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Detecting the preoperative peripheral blood systemic immune-inflammation index (SII) as a tool for early diagnosis and prognosis of gallbladder cancer

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Abstract

Objective Evidence indicates that the systemic immune-inflammation index (SII) correlates with poor prognosis in various solid tumors. This retrospective study aimed to evaluate the diagnostic and prognostic significance of preoperative SII combined with tumor markers for early detection and prognosis of gallbladder cancer (GBC).

Methods Preoperative SII levels and serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and carbohydrate antigen 19 – 9 (CA19-9)] were measured in GBC patients. Correlations and diagnostic efficacy were analyzed using Spearman correlation and receiver operating characteristic (ROC) curve analyses. The relationship between SII and clinical data was analyzed, and cumulative survival rates of the two groups were compared. Independent risk factors for poor prognosis in GBC patients were assessed using Kaplan-Meier curves and Cox multivariate analysis.

Results Preoperative SII, CEA, CA125, and CA19-9 levels were significantly elevated in GBC patients compared to those with benign lesions. SII positively correlated with CEA, CA125, and CA19-9 levels ($r = 0.434$, 0.570, 0.614, respectively, all $P < 0.001$). The area under the ROC curve (AUC) for the combination of SII, CEA, CA125, and CA19-9 was 0.877 for early GBC diagnosis and 0.923 for predicting postoperative mortality, outperforming each marker individually. An SII threshold > 889.52 was predictive of postoperative death. High SII was associated with tumor size, differentiation, tumor-node-metastasis stage, lymph node metastasis, perineural invasion, surgical type, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and serum tumor marker levels. Kaplan-Meier analysis revealed poorer survival in the high SII group. Preoperative SII was identified as an IRF for poor prognosis in GBC patients.

Conclusion Preoperative SII correlates strongly with CEA, CA125, and CA19-9 levels. The combined use of SII and tumor markers offers high diagnostic value for early GBC detection and robust predictive value for postoperative mortality. Preoperative SII serves as an IRF for poor prognosis in GBC patients.

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Keywords Gallbladder cancer, Preoperative system immune-inflammation index, Clinical pathological factors, Early diagnosis, Prognosis, Receiver operating characteristic curve, Cox multivariate analysis, Independent risk factors

Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract [1, 2]. Its incidence varies geographically, with the highest rates observed in populations aged 50 to 70 years, and it is more prevalent in women than in men [3]. Radical resection, involving the removal of the gallbladder, liver bed, and regional lymph nodes, remains the most effective treatment for sporadic GBC [4]. However, the surgical procedure is technically challenging, and many patients present with advanced disease at diagnosis, rendering tumors unresectable tumor [5]. The aggressive nature of GBC, combined with delayed diagnosis, the lack of reliable biomarkers, and limited treatment options, contributes to its poor prognosis, particularly in advanced stages [6, 7]. While the five-year survival rate for stage I cancer is approximately 50%, it plummets to just 5% for stage IV disease [8]. This underscores the critical need for timely diagnosis and accurate disease assessment to improve patient outcomes [9]. Additionally, identifying novel diagnostic and prognostic biomarkers is essential for enhancing early detection and developing targeted therapies for GBC [10].

Efforts to detect cancer cells using immune-based assays date back to the 1980s [11, 12]. In recent years, Recently, immune response-related parameters derived from blood samples have proven valuable in predicting treatment efficacy and prognosis in patients with various tumors [13, 14]. Among these, the system immune-inflammation index (SII) has emerged as a comprehensive marker calculated using platelet count, neutrophil count, and lymphocyte count (SII = platelet count × neutrophil count/lymphocyte count). By integrating these three types of inflammatory cells, SII provides a broader perspective on the body's inflammatory and immune balance compared to traditional markers such as the neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) [15, 16]. This novel marker is not only cost-effective and easy to measure but also reflects both inflammatory and immune pathways. SII has been validated as a prognostic risk factor in multiple malignancies, including colorectal cancer [17], hepatocellular carcinoma [18], non-small cell lung cancer [19], and gastric cancer [20].

Carbohydrate antigen 19 – 9 (CA19-9), carbohydrate antigen 125 (CA125), and carcinoembryonic antigen (CEA) levels are widely used as monitoring indicators for GBC, offering clinical value for both diagnosis and prognosis [21–23]. In recent years, multi-index combined diagnostic approaches have gained prominence in clinical research. Evidence suggests that the combined detection of serum tumor markers, including CEA, CA125, and CA19-9, has specific diagnostic utility for GBC. However, the sensitivity and specificity of these markers remain suboptimal [24].

The SII has emerged as a reliable independent predictor for the diagnosis and prognosis of various malignancies, including GBC [25, 26]. Previous studies have demonstrated that an elevated SII is associated with poor long-term outcomes in GBC patients undergoing radical surgery. Moreover, the combination of SII and CA19-9 grading has shown improved prognostic value in such patients. However, elevated CA19-9 levels are not specific to GBC and can occur in other cancers and inflammatory conditions, often resulting in false positives that may compromise the prognostic accuracy of SII-CA19-9 classification [27]. This underscores the need for more effective and precise tools for the early diagnosis and prognosis evaluation of GBC.

Despite the potential utility of combining SII with tumor markers such as CEA, CA125, and CA19-9, there are limited studies investigating their preoperative combined application for the early detection and prognosis of GBC. To address this gap, we sought to explore the diagnostic and prognostic value of combining SII with these tumor markers, providing a more robust framework for the early detection and treatment of GBC. Additionally, we analyzed the impact of peripheral blood SII on the risk of postoperative mortality in GBC patients, aiming to offer new clinical reference indices for surgical decision-making and prognosis evaluation. This study aims to evaluate the clinical significance of preoperative combined detection of SII and tumor markers for the early diagnosis and prognosis of GBC. By identifying novel biomarkers and predictive methods, this work seeks to enhance the early detection and improve the clinical management of GBC patients.

