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ORIGINAL ARTICLE

Retrospective Study

Platelet to lymphocyte ratio as a novel prognostic tool for gallbladder carcinoma

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Data sharing: The technical appendix, statistical code, and dataset are available from the corresponding author at the following email address: liuchangdoctor@163.com. The participants gave informed consent for data sharing. No additional data are available.

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Abstract

AIM: To preliminarily investigate the prognostic significance of the platelet to lymphocyte ratio (PLR) in patients with gallbladder carcinoma (GBC).

METHODS: Clinical data of 316 surgical GBC patients were analyzed retrospectively, and preoperative serum platelet and lymphocyte counts were used to calculate the PLR. The optimal cut-off value of the PLR for detecting death was determined by the receiver operating characteristic (ROC) curve. The primary outcome was overall survival, which was estimated by the Kaplan-Meier method. The log-rank test was used to compare the differences in survival. Then, we conducted multivariate Cox analysis to assess the independent effect of the PLR on the survival of GBC patients.

RESULTS: For the PLR, the area under the ROC curve was 0.620 (95%CI: 0.542-0.698, P = 0.040) in detecting death. The cut-off value for the PLR was determined to be 117.7, with 73.6% sensitivity and 53.2% specificity. The PLR was found to be significantly

positively correlated with CA125 serum level, tumor-node-metastasis (TNM) stage, and tumor differentiation. Univariate analysis identified carcinoembryonic antigen (CEA), CA125 and CA199 levels, PLR, TNM stage, and the degree of differentiation as significant prognostic factors for GBC when they were expressed as binary data. Multivariate analysis showed that CA125 > 35 U/mL, CA199 > 39 U/mL, PLR ⩾ 117.7, and TNM stage Ⅳ were independently associated with poor survival in GBC. When expressed as a continuous variable, the PLR was still an independent predictor for survival, with a hazard ratio of 1.018 (95%CI: 1.001-1.037 per 10-unit increase, P = 0.043).

CONCLUSION: The PLR could be used as a simple, inexpensive, and valuable tool for predicting the prognosis of GBC patients.

Key words: Platelets; Lymphocyte; Gallbladder carcinoma; Prognosis; Survival

Core tip: The platelet to lymphocyte ratio (PLR) has been identified as a useful prognostic tool for various types of cancer; however, its prognostic value in gallbladder carcinoma (GBC) has never been investigated. We recruited 316 patients at our institute to determine the significance of the PLR in GBC. It was found to be significantly correlated with the serum level of CA125, tumor-node-metastasis stage, and tumor differentiation. Our results showed that a PLR ⩾ 117.7 was independently associated with poor survival in GBC. We emphasize that this ratio could be used as a simple, inexpensive, and valuable tool for predicting the prognosis of GBC.

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INTRODUCTION

Gallbladder carcinoma (GBC) is a rare disease with an increasing morbidity worldwide. The incidence of this malignancy has been recently reported to be approximately 2.5 per 100000 persons[1]. Predisposing factors for GBC mainly include gallstones, chronic cholecystitis, chronic bacterial cholangitis, environmental exposures, *etc*[2].

Although the diagnosis and treatment of GBC have improved dramatically with the advance in surgical techniques, the prognosis for this malignancy is still typically poor because the majority of patients are diagnosed and treated at a late stage. It has been previously reported that the overall 5-year survival rate of GBC ranges from 2.7% to 20.1%[3,4]. To date, the relative prognostic factors for GBC have not yet been clearly identified, and previous research has suggested that age[5], sex[5], CA125[6] and CA199 levels[7], and tumor-node-metastasis (TNM) stage[5,8] might affect the survival of these patients.

Recently, numerous studies have shown that the inflammatory response plays a crucial role in the formation and development of various malignancies[9,10]. In addition, a high platelet count (PLT) has been found to be associated with poor prognosis in many solid tumors[11]. The platelet to lymphocyte ratio (PLR), which is a combination of the PLT and lymphocyte counts, is also regarded as a representative index of inflammation. An elevation in the PLR has been found to be a negative predictor for survival in patients with colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, and ovarian cancer[12,13]. However, the prognostic significance of PLR in GBC, which is one of the malignancies that is strongly associated with chronic inflammation[14], has never been investigated. We therefore conducted a retrospective cohort study to reveal the prognostic value of PLR in GBC.

