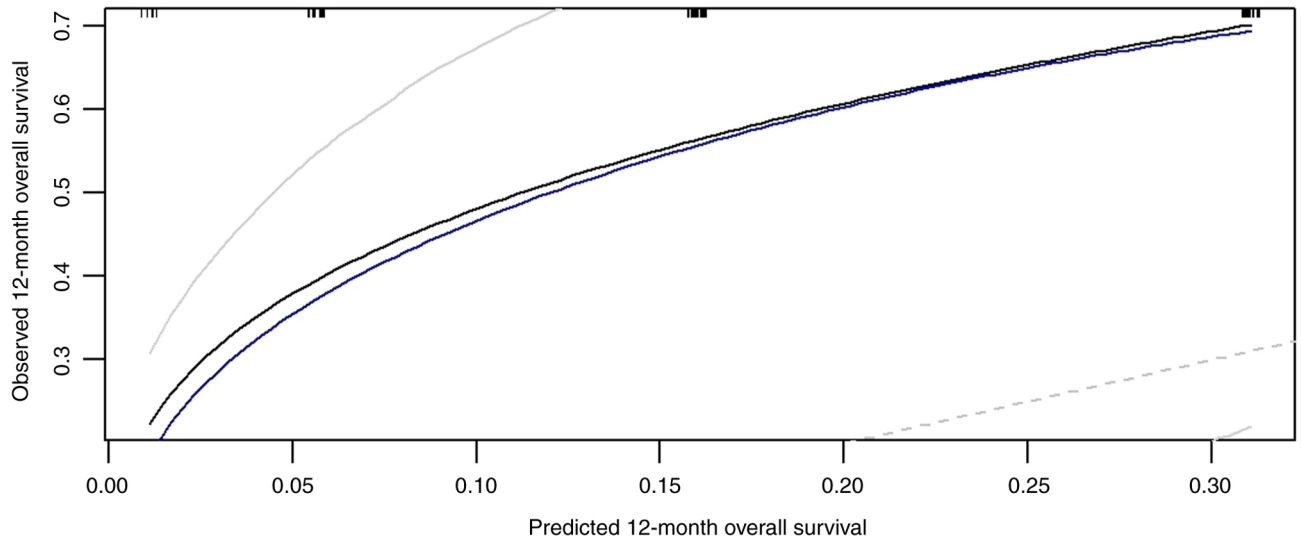

Figure 4. Calibration plot for 12-month overall survival predicted by the NCC score. NCC, neutrophil-C-reactive protein-CA19-9.

clinically meaningful biological heterogeneity in metastatic gastric cancer using simple and readily available parameters.

Systemic inflammation and tumor burden are well-established determinants of disease progression and survival in gastric cancer. Among inflammation-based biomarkers, an elevated NLR has been consistently associated with poorer survival outcomes, reflecting an imbalance between pro-tumor inflammatory activity and anti-tumor immune response (17). Similarly, CRP, a reliable marker of systemic inflammatory burden, reflects the host inflammatory response and has been shown to be associated with adverse prognosis. It is also a key component of validated prognostic tools such as the mGPS in gastric cancer (18). In parallel, tumor burden-associated biomarkers provide prognostic information in advanced disease. Elevated baseline CA19-9 levels have been associated with advanced tumor stage, aggressive tumor biology and poorer survival outcomes in patients with gastric cancer receiving systemic therapy (19). When used individually, these biomarkers may not fully capture the interaction between tumor biology and host inflammatory response. In the present study, it was demonstrated that integrating NLR, CRP and CA19-9 into a composite NCC score yielded a more robust prognostic tool, effectively stratifying both OS and PFS in metastatic gastric cancer. By combining markers of immune balance, systemic inflammation and tumor burden, the NCC score may further reflect the complex biological interplay underlying disease progression.

A number of composite inflammation- and nutrition-based prognostic indices have previously been proposed in gastric cancer. mGPS has been widely validated as a prognostic marker reflecting systemic inflammation and nutritional status (20). The mGPS emphasizes the prognostic importance of CRP; elevated CRP represents the dominant determinant of the score, whereas hypoalbuminemia contributes additional prognostic information only in the presence of CRP elevation (21). In the original mGPS, the CRP cut-off value was

Table II. Comparison of Harrell's C-index for NCC and established prognostic scores in overall survival.