Materials and methods

Ethics statement

The study was reviewed and approved by the Academic Ethics Committee of The First Hospital of Shanxi Medical University and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Research subjects

A retrospective study was performed on 120 patients diagnosed with GBC who underwent surgical treatment at the Hepatobiliary Surgery Department of The First Hospital of Shanxi Medical University between December 2015 and December 2017. Among these, nine

patients were lost to follow-up, and 25 did not meet the inclusion or exclusion criteria. Ultimately, 86 patients (33 males and 53 females) were included in the GBC group. Simultaneously, 90 patients with benign gallbladder conditions such as cholecystitis, gallbladder polyps, or gallstones were enrolled as the benign lesion group for comparison.

Inclusion and exclusion criteria

Inclusion criteria were as follows: [1] Diagnosed with GBC based on clinical evaluation and confirmed by histopathology according to the "Guidelines for the Diagnosis and Treatment of Gallbladder Cancer"; [2] Underwent hepatobiliary surgery; [3] Possessed complete clinical case data and follow-up data; [4] Aged between 18 and 85 years; [5] Did not receive preoperative chemoradiotherapy or other anti-tumor treatments.

Exclusion criteria were as follows: [1] Diagnosed with other malignant tumors, systemic inflammatory diseases, or chronic hepatitis; [2] Diagnosed with blood disorders, infectious diseases, or autoimmune diseases; [3] Lacked complete case data or were lost to follow-up; [4] Received preoperative immunotherapy or had a recent history of blood transfusion.

Data and sample collection

Baseline clinical data, including age, sex, body mass index (BMI), cancer type, tumor size (≤ 5 cm or > 5 cm), degree of differentiation (low, medium, or high), tumor-node-metastasis (TNM) stage, lymph node metastasis, perineural invasion, surgical type, and postoperative neoadjuvant chemotherapy were documented. One week prior to surgery, 5 mL of peripheral venous blood was collected into standard anticoagulant-free tubes. Of this, 2 mL was utilized to measure platelet (P) count, neutrophil (N) count, and lymphocyte (L) count. The SII was calculated using the formula SII = platelet count × neutrophil count/lymphocyte count (P × N/L). Additionally, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were determined [16, 27].

The remaining 3 mL of blood was allowed to clot for 30 min, centrifuged at 4 °C and 3000 rpm for 10 min, and the serum was collected, transferred to Eppendorf tubes, labeled, and stored at -80 °C. Serum levels of CEA, CA125, and CA19-9 were measured using electrochemiluminescence, strictly adhering to the manufacturer's protocols [28]. The CEA kit (LM-EL-1265), CA125 kit (LM-CA125-Mu), and CA19-9 kit (LM-CA19-9-Hu) were obtained from LMAI Bio, Shanghai, China.

Follow-up

Postoperatively, all assessments were followed up regularly through telephone or outpatient visits. Follow-up contents included current health status, tumor recurrence (if applicable), recurrence time, and information about postoperative adjuvant therapies and treatment plans. For GBC patients, follow-ups were conducted every six months to record their survival status. The total follow-up period was 60 months (5 years). Overall survival (OS) was defined as the time from the day of surgery to either death or the end of the follow-up period.

Statistical analysis

All statistical analyses and plotting were conducted using SPSS 21.0 (IBM Corp. Armonk, NY, USA), GraphPad Prism 8.01 (GraphPad Software Inc., San Diego, CA, USA), and Medcalc® version 15.0 (Medcalc Software Ltd, Ostend, Belgium). The normality of numerical variable data was assessed using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation (SD) and compared between groups using an unpaired *t*-test. Data that did not follow a normal distribution were presented as median (minimum, maximum) and compared using the Mann-Whitney U test (rank sum test). Categorical data were summarized as counts (n) and percentages (%), with inter-group comparisons conducted using the Chi-squared test or Fisher's exact test, as appropriate. To evaluate the diagnostic efficacy of combining SII, CEA, CA125, and CA19-9 for GBC and the predictive accuracy of SII for postoperative death, receiver operating characteristic (ROC) curve analyses were performed. Prognostic cut-off values were determined based on the ROC curves. Patients with GBC were divided into high-SII and low-SII groups according to the prognostic cut-off value. The impact of SII on patient prognosis was analyzed by the Kaplan-Meier method, and survival curves were compared using the log-rank test. To identify independent risk factors (IRFs) influencing the prognosis of GBC patients, a Cox proportional hazards regression analysis was conducted. All tests were two-sided, a P value < 0.05 was considered statistically significant.

Results

Preoperative SII correlates significantly with biomarker levels (CEA, CA125, CA19-9) in GBC patients

Preoperative levels of SII, CEA, CA125, and CA19-9 were significantly elevated in the GBC group compared to the benign lesion group, with statistically significant differences observed between the two groups (all $P < 0.001$, Fig. 1A-D). To further investigate the relationship between preoperative SII and these biomarkers, Spearman correlation analysis was performed. Results showed a significant positive correlation between SII and serum levels of CEA, CA125, and CA19-9 in GBC patients ($r = 0.434$, 0.570, 0.614, respectively, all $P < 0.001$, Fig. 1E-G).