MATERIALS AND METHODS

Patients

From 2002 until 2012, a total of 316 surgical GBC patients (238 with radical surgery and 78 without radical surgery) who had complete follow-up information were analyzed at our institute. Patients who had been previously treated for GBC were excluded. In addition, patients who had concomitant diseases that could significantly alter PLT, such as severe hypertension, splenic disease, or blood coagulation disorders, and patients who used aspirin or other acetylsalicylic acid drugs in the month before the surgery were excluded. Similarly, patients who had autoimmune diseases (Crohn's disease, rheumatoid arthritis, autoimmune hepatitis, *etc.*), leukemia, viral infection-related diseases, or other diseases that influence lymphocyte count were also excluded. Our study complied with the provisions of the Declaration of Helsinki[15] and was approved by the Ethical Committee of the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine.

Data collection

We extracted information of potential prognostic factors for GBC from the electronic medical records. Specifically, the following data were collected: age and sex; history of gallstones; history of metabolic diseases, such as diabetes and hypertension; PLT; lymphocyte, neutrophil, and white blood cell (WBC) counts; carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CA125, and CA199 levels, and the results of pathological reports. The TNM staging

Table 1 Basic characteristics of gallbladder carcinoma patients stratified according to serum level of platelet to lymphocyte ratio

Variable	Overall (*n* = 316)	PLR < 117.7 (*n* = 100)	PLR ≥ 117.7 (*n* = 216)	*P* value
Age (yr)	65 (30-87)	65 (43-87)	64 (30-87)	0.155[1]
Men/Women	101/215	39/61	62/154	0.068[1]
Gallstone/No	160/156	50/50	110/106	0.878[1]
Diabetes/No	30/286	10/90	20/196	0.835[1]
Hypertension/No	57/259	19/81	38/178	0.762[1]
PLT (10^9/L)	184 (37-525)	139 (37-261)	216 (37-525)	< 0.001[2]
Lymphocytes (10^9/L)	1.3 (0.3-3.5)	1.6 (0.4-3.5)	1.1 (0.2-2.9)	< 0.001[2]
PLR	152.4 (13.8-2282.6)	93.6 (13.8-117.6)	185.5 (117.9-2282.6)	< 0.001[2]
WBC (10^9/L)	6.2 (1.6-33.4)	5.6 (1.9-33.4)	6.6 (1.6-23.4)	0.013[2]
Neutrophils (10^9/L)	4.2 (1.0-25.9)	3.4 (1.0-25.9)	4.6 (1.0-19.3)	< 0.001[2]
CEA (ng/mL)	3.6 (0.5-264.8) (*n* = 168)	3.8 (1.0-90.6) (*n* = 44)	3.6 (0.5-264.8) (*n* = 124)	0.847[2]
AFP (ng/mL)	2.9 (1.1-615.4) (*n* = 150)	3.0 (1.1-53.0) (*n* = 36)	2.8 (1.1-615.4) (*n* = 114)	0.763[2]
CA-125 (U/mL)	30.8 (6.1-3684) (*n* = 146)	21.0 (6.1-345.6) (*n* = 41)	36.5 (6.5-3684.0) (*n* = 105)	0.004[2]
CA-199 (U/mL)	100.5 (0.5-10000) (*n* = 158)	99.6 (0.5-4306) (*n* = 45)	125.0 (0.5-10001) (*n* = 113)	0.384[2]
TNM stage Ⅰ/Ⅱ/Ⅲ/ⅣA/ⅣB	5/24/59/121/107	4/12/21/36/27	1/12/38/85/80	0.019[1]
Differentiation: high/moderate/low	26/134/156	13/48/39	13/86/117	0.031[1]
Survival time (mo)	9 (1-97)	12 (1-77)	8 (1-97)	< 0.001[2]
Death/No	254/62	71/29	183/33	0.004[1]

[1]χ^2 test; [2]Wilcoxon test. The values are expressed as the median (range) or number. PLR: Platelet to lymphocyte ratio; PLT: Platelet count; WBC: White blood cell count; CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein.

system (5th edition), based on the criteria of the American Joint Committee on Cancer, was adopted[5].

Diagnosis and follow-up protocol for GBC patients

Resected tumor samples were uniformly sent to the Department of Pathology, and the presence of GBC was determined by clinical pathologists.

After discharge, patients were followed with either abdominal computes tomography and/or magnetic resonance imaging scans as well as serological tests, including measurement of CEA, AFP, CA125, and CA199 levels. The follow-up evaluations consisted of the above tests every 3 mo for the first year, every 4 mo for the second year, and every 6 mo thereafter. During follow-up, the date of death and the time of the last follow-up were recorded.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation for the normally distributed variables (Kolmogorov-Smirnov test, $P > 0.05$), and median (min-max) for the other variables. Comparisons between two groups were performed using the *t* test or Wilcoxon test for continuous variables and the χ^2 test for categorical data. The receiver operating characteristic (ROC) curve was adopted to determine the optimal cut-off point (with the highest sum of specificity plus sensitivity) for the PLR for discriminating between deceased and living patients. The statistical methods of this study were reviewed by Dr. Kai Qu from Department of Epidemiology, MD Anderson Cancer Center, University of Texas, United States.