Score	C-index	Standard error
NCC	0.600	0.031
mGPS	0.583	0.036
PIV	0.581	0.043
SII	0.560	0.044
PNI	0.556	0.048

NCC, neutrophil-C-reactive protein-CA19-9 score; mGPS, modified Glasgow Prognostic score; PIV, prognostic inflammatory value; SII, systemic immune-inflammation index; PNI, prognostic nutritional index.

set at 10 mg/l. Subsequently, to enhance the predictive performance of the score, the high-sensitivity GPS was developed by increasing the CRP threshold to 30 mg/l. In this context, selecting an intermediate CRP cut-off value of 20 mg/l for the present NCC score aligns with previous efforts to optimize prognostic discrimination by refining CRP thresholds (22,23). Similarly, the PIV, SII and PNI have all demonstrated prognostic relevance in gastric cancer across numerous clinical settings (14-16). The PNI has been investigated in a number of studies, with a high PNI being markedly associated with improved OS and disease-free survival (DFS) in patients with gastric cancer (24,25).

In a study involving patients with metastatic gastric cancer who received neoadjuvant treatment, the prognostic value of SII was emphasized, with lower SII levels associated with improved outcomes, suggesting that patients with low SII may derive greater benefit from neoadjuvant therapy (26). A negative association between PIV and survival outcomes has been reported across a number of cancer types. In a large cohort study of 1,879 patients with colorectal cancer, PIV was notably associated with both OS and DFS (27). In the present cohort, these established indices showed moderate discriminative ability for OS. Notably, however, the NCC score consistently demonstrated improved discriminative performance compared with mGPS, PIV, SII and PNI, indicating that the combined assessment of systemic inflammation and tumor burden provides added prognostic value beyond existing indices.

From a clinical perspective, the NCC score provides a simple and easily applicable tool for risk stratification in patients with metastatic gastric cancer. In the absence of widely accepted prognostic tools for the metastatic setting, this score addresses an important clinical need. Given that it is derived from routinely available laboratory parameters, it can be calculated at baseline without additional cost or specialized testing.

The ability of the NCC score to stratify both OS and PFS suggests that it may help identify patients with particularly unfavorable prognosis who could benefit from closer monitoring, early treatment modification or enrollment in clinical trials. In clinical practice, prognostic tools are most valuable when they inform key decision points along the treatment pathway. In this context, the NCC score may assist clinicians in identifying high-risk patients at the initiation of treatment who may require more intensive radiological monitoring, closer clinical follow-up or earlier reassessment of treatment efficacy. Conversely, patients in the low-risk group may be suitable candidates for standard follow-up strategies and continuation of first-line therapy in the absence of clinical progression.

Similar inflammation-based prognostic indices have previously been proposed to support risk stratification and guide clinical decision-making in oncology (28). Therefore, the NCC score may serve as a practical complementary tool to aid individualized treatment planning in patients with metastatic gastric cancer. Importantly, the NCC score is not intended to replace established clinical or pathological prognostic factors but rather to complement existing clinical assessments and contribute to a more comprehensive evaluation of patient prognosis in routine practice. Although the NCC score was developed using baseline laboratory parameters obtained before treatment initiation, growing evidence suggests that dynamic changes in inflammatory and tumor-related biomarkers during systemic therapy may also provide valuable prognostic information.

Numerous studies have demonstrated that longitudinal changes in markers such as the NLR during treatment are associated with treatment response and survival outcomes in patients with advanced malignancies (29,30). Dynamic changes in CRP have also been reported to carry prognostic information, as decreases in CRP or CRP-based inflammatory indices during systemic therapy have been associated with improved treatment response and survival outcomes in patients with gastrointestinal malignancies, including gastric cancer (31). Similarly, dynamic changes in tumor markers such as CA19-9 during systemic therapy may reflect tumor burden evolution and treatment sensitivity and have been associated with prognosis in patients with advanced gastric cancer (32). These findings indicate that monitoring temporal changes in inflammatory and tumor-related biomarkers could enhance prognostic stratification beyond baseline assessment alone. Therefore, future studies evaluating longitudinal changes in NCC components during treatment may help refine the prognostic accuracy of the score and provide additional insights into treatment response and disease progression.