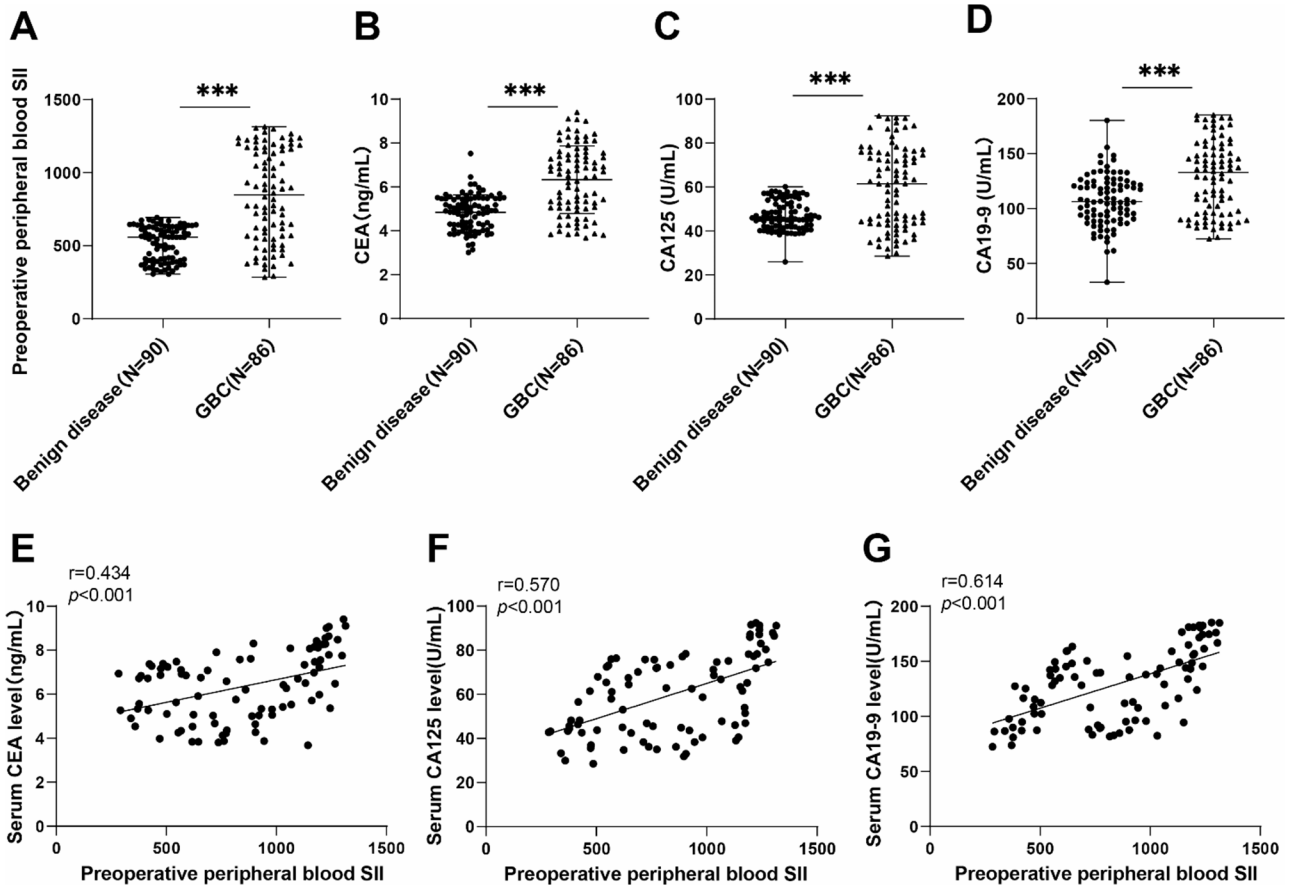

Fig. 1 Preoperative SII and tumor marker expression levels (CEA, CA125, and CA19-9) in GBC patients and their correlations. The differences in preoperative SII (**A**), CEA (**B**), CA125 (**C**), and CA19-9 (**D**) expression levels between 90 patients with benign gallbladder lesions and the GBC group were analyzed and compared. Data that conformed to the normal distribution of measures were compared between the two groups using the independent sample *t*-test, and data that did not conform to the normal distribution of measures were compared using the Mann-Whitney U test. *** $P < 0.001$. Spearman was used to analyze the correlations of preoperative SII with serum biomarkers CEA (**E**), CA125 (**F**), and CA19-9 (**G**) levels in GBC patients

Combined preoperative biomarkers (CEA, CA125, CA19-9) and SII demonstrate high diagnostic value for GBC

The diagnostic performance of preoperative CEA, CA125, CA19-9, and SII for identifying GBC was assessed using the ROC curve analysis. Individual biomarkers showed significant early diagnostic value for GBC patients, with the following areas under the curve (AUC): CEA: AUC = 0.774, $P < 0.001$, CA125: AUC = 0.686, $P < 0.001$, CA19-9: AUC = 0.686, $P < 0.001$, and SII: AUC = 0.794, $P < 0.001$. When combined, the diagnostic efficacy of CEA, CA125, CA19-9, and SII (denoted as "Combination") was significantly superior to any single marker, with an AUC = 0.872, $P < 0.001$ (Fig. 2; Table 1). wise comparisons demonstrated that the combination outperformed each individual biomarker ($P < 0.05$), confirming its higher diagnostic accuracy for GBC patients.

Predictive value of preoperative SII for postoperative death in GBC patients and its relationship with clinical data

During the 60-month follow-up, 29 deaths were recorded among GBC patients. The predictive value of SII for postoperative death was analyzed using ROC curves. Results showed that (Fig. 3) preoperative: CEA: AUC = 0.535, $P < 0.001$ (95% CI = 0.424–0.643), CA125: AUC = 0.659, $P < 0.001$ (95% CI = 0.549–0.758), CA19-9: AUC = 0.875, $P < 0.001$ (95% CI = 0.787–0.937), SII: AUC = 0.814, $P < 0.001$ (95% CI = 0.716–0.890). The combined analysis of CEA, CA125, CA19-9, and SII (termed "Combination-death") demonstrated significantly higher predictive efficiency for postoperative death (AUC = 0.923, $P < 0.001$, 95% CI: 0.844–0.969) compared to any single test ($P < 0.05$, Table 2). The optimal SII cut-off value was determined to be 889.52, with preoperative SII > 889.52 identified as a predictor of postoperative death in GBC patients.