The primary outcome observed was overall survival (OS), which was estimated by the Kaplan-Meier method. Differences in survival were analyzed by the log-rank test. The variables found to be significant ($P < 0.05$) in the univariate analysis were subjected to multivariate analysis with the backward Wald Cox proportional hazard regression method. All statistical analyses were performed using PASW Statistics 18.0 software (SPSS Inc., Chicago, IL, United States). A bilateral *P* value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Demographic data, serological tests, tumor stage, and the characteristics of the study population stratified according to the PLR are summarized in Table 1. The cohort included 101 men and 215 women, with a median age 65 years. Of these, 160, 30, and 57 patients had a history of gallbladder stones, diabetes, and hypertension, respectively. There were 155 (49.05%) patients with lymph node invasion, and 85 (26.9%) patients with remote metastasis. The median survival time of the patients after surgical resection was 9 mo, with 1-, 3-, and 5-year OS probabilities of 37.1%, 18.9%, and 11.8%, respectively. During the median follow-up time of 42 mo, 254 (80.4%) patients died.

Determination of the cut-off value for the PLR

The diagnostic potential of the PLR in detecting death

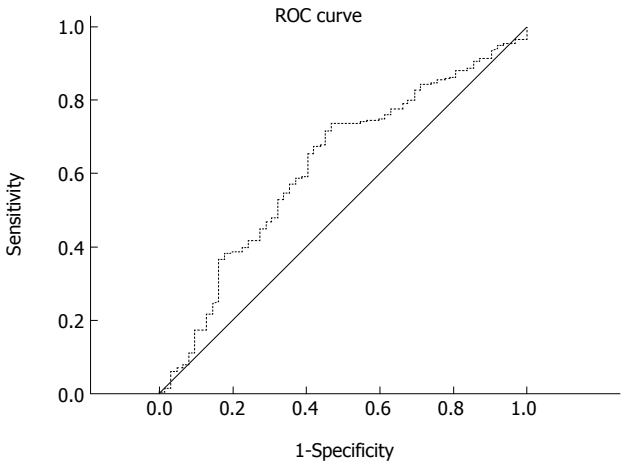

Figure 1 Diagnostic performance of the platelet to lymphocyte ratio in detecting death due to gallbladder carcinoma.

Table 2 Spearman's correlation analysis between platelet to lymphocyte ratio and clinical characteristics of gallbladder carcinoma patients

Variable	Coefficient	*P* value
Age (yr)	-0.017	0.758
Gender	0.030	0.600
PLT (10^9/L)	0.568	< 0.001
Lymphocytes (10^9/L)	-0.587	< 0.001
Neutrophils (10^9/L)	0.356	< 0.001
WBC (10^9/L)	0.207	< 0.001
CEA (ng/mL)	0.032	0.678
AFP (ng/mL)	-0.073	0.375
CA-125 (U/mL)	0.262	0.001
CA-199 (U/mL)	0.133	0.096
TNM stage	0.104	0.064
Differentiation	0.181	0.001
Survival time (mo)	-0.237	< 0.001

is shown in Figure 1. In general, the PLR was found to be a significant indicator for distinguishing death from survival (area under the ROC curve = 0.620, 95%CI: 0.542-0.698, P = 0.040). The ROC curve showed an optimal cut-off value of 117.7 for the PLR, with 73.6% sensitivity and 53.2% specificity.

Associations between the PLR and clinical characteristics

As shown in Table 1, the PLR was significantly positively associated with the lymphocyte, WBC, and neutrophil counts, CA125 level, TNM stage, and degree of differentiation (all $P < 0.05$).

Spearman's correlation analysis showed that the PLR was significantly associated with the PLT, lymphocyte count, neutrophil count, WBC count, differentiation, and survival time, with Spearman's coefficients of 0.568, -0.587, 0.356, 0.207, 0.262, 0.181 and -0.237 (all $P < 0.01$, Table 2), respectively. The box plots revealed the relationship between the PLR and the serum level of CA125 (Figure 2A) and survival time (Figure 2B). Furthermore, Figure 2C and 2D show the linear relationships of the PLR with the CA125 level and survival time.

Predictors of survival by log-rank test

Figure 3A shows the survival curves for our study cohort. Of the clinical parameters, a high PLR, high levels of CA125 and CA199, TNM stage Ⅳ, and poor differentiation were found to be significantly associated with poor OS by the log-rank test. Figures 3B to D show Kaplan-Meier curves stratified according to the PLR, CA125 level, and TNM stage, respectively. The respective cumulative survival rates at 1, 3, and 5 years were 51.7%, 32.3%, and 21.0% for patients with a PLR < 117.7, and 30.3%, 12.2%, and 7.4% for those with a PLR ⩾ 117.7.