The present study exhibits a number of notable strengths. The analysis was conducted in a clinically homogeneous population of MSS, HER2-negative metastatic gastric cancer patients treated with first-line 5-FU-based chemotherapy, thereby minimizing biological and treatment-related heterogeneity. In addition, the NCC score comprises simple and routinely available laboratory parameters, enhancing its feasibility in daily clinical practice. The use of internal validation through bootstrap resampling and direct comparison with established prognostic indices further strengthened the robustness of the present findings.

Despite this, limitations should be acknowledged. First, the present study population was relatively small, comprising 70 patients. A small proportion of patients (~8%) had received neoadjuvant treatment prior to the diagnosis of metastatic disease, which may have influenced baseline inflammatory parameters. Second, while 41.4% of patients received second-line systemic therapy, others did not, which could have affected OS outcomes. Due to the limited sample size,

subgroup analyses based on histopathological subtypes could not be reliably performed, although signet ring cell carcinoma is known to be associated with a poorer prognosis (33). Third, a subset of patients was initially diagnosed at an early stage and received adjuvant chemotherapy, potentially resulting in increased cumulative chemotherapy exposure and treatment-related toxicity at the metastatic stage, which may have introduced survival bias. Fourth, the retrospective single-center design and relatively small sample size limited the generalizability of the results; therefore, external validation in independent cohorts is warranted. Fifth, although the NCC score demonstrated stable performance in internal validation, the overall discriminative ability of the model was moderate, as reflected by the C-index. This may be partly explained by the limited sample size and the biological heterogeneity of metastatic gastric cancer. Additionally, the NCC score was constructed using only baseline laboratory parameters and dynamic changes in inflammatory biomarkers or tumor markers during treatment were not evaluated, although such temporal changes may also represent important prognostic information. Finally, the present study included only patients with MSS, HER2-negative metastatic gastric cancer receiving first-line fluoropyrimidine-based chemotherapy, resulting in a relatively homogeneous cohort. While this design minimized potential confounding related to tumor biology and treatment heterogeneity, it may have limited the generalizability of the NCC score to other molecular or treatment-defined subgroups. Specifically, patients with HER2-positive or MSI-H tumors, as well as those treated with targeted therapies or immunotherapy, may exhibit distinct tumor biology and immune-inflammatory dynamics that could affect the prognostic importance of inflammatory biomarkers. Previous studies have suggested that the prognostic impact of systemic inflammatory markers, such as the NLR, may vary across different therapeutic contexts, including immunotherapy-based treatments (34,35). Therefore, further studies are warranted to evaluate the performance of the NCC score in these patient populations and in treatment settings involving modern systemic therapies. Despite these limitations, the internal consistency of the findings supports the potential clinical relevance of the NCC score.

Future studies are needed to externally validate the NCC score in larger, multicenter cohorts to determine its generalizability and reproducibility. In addition, evaluating the performance of the NCC score across different treatment settings, including immunotherapy-based regimens and combination strategies, could help clarify its broader clinical applicability. Furthermore, investigating dynamic changes in NCC components during treatment may provide additional insights into treatment response and disease progression. Prospective studies that integrate the NCC score with established clinical and molecular factors may further enhance risk stratification in metastatic gastric cancer.

In conclusion, the NCC score is a simple and practical prognostic tool that integrates systemic inflammation and tumor burden using routine laboratory parameters. It effectively stratified both OS and PFS in patients with metastatic gastric cancer and demonstrated improved discriminative performance compared with established inflammation- and nutrition-based indices. Although external validation is necessary, the present findings suggested that the NCC score may serve as a valuable complementary tool for prognostic assessment and risk stratification in routine clinical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BK wrote the original manuscript draft. BK and MEY conceptualized the present study. MB provided supervision, validation and resources and conceived and designed the study. EKK and MEY conducted the statistical analysis. BK and EK contributed to the methodology used and STB, ÖA and EA conducted the investigation. OBK and AU contributed to data acquisition and interpretation of clinical data. All authors wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript. BK and EKK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Non-Interventional Ethics Committee of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (approval no. 2025-11/172-18/12/2025). The Non-Interventional Ethics Committee of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital waived the requirement for informed consent for archive-based (retrospective) studies.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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