To explore the relationship between preoperative SII and clinical characteristics, GBC patients were stratified

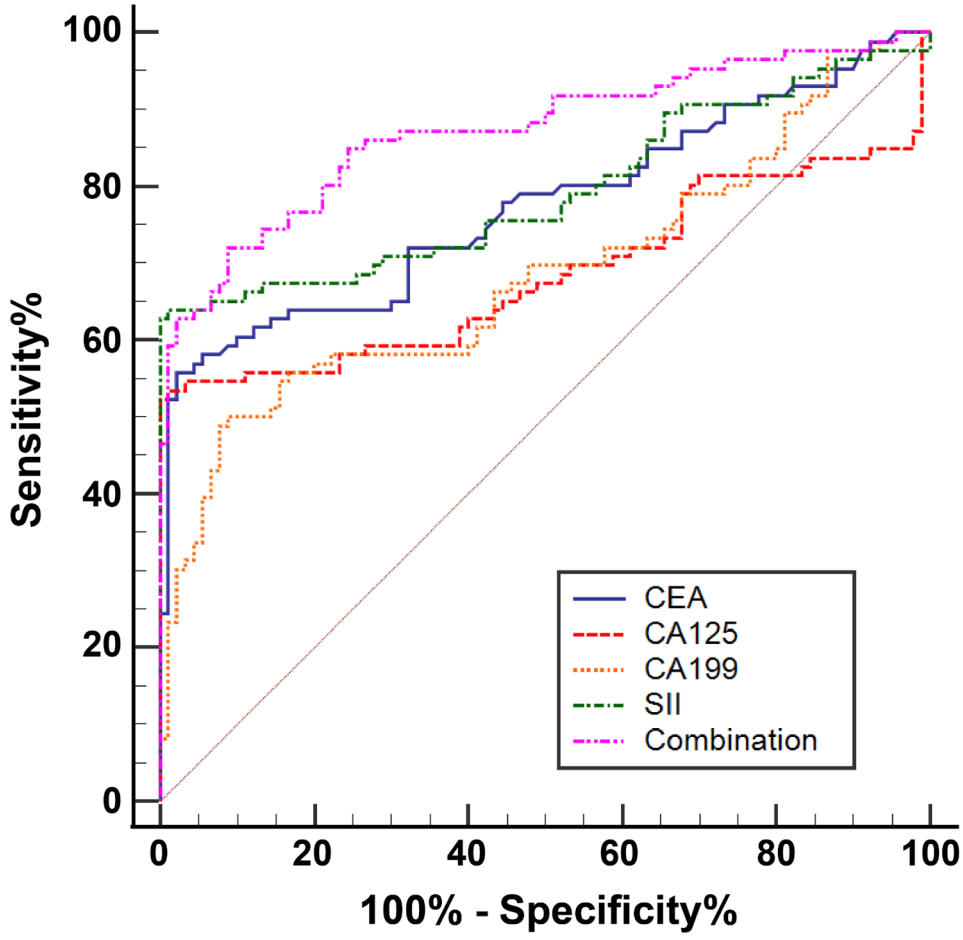

Fig. 2 Early diagnostic value of combined detection of preoperative CEA, CA125, and CA19-9, and SII in GBC patients. The ROC curve demonstrates the diagnostic performance of combining preoperative SII with tumor markers (CEA, CA125, and CA19-9) for early detection of GBC

Table 1 Preoperative CEA, CA125, and CA19-9 combined with SII have high early diagnostic value for GBC patients

Item	Sensitivity	Specificity	AUC	*P*
CEA	55.81%	80.74%	0.774	< 0.001
CA125	53.49%	88.89%	0.686	< 0.001
CA19-9	50.00%	81.11%	0.686	< 0.001
SII	63.89%	98.89%	0.794	< 0.001
Combination	72.09%	91.11%	0.872	< 0.001
CEA vs. Combination	*P* = 0.003			
CA125 vs. Combination	*P* < 0.001			
CA19-9 vs. Combination	*P* < 0.001			
SII vs. Combination	*P* = 0.003			

Note: Multiple areas under the ROC curves (AUCs) were compared using the Delong test in MEDCALC software

into the low SII group (≤ 889.52, $n = 46$) and the high SII group (> 889.52, $n = 40$). No significant differences were observed in age, sex, BMI, cancer type, postoperative neoadjuvant chemotherapy, or chemotherapy regimen between the groups (all $P > 0.05$). However, significant differences were found in: tumor differentiation degree, tumor size, TNM staging, lymph node metastasis, perineural invasion, operation type, NLR, PLR, and serum levels of CA19-9, CEA, and CA125 levels (all $P < 0.05$, Table 3). These findings underscore that preoperative SII is a valuable predictor of postoperative death in GBC patients. Regular monitoring of SII changes could assist in evaluating prognosis, especially for high-risk patients.