Univariate and multivariate analyses of clinical and biochemical parameters

When the parameters were expressed as binary data, univariate analysis identified CEA, CA125, and CA199 levels, TNM stage, degree of differentiation, and PLR as significant tools for predicting OS in patients with GBC (Table 3). However, neither the PLT nor the lymphocyte count was a useful predictor. Multivariate analyses showed that patients with a higher PLR [hazard ratio (HR): 2.02; 95%CI: 1.24-3.28], a higher CA125 level (HR: 1.72; 95%CI: 1.16-2.56), a higher CA199 level (HR: 1.85; 95%CI: 1.19-2.86), and TNM stage Ⅳ (HR: 2.70; 95%CI: 1.49-4.87) had a significantly poorer prognosis compared with those with lower levels of these factors or a lower TNM stage (Figure 4).

We then assessed the prognostic values of these parameters when they were expressed as quantitative or ordinal data. Similarly, univariate analysis identified the same significant factors (Table 3), and multivariate analysis added the degree of differentiation as another independent prognostic factor (Figure 4).

Prognostic value of PLR at each TNM stage

TNM stage is considered to be a crucial prognostic factor for GBC, and it was the most powerful predictor in our survival analysis. To clarify whether the subgroups of GBC patients could be negatively influenced by the PLR, the patients were classified according to TNM stage. A high PLR was found to significantly increase the recurrence probability in GBC patients with TNM stage ⅣB but not with any of the other stages (Figure 5).

DISCUSSION

GBC is a rare disease; however, it is the most common malignant tumor of the biliary tract and represents 46%-95% of all biliary tract malignancies worldwide[1,16]. The incidence of GBC differs worldwide, with high prevalences in Chile, Japan, and northern India[16]. Few valuable prognostic factors for GBC have been identified, and it is necessary to identify several novel biomarkers.

Gallstones are a major risk factor for GBC[2].

Table 3 Univariate analysis of factors associated with overall survival of gallbladder carcinoma patients

As binary data			As quantitative/ordinal data		
Variable	***P* value**	**HR (95%CI)**	**Variable**	***P* value**	**HR (95%CI)**
Age > 60 yr	0.574	1.078 (0.829-1.403)	Age (per 1 yr increase)	0.456	1.004 (0.993-1.016)
Women *vs* men	0.829	1.030 (0.788-1.345)			
Gallstone (yes *vs* no)	0.309	1.137 (0.887-1.458)			
Diabetes (yes *vs* no)	0.420	1.194 (0.777-1.835)			
Hypertension (yes *vs* no)	0.997	1.001 (0.725-1.382)			
CEA > 3.4 ng/mL	0.012	1.620 (1.114-2.355)	CEA (per 1 ng/mL increase)	0.071	1.005 (1.000-1.011)
AFP > 20 ng/mL	0.420	0.663 (0.244-1.801)	AFP (per 1 ng/mL increase)	0.296	0.997 (0.990-1.003)
CA-125 > 35.0 U/mL	0.002	1.813 (1.236-2.658)	CA-125 (per 10 U/mL increase)	0.027	1.005 (1.001-1.009)
CA-199 > 39.0 U/mL	0.002	1.930 (1.284-2.903)	CA-199 (per 10 U/mL increase)	0.028	1.001 (1.000-1.002)
PLT > 300 × 10^9/L	0.956	1.013 (0.647-1.594)	PLT (per 10^9/L increase)	0.053	1.001 (1.000-1.003)
Lymphocytes < 1.5 × 10^9/L	0.243	1.173 (0.897-1.534)	Lymphocytes (per 10^9/L increase)	0.064	0.801 (0.633-1.013)
PLR ≥ 117.7	< 0.001	1.644 (1.246-2.169)	PLR (per 10 increase)	0.023	1.007 (1.001-1.013)
TNM Ⅳ *vs* Ⅰ-Ⅲ	< 0.001	1.692 (1.260-2.274)	TNM (per 1 stage increase)	< 0.001	1.377 (1.213-1.564)
Differentiation (low *vs* moderate/high)	< 0.001	1.563 (1.217-2.006)	Differentiation (per 1 grade increase)	< 0.001	1.523 (1.256-1.845)

HR: Hazard ratio; CI: Confidence interval.