High preoperative SII predicts poor prognosis in GBC patients

Postoperative follow-up over 60 months revealed a significant difference in prognosis between the low SII and high SII groups ($\chi^2 = 18.920$, $P < 0.001$). Among the 29 GBC patients who died, 23 were from the high SII group and 6 from the low SII group (Table 4). Kaplan-Meier survival analysis further showed that the high SII group had a significantly worse prognosis, as indicated by a leftward shift of the survival curve ($P < 0.05$, Fig. 4). The high SII group exhibited a higher cumulative incidence of postoperative death within the same follow-up period. These results indicate that elevated preoperative SII

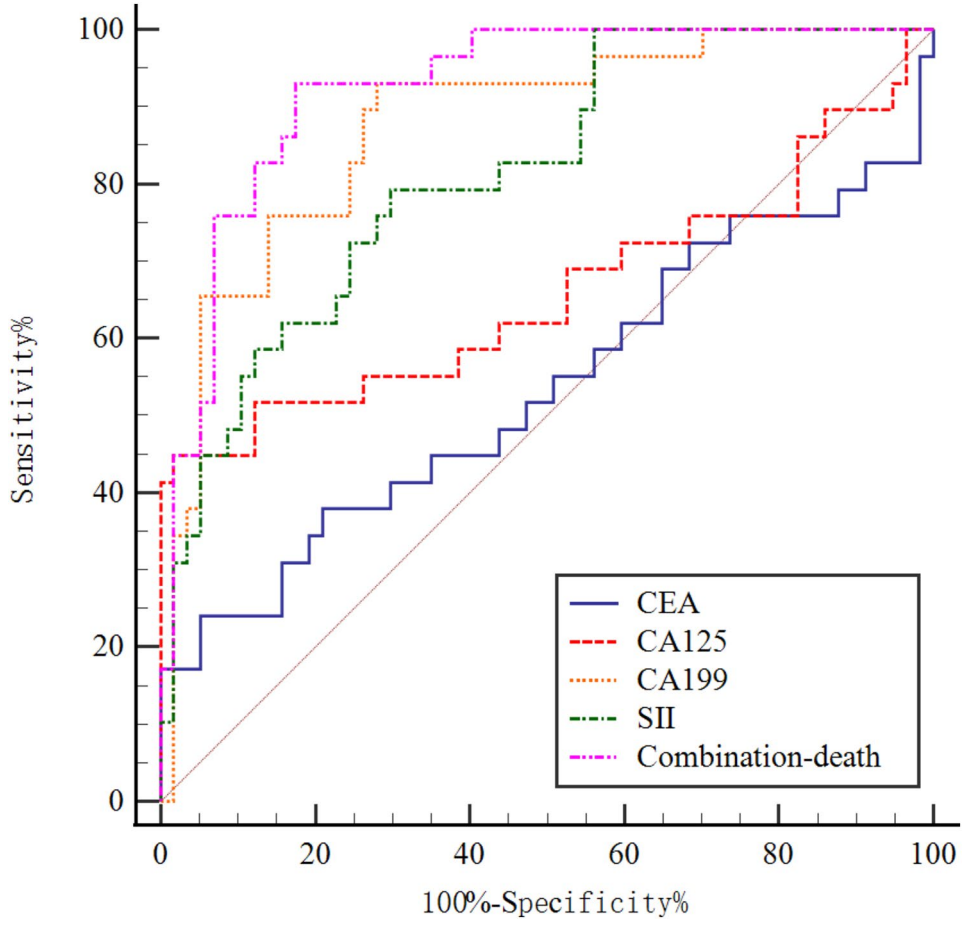

Fig. 3 Predictive value of CEA, CA125, CA19-9, and SII for postoperative mortality in GBC patients. ROC curve analysis evaluating the predictive accuracy of combining preoperative SII with CEA, CA125, and CA19-9 for postoperative mortality in GBC patients

Table 2 Preoperative CEA, CA125, and CA19-9 combined with SII have high predictive value for postoperative death in patients with GBC

Item	Sensitivity	Specificity	AUC	*P*
CEA	44.14%	84.74%	0.535	< 0.001
CA125	44.83%	88.25%	0.659	< 0.001
CA19-9	93.10%	71.93%	0.875	< 0.001
SII	79.31%	70.18%	0.814	< 0.001
Combination-death	93.10%	82.46%	0.923	< 0.001
CEA vs. Combination-death	*P* < 0.001			
CA125 vs. Combination-death	*P* = 0.003			
CA19-9 vs. Combination-death	*P* = 0.043			
SII vs. Combination-death	*P* = 0.004			

Note: Multiple areas under the ROC curves (AUCs) were compared using the Delong test in MEDCALC software

serves as a reliable predictor of poor prognosis in GBC patients and has specific value in assessing their survival outcomes.

Preoperative SII as an independent risk factor (IRF) for poor prognosis in GBC patients

To evaluate the impact of preoperative SII on GBC prognosis, we performed a Cox multivariate regression analysis. The analysis included patient mortality as the dependent variable and selected independent variables with $P < 0.05$ from Table 1, along with other reported risk factors for GBC prognosis [29, 30]. After excluding the linear interference of NLR and PLR, the following variables were included in the model: age, sex, tumor size, TNM staging, degree of differentiation, lymph node metastasis, perineural invasion, surgical type, CEA, CA125, and CA19-9, and preoperative SII. The results demonstrated that after adjusting for serum CA19-9, preoperative SII was identified as an IRF for poor prognosis in GBC patients ($P = 0.022$, HR = 1.003, 95% CI: 1.001–1.006) (Tables 5 and 6). This finding highlights that preoperative SII is a critical prognostic marker, and

Table 3 The relationship between preoperative peripheral blood SII and clinical data in GBC patients

Clinical pathological factors	Cases	Low SII group ($n=46$)	High SII group ($n=40$)	*P* value
Age (years) [n (%)]				
≤ 60	37	21 (45.65%)	16 (40.00%)	0.665
> 60	49	25 (54.35%)	24 (60.00%)	
Sex [n (%)]				
Male	33	17 (36.96%)	16 (40.00%)	0.826
Female	53	29 (63.04%)	24 (60.00%)	
BMI [n (%)]				
≥ 23 kg/m^2	30	13 (28.26%)	17 (42.50%)	0.182
< 23 kg/m^2	56	33 (71.74%)	23 (57.50%)	
Cancer type				
Adenocarcinoma	52	30 (65.22%)	22 (55.00%)	0.507
Mixed adenocarcinoma	15	8 (17.39%)	7 (17.50%)	
Adenosquamous carcinoma	19	8 (17.39%)	11 (27.50%)	
Tumor size [n (%)]				
≤ 5 cm	30	24 (52.17%)	6 (15.00%)	< 0.001
> 5 cm	56	22 (47.83%)	34 (85.00%)	
Differentiation degree [n (%)]				
Low differentiation	26	19 (41.30%)	7 (15.70%)	0.020
Medium/high differentiation	60	27 (58.70%)	33 (82.50%)	
TNM staging [n (%)]				
I-II stage	33	24 (52.17%)	9 (22.50%)	0.007
III-IV stage	53	22 (47.83%)	31 (77.50%)	
Lymph node metastasis				
Yes	39	13 (28.26%)	26 (65.00%)	0.001
No	47	33 (71.74%)	14 (35.00%)	
Perineural invasion				
Yes	30	10 (21.74%)	20 (50.00%)	0.007
No	56	36 (78.26%)	20 (50.00%)	
Surgery type				
Simple cholecystectomy	25	17 (36.96%)	8 (20.00%)	0.001
Radical cholecystectomy	23	18 (39.13%)	5 (12.50%)	
Enlarged radical cholecystectomy	21	5 (10.87%)	16 (40.00%)	
Palliative surgery	17	6 (13.04%)	11 (27.50%)	
Postoperative neoadjuvant chemotherapy				
Yes	30	14 (30.43%)	16 (40.00%)	0.374
No	56	32 (69.57%)	24 (60.00%)	
Chemotherapy regimen				
Cisplatin + Gemcitabine		8 (17.39%)	6 (15.00%)	0.282
Cisplatin + Tegafur		6 (13.04%)	10 (25.00%)	
NLR		1.95(0.63, 8.28)	3.12 (2.08, 5.97)	< 0.001
PLR		144.60 ± 26.16	181.91 ± 21.23	< 0.001
CEA (ng/mL)		5.80 ± 1.30	6.94 ± 1.58	< 0.001
CA125 (U/mL)		47.53 (28.54, 77.11)	71.54 (31.84, 92.39)	< 0.001
CA19-9 (U/mL)		110.35 (72.39, 163.45)	148.81 (82.45, 185.30)	< 0.001

Note: BMI: body mass index; TNM: T: extent of the primary tumor; N: lymph node involvement; M: metastatic disease; NLR (neutrophil-to-lymphocyte ratio); PLR (platelet-to-lymphocyte ratio); CEA: carcinoembryonic antigen; CA125: carbohydrate antigen 125; CA19-9: carbohydrate antigen 19 – 9. Fisher's exact test was for the comparative analysis of categorical variable, and unpaired *t*-test was for the comparative analysis of continuous variables between two groups. Measurement data with non-normal distribution were expressed as median (minimum, maximum). Mann-Whitney U test was used for comparisons between groups. $P<0.05$ indicated a statistically significant difference

Table 4 Postoperative death in GBC patients with different SII

	Death	Survival	Total
Low SII group	6	40	46
High SII group	23	17	40
Total	29	57	86

its elevation is significantly associated with adverse outcomes in GBC patients. These results underscore the importance of incorporating SII into prognostic assessments to identify high-risk individuals and guide clinical decision-making.

Discussion

Gallbladder cancer (GBC) is an aggressive malignancy posing significant healthcare challenges, particularly in regions such as Latin America and Southeast Asia [31]. The asymptomatic nature of GBC in its early stages, combined with its frequent incidental discovery during cholecystectomy for gallstone-related symptoms, makes early detection exceedingly difficult [6]. As a result, GBC remains highly lethal [32], underscoring the critical need for improved diagnostic and prognostic strategies. Identifying reliable biomarkers for early detection and precise disease evaluation is essential for improving the survival rates of GBC patients [10]. Tumor markers such as CEA, CA125, and CA19-9 have been extensively studied for their diagnostic and prognostic utility in GBC [33, 34]. In parallel, systemic inflammation markers like the systemic immune-inflammation index (SII) have been implicated in the progression and outcomes of various malignancies [15, 19]. Our study demonstrates that combining SII with CEA, CA125, and CA19-9 enhances the early diagnostic accuracy for GBC and highlights the high predictive value of SII for postoperative mortality.

Markers of systemic inflammation have long been associated with increased cancer risk and poor outcomes [35]. Among these, SII has emerged as a potential biomarker

Table 5 The meaning and assignment method of variables

Factors	Meaning	Assignment
y	Prognosis	y = 1 death, y = 0 survival
x_1	Age	> 60 = 1, ≤ 60 = 0
x_2	Sex	Male = 1, female = 0
x_3	Tumor size	> 5 cm = 1, ≤ 5 cm = 0
x_4	Differentiation degree	Medium/high differentiation = 1, low differentiation = 0
x_5	TNM staging	III-IV stage = 1, I-II stage = 0
x_6	Lymph node metastasis	Yes = 1, no = 0
x_7	Perineural invasion	Yes = 1, no = 0
x_8	Surgery type	Non-simple cholecystectomy = 1, simple cholecystectomy = 0
x_9	CEA	Continuous variable (ng/mL)
x_{10}	CA125	Continuous variable (U/mL)
x_{11}	CA19-9	Continuous variable (U/mL)
x_{12}	SII	Continuous variable