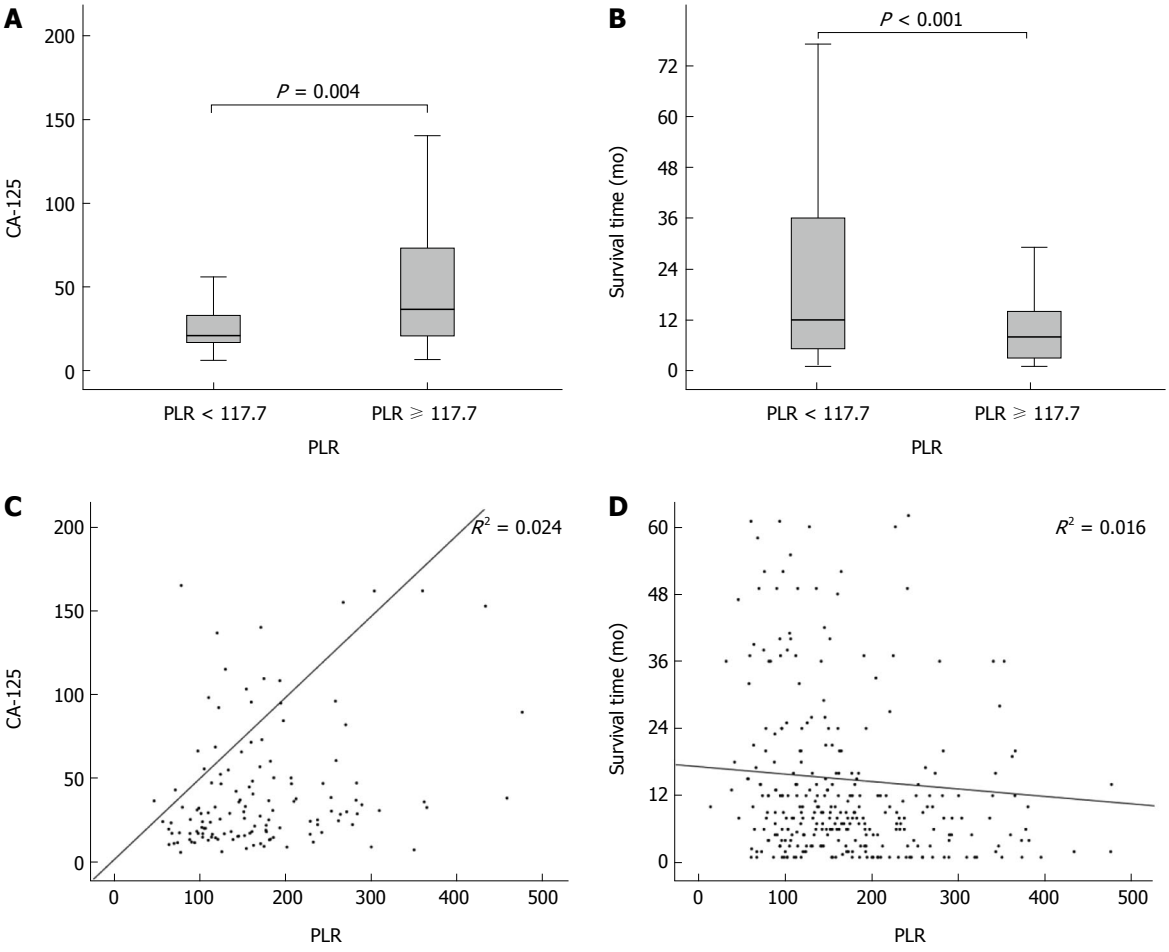

Figure 2 Box plots comparing platelet to lymphocyte ratio with CA125 (A) and survival time (B) and correlation analyses between PLR and CA125 (C) and survival time (D).

However, it is unknown whether there presence is a useful prognostic factor for this disease. Our study showed no significant association between gallstones and the survival of patients with GBC, which is consistent with a previous small-sample study conducted by Shiba *et al*[17]. Kayahara *et al*[5] have demonstrated that men and aged patients with GBC have decreased survival times; however, neither of these factors significantly affected survival time in our cohort. Ren and his colleagues[18] performed a meta-analysis of 21 studies and concluded that diabetes mellitus increased the incident risk of GBC by 52%. In