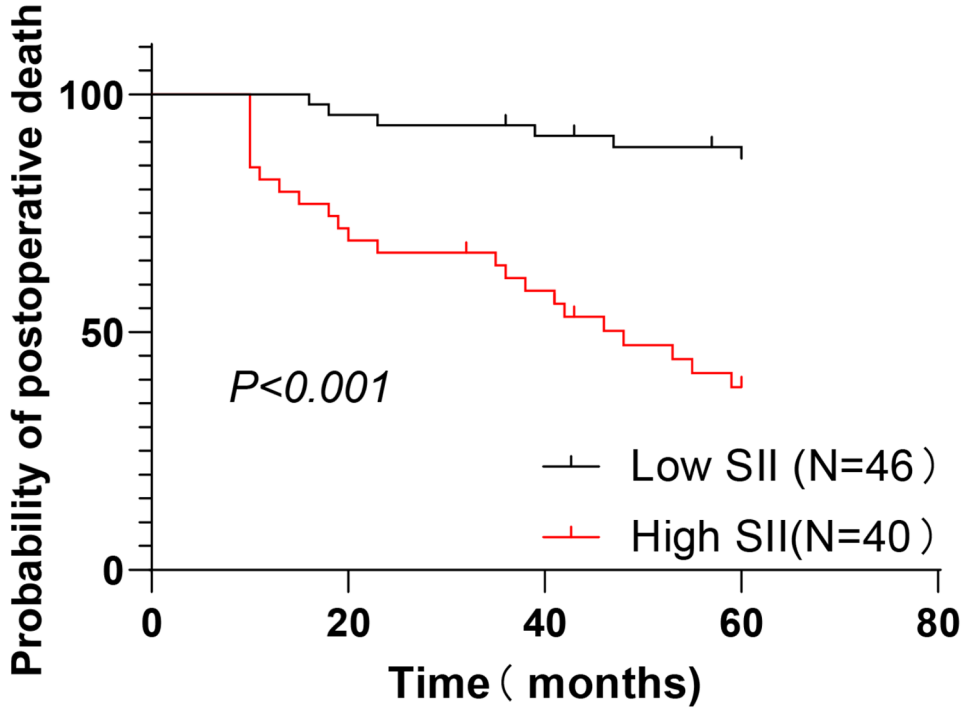

Fig. 4 High preoperative SII levels predict poor prognosis in GBC patients. Kaplan-Meier survival curves depict the cumulative survival rates of GBC patients stratified by high and low preoperative SII levels in peripheral blood. Differences in cumulative survival rates between groups were assessed using log-rank tests. During the follow-up period, four patients in the low SII group and three patients in the high SII group were censored

Table 6 Cox multivariate analysis of IRFs for the poor prognosis in GBC patients

Variable	*P* value	HR	HR 95% CI
Age	0.477	1.434	0.531–3.876
Sex	0.851	1.097	0.419–2.871
Tumor size	0.612	0.732	0.220–2.437
Differentiation degree	0.405	0.645	0.230–1.81
TNM staging	0.818	0.88	0.295–2.623
Lymph node metastasis	0.893	0.936	0.361–2.429
Perineural invasion	0.646	1.217	0.526–2.814
Surgery type	0.456	0.657	0.218–1.982
CEA	0.093	0.764	0.557–1.046
CA125	0.068	0.973	0.945–1.002
CA19-9	0.042	1.022	1.001–1.044
SII	0.022	1.003	1.001–1.006

Note: TNM: T:extent of the primary tumor; N: lymph node involvement; M: metastatic disease; CEA: carcinoembryonic antigen; CA125: carbohydrate antigen 125; CA19-9: carbohydrate antigen 19−9; SII: System immune inflammation index. $P < 0.05$ indicated a statistically significant difference

for identifying cancer risk and facilitating earlier detection. Similarly, tumor markers such as CEA, CA19-9, and CA125 have been explored for their utility in the early detection of GBC [28, 36, 37]. In our study, preoperative levels of SII, CA125, CA19-9, and CEA were significantly elevated in GBC patients, corroborating previous findings on their diagnostic and prognostic relevance [24, 28, 38].

Additionally, GBC is unique among digestive system cancers for its higher prevalence in women compared to males [39]. Recent epidemiological data indicate that females account for approximately 62% of GBC cases, with a female-to-male ratio of 1.6:1 [40]. Hormonal factors, particularly the influence of female hormones on CA125 levels, likely contribute to this disparity, as males tend to exhibit lower CA125 values [41]. Consistent with these observations, our study found that preoperative serum CA125 levels were higher in female GBC patients than in male patients. However, no significant sex-based differences were observed in serum CEA, CA19-9, or SII, suggesting that SII may serve as a robust, sex-independent biomarker for GBC. These findings underscore the potential of integrating systemic inflammatory markers with tumor markers to enhance diagnostic accuracy and prognostic evaluations in GBC, paving the way for earlier detection and improved clinical management of this challenging disease.

In our study, we also investigated the relationship between preoperative SII and biomarkers (CEA, CA125, CA19-9) in GBC patients. Notably, the results revealed positive correlations between SII and CA19-9, CA125, and CEA. These findings align with prior studies on colorectal cancer, where higher inflammatory indices, including SII, were associated with unfavorable disease-free survival and OS, particularly in patients with a high Gustave Roussy Immune Score [42]. Similarly, previous research has shown that patients with colon cancer exhibit elevated median SII values compared to healthy controls. Additionally, SII positively correlates with longer hospital stays, increased medical expenses, and higher serum CEA levels [43]. Further evidence has reported a positive correlation between percentage changes in CA19-9 and SII as continuous variables [44]. Consistent with these observations, our findings underscore the positive association between preoperative SII and biomarker levels (CA125, CEA, and CA19-9), suggesting a synergistic role in evaluating GBC.

Numerous studies have highlighted the potential of combining multiple serum biomarkers to enhance diagnostic accuracy [45, 46]. In our study, we assessed the early diagnostic efficacy of individual biomarkers (CA19-9, CA125, CEA, and SII) and their combined diagnostic value. The MEDCALC analysis demonstrated that the combination of these four markers exhibited superior diagnostic efficiency compared to any single marker. This finding aligns with research in endometrial cancer, where combining SII, CA125, CA153, and lymph vascular space invasion significantly enhanced diagnostic performance (AUC = 0.865, $P < 0.001$) [47]. Similarly, the combination of CA125, human epididymis protein 4 (HE4), fibrinogen-to-albumin ratio, SII, and prognostic nutritional index has been shown to outperform CA125 or HE4 alone, as well as their dual combination [48]. Collectively, these findings reinforce the high early diagnostic value of combining SII, CA125, CEA, and CA19-9 for GBC. The integration of these markers holds great promise for improving diagnostic accuracy, enabling earlier detection, and facilitating more effective clinical management of GBC patients.

Growing evidence suggests that elevated SII is associated with worse outcomes in various solid tumors [49, 50]. In our study, ROC curve analysis demonstrated the predictive value of SII for postoperative mortality in GBC patients, identifying a cut-off value of 889.52. Patients with preoperative SII levels exceeding this threshold were found to have a higher risk of postoperative mortality, suggesting that SII is a reliable predictor of postoperative death in GBC. Furthermore, significant differences in prognosis were observed between patients in the high and low SII groups, with the high SII level group showing a markedly higher cumulative incidence of postoperative death. These findings align with prior studies, which reported that elevated SII levels are associated with increased rates of postoperative complications and mortality in colorectal cancer patients [51]. Similarly, research has highlighted the prognostic significance of SII in ovarian cancer, where it predicts postoperative mortality with an AUC of 0.646 (95% CI: 0.537–0.756, $P = 0.012$) [52]. Moreover, SII has shown prognostic value in several

malignancies, including hepatocellular carcinoma and lung cancer [53, 54]. Taken together, our findings suggest that preoperative SII can serve as an effective tool for predicting both postoperative mortality and prognosis in GBC patients.

Additionally, we identified preoperative SII as one of the independent risk factors (IRFs) for poor prognosis in GBC patients. This observation is consistent with previous studies demonstrating that factors such as advanced age ≥ 65 years, advanced TNM stage, tumor site, elevated SII, and serum CA19-9 > 37 mU/mL are significant predictors of poor survival cancer patients [55]. Specifically, colorectal cancer patients with intermediate and high SII levels exhibit poorer survival outcomes. Similarly, SII has been established as an independent predictor of cancer-specific recurrence and survival in patients with resectable pancreatic ductal adenocarcinoma [56]. In patients with EGFR-mutant advanced non-small cell lung cancer, those with low SII levels have superior progression-free survival and significantly prolonged overall survival [57]. Moreover, research has identified SII ≥ 1450, portal vein resection, and microscopic venous invasion as independent factors for poor survival in distal cholangiocarcinoma. In conclusion, our findings reinforce the prognostic significance of elevated preoperative SII, which is not only a marker for postoperative mortality but also an IRF for poor survival outcomes in GBC patients. Regular monitoring of SII may provide valuable insights for tailoring management strategies and improving patient prognosis.

In summary, SII, as a simple, cost-effective, and non-invasive marker of systemic inflammation, can complement traditional tumor markers (CEA, CA125, and CA19-9) in the early diagnosis of GBC and prediction of postoperative mortality. Our findings highlight that the combination of SII with CEA, CA125, and CA19-9 enhances the sensitivity and diagnostic efficacy compared to the use of any single marker. Moreover, preoperative SII correlates with clinical parameters and is a strong predictor of poor prognosis. These findings offer valuable insights into the potential role of SII as an adjunctive tool for early diagnosis and prognosis evaluation in GBC patients.

Prospective and multicenter studies are crucial for minimizing biases and ensuring the generalizability of findings [58–61]. For example, a multicenter study identified SII > 510 as an independent predictive factor for overall survival following radical cholecystectomy for GBC [62]. Interestingly, this study revealed that SII's prognostic value diminished at high CA19-9 levels, suggesting that SII might only serve as a reliable prognostic marker when CA19-9 levels are < 40 U/mL. These results underscore the need for caution when interpreting SII in the presence of elevated CA19-9 levels. Similarly, cross-sectional studies, such as one demonstrating a positive correlation between SII and kidney stone risk among US adults under 50 [63], emphasize the importance of large-scale validation to support preliminary findings. Retrospective analyses also indicate that incorporating longitudinal measurements of CEA, CA19-9, and CA125 enhances the predictive accuracy of prognostic models in colorectal cancer, with consistent external validation results [24].

Despite its potential, our study still has certain limitations. As a single-center retrospective analysis, it may be subject to incomplete historical data and confounding factors that could influence the results. Additionally, the prognostic utility of SII has yet to be validated prospectively. Future research should involve multicenter, prospective data collection to confirm the robustness of SII as a prognostic factor for GBC. Furthermore, the biological mechanisms underlying SII's role in the pathogenesis and progression of GBC remain unclear and warrant further exploration.

Another limitation is the inability of SII combined with CEA, CA125, and CA19-9 to distinguish benign from malignant gallbladder neoplasms with high precision. While the combined approach enhances diagnostic sensitivity, it does not overcome the inherent limitations of each marker. Future studies should investigate the utility of SII in combination with novel biomarkers or advanced diagnostic techniques to improve the early detection of GBC. Expanding the clinical applications of SII and exploring its integration with other indicators could further strengthen its role in the early diagnosis and management of GBC.

Supplementary Information

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Supplementary Material 1

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Author contributions
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Data availability
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethical approval
The study was reviewed and ratified by the Academic Ethics Committee of The First Hospital of Shanxi Medical University and complied with the Declaration of Helsinki.

Consent to participate
Informed consent was waived due to the retrospective nature of the analysis.

Competing interests
The authors declare no competing interests.

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