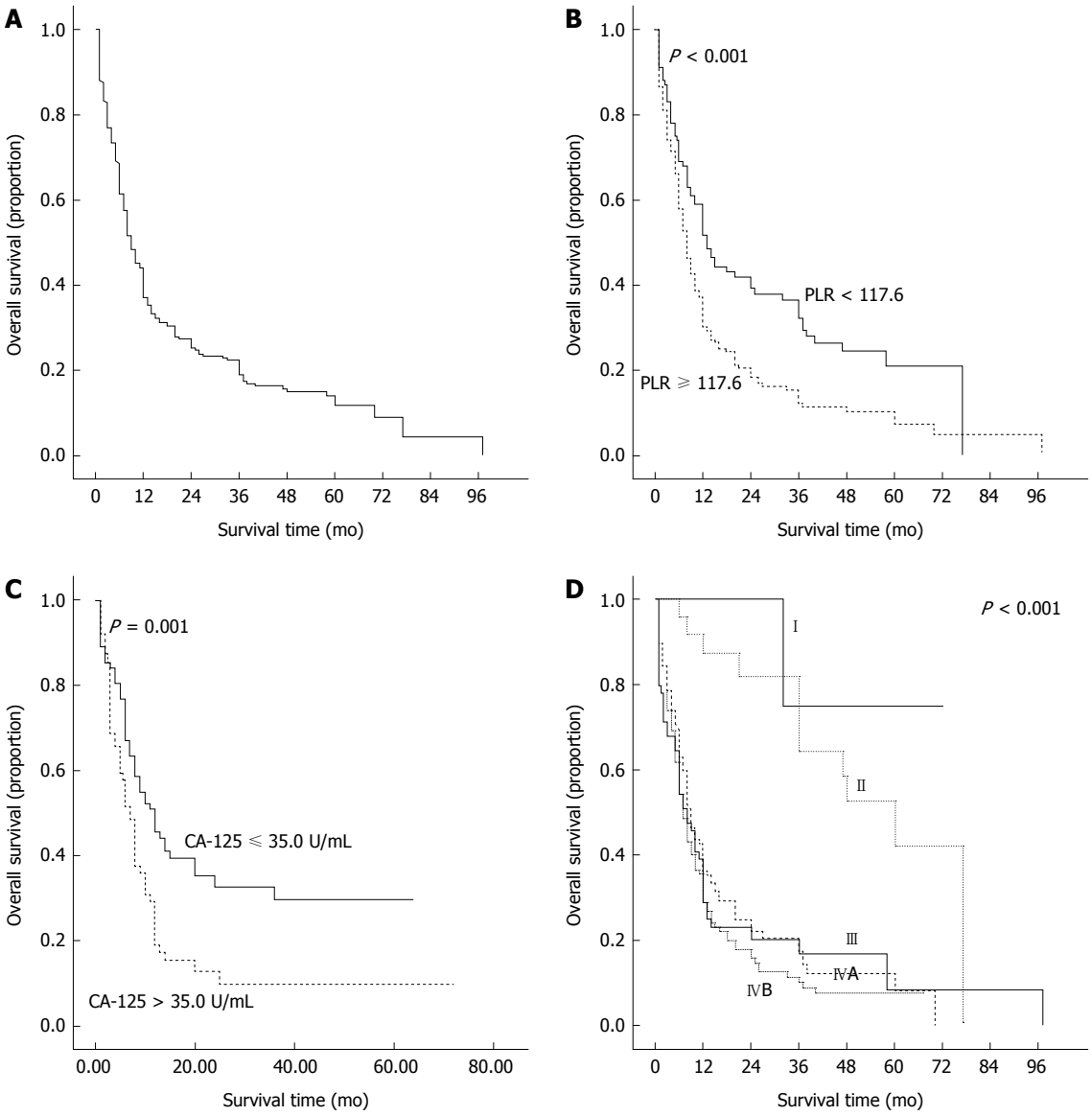

Figure 3 Kaplan-Meier curves for cumulative overall survival of the study population (A) and overall survival of patients stratified according to platelet to lymphocyte ratio (B), CA125 (C), and tumor-node-metastasis stage (D).

contrast, our study showed no links between diabetes mellitus and the prognosis of GBC.

Recent studies have shown that an abnormal PLT[19] or lymphocyte count alone[20] are predictive of poor survival in patients with GBC. However, in our cohort, neither the PLT count alone nor the lymphocyte count alone was able to significantly predict survival. However, the PLR, which is a simple combined index, strengthened both the role of PLTs and the significance of lymphocytes and was a powerful independent predictor. We confirmed the prognostic significance of the PLR both when it was expressed as binary data and when it was used as a continuous variable. In addition, TNM stage was identified as the other most useful tool for predicting the outcome of GBC.

Obviously, the possible mechanisms underlying the prognostic role of the PLR in the survival of GBC patients could involve two factors, the PLT and lymphocyte counts. On the one hand, although the PLT count was not a significant indicator of survival time in our study, a high level of PLTs has been previously reported to significantly increase the risk of death from various cancers[11], including GBC[6,19]. Moreover, an elevated serum level of PLTs has been positively correlated with tumor size[21]. *In vitro*, PLTs accelerate the growth and invasion of tumors *via* the release of platelet-derived proangiogenic mediators[22,23]. On the other hand, previous data have also shown that a lymphocyte count of less than 1000/μL is a predictor of poor outcome in GBC[20]. Furthermore, the lymphocyte count has been found to be negatively correlated with TNM stage[20]. Dunn *et al*[24] have demonstrated the cancer immune-surveillance role of lymphocytes, by which lymphocytes can prevent tumor development. In addition, we showed the positive associations between the PLR and the CA125 level as well as the

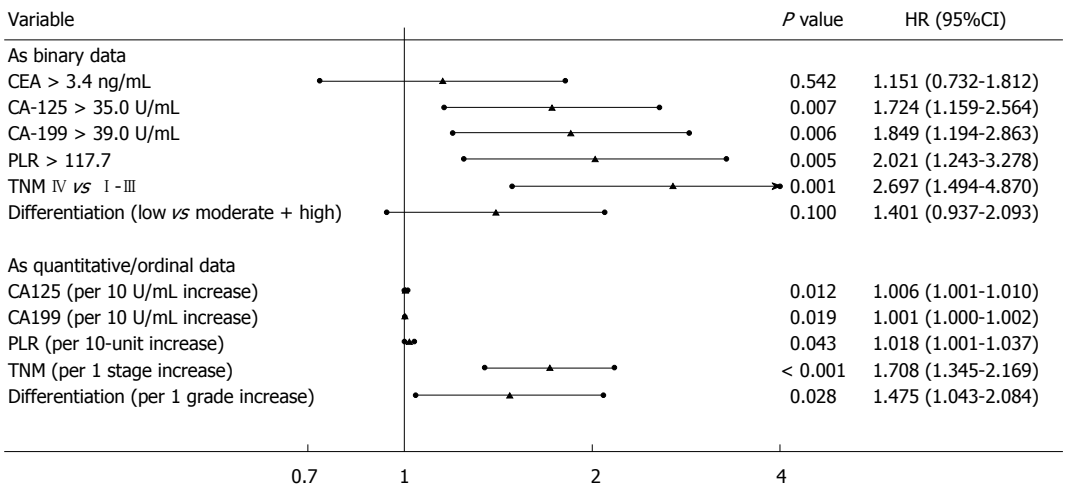

Figure 4 Forest plot based on results of multivariate analysis of factors associated with overall survival of gallbladder carcinoma patients. TNM: Tumor-node-metastasis.

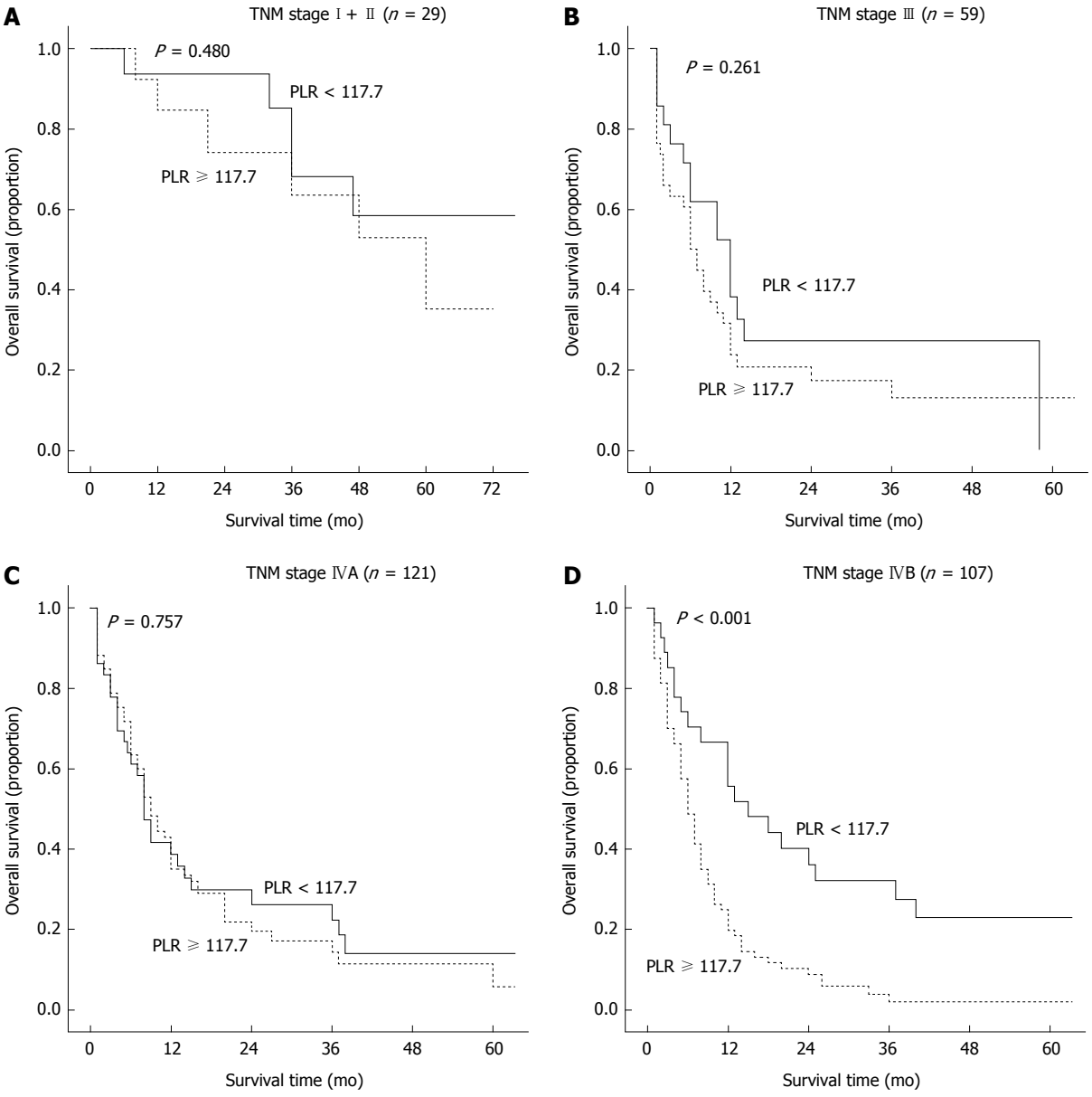

Figure 5 Cumulative survival curves for gallbladder carcinoma patients with TNM stages Ⅰ-Ⅱ (A), Ⅲ (B), ⅣA (C), and ⅣB (D), stratified according to PLR.

TNM stage, which were important prognostic factors for GBC.

This study is the first to demonstrate a link between the PLR and survival in patients with GBC. Inevitably, there were some limitations in the current study. First, the PLR was a useful tool only for the assessment of the GBC patients with TNM stage ⅣB, but not in those with any of the other stages. The limited sample size evaluated for each TNM stage, particularly stages Ⅰ-Ⅲ (Figure 5), may have been the main reason for the limited utility of the PLR. Second, to obtain more data, we did not distinguish between patients who underwent radical surgery and those who received palliative cholecystectomy or extended resection. Finally, our results were obtained from data collected at a single center, and there is a need for further large, multicenter cohort studies to validate our findings.

In conclusion, our findings suggest that the PLR could be used as a simple, inexpensive, and valuable tool for predicting the prognosis of GBC patients.

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COMMENTS

Background

Gallbladder cancer (GBC) is a rare disease associated with poor survival. The overall 5-year survival rate ranges from 2.7% to 20.1%. To date, the relative prognostic factors of GBC have not been clearly identified. Recently, numerous studies have shown that the inflammatory response plays a crucial role in the formation and development of various malignancies. The platelet to lymphocyte ratio (PLR), which is a combination of the platelet and lymphocyte counts, is regarded as a representative index of inflammation.

Research frontiers

The PLR has been identified as a significant prognostic tool for various types of cancer. An elevation in the PLR has been determined to be a negative predictor for survival in patients with colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, *etc*. The current study demonstrates that the PLR may be a valuable tool for predicting the prognosis of GBC patients.

Innovations and breakthroughs

Recent studies have identified the platelet and lymphocyte counts as significant prognostic factors for GBC. In contrast, this study is the first to suggest that the PLR, which is a combination of the platelet and lymphocyte counts, is an independent prognostic factor for GBC regardless of whether binary data or continuous variables are used. In addition, the PLR is more valuable than the platelet or lymphocyte count alone. Patients with a PLR ⩾ 117.7 have poorer survival compared with those with a low PLR, especially for those with TNM stage ⅣB.

Applications

By simply measuring the platelet and lymphocyte counts before surgery, we were able to estimate postoperative survival for patients with GBC. This finding may also be used to improve the prognosis of GBC patients by improving the preoperative PLR.

Terminology

The platelet count is a reflection of platelet function, and it normally ranges from 100 × 10^9/L-300 × 10^9/L. Lymphocytes are a type of white blood cell, and their levels normally range from 1.1 × 10^9/L-3.2 × 10^9/L in adults.

Peer-review

This study is well supported by the data, and the authors have confirmed the predictive power of the PLR for a rare malignancy for the first time in the literature. The findings of this study were supported by adequate statistical analyses.

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