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ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of preoperative platelet count in patients with gallbladder cancer

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Abstract

AIM: To investigate the prognostic value of preoperative platelet count (PLT) in patients with primary gallbladder cancer (GBC).

METHODS: The clinical data of 223 GBC patients after surgery was retrospectively reviewed. A receiver operating characteristic (ROC) curve was plotted to verify the optimum cutoff point for PLT. Univariate and multivariate survival analyses were performed to identify the factors associated with the prognosis.

RESULTS: The ROC curve showed that the optimum cutoff point for PLT was 178 × 10^9/L, and the entire cohort was stratified into group A with PLT > 178 × 10^9/L and group B with PLT ≤ 178 × 10^9/L. Group A had a better survival than group B (P < 0.001). There was an obvious difference between the two groups in terms of the differentiation degree, advanced tumor stage, lymph node metastasis (P < 0.001) and pathological type (P < 0.05). The univariate analysis demonstrated that tumor location, differentiation degree, TNM stage, Nevin stage, lymph node metastasis and PLT were associated with overall survival (P < 0.001). In the multivariate analysis, PLT (P = 0.032), lymph node metastasis (P = 0.007), tumor location (P < 0.001) and TNM stage (P = 0.005) were independent prognostic

factors.

CONCLUSION: PLT is closely correlated with GBC prognosis and could be used to identify the population with a poorer prognosis after surgery.

Key words: Prognostic factor; Platelet count; Survival; Gallbladder cancer

Core tip: Platelet count (PLT) is implicated with a poor prognosis in many types of malignancies. Its prognostic value has not been reported in gallbladder carcinoma (GBC). The most important finding in this study was that PLT was correlated with GBC prognosis, and was an independent prognostic factor after surgery.

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INTRODUCTION

Primary gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract[1] and the seventh most common gastrointestinal cancer[2]. The Surveillance, Epidemiology, and End Results program estimated the incidence of GBC at 2.5 per 100000 persons[3]. GBC has a poor prognosis because of early metastasis *via* the lymphatic, perineural, and hematogenous routes, as well as by direct invasion into the liver[3,4]. GBC is asymptomatic until aggressive disease progresses to an advanced and noncurative stage. The overall survival (OS) for GBC is 6 mo, with a 5-year survival rate of 5%[5,6]. Although the TNM staging system is widely used in clinical practice, there is no global consensus on the preoperative markers to predict the prognosis of GBC patients[3].

Numerous studies have revealed that elevated platelet count (PLT) is typically related to poor cancer prognosis[7-11]. Hernandez *et al*[12] showed that thrombocytosis is an independent indicator of poor prognosis in cervical cancer. Recently, Stone *et al*[13] confirmed that thrombocytosis was significantly associated with advanced disease and shortened survival in ovarian cancer. Numerous clinical data have shown that increasing PLT is associated with poor survival in patients with tumors including pancreatic adenocarcinomas[9], esophageal squamous cell carcinomas[7], and gastrointestinal cancers[14] as well as colorectal cancer[15]. Whether PLT plays important roles in the prognosis of GBC has not been reported.

GBC is a relatively rare disease with high mortality. Improving the survival rate after surgery is an enormous challenge. Based on the advances in PLT research and tumor prognosis, we hypothesized that PLT is a possible prognostic factor for GBC patients and aimed to find a novel prognostic marker for this malignancy.

MATERIALS AND METHODS

Study population

From January 2006 to December 2012, a retrospective analysis was conducted on 223 GBC patients after surgery in the Department of Hepatobiliary Surgery at the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine. The patients included in the analysis fit the following criteria: (1) GBC diagnosis confirmed by histopathology; and (2) gallbladder resection was neither preceded nor followed by adjuvant chemotherapy and/or radiotherapy. The patients with the following characteristics were excluded: (1) coexisting or previous cancers other than GBC; (2) concomitant diseases suspected of increasing the serum platelet concentration, including severe hypertension, splenic disease and blood coagulation disorders; and (3) the use of aspirin or other acetylsalicylic acid drugs one month before the surgery. Based on the medical records, the following data were collected for each patient: age, gender, PLT, complications, tumor location, gallstone history, tumor differentiation, TNM stage, Nevin stage, lymph node metastasis, pathological type and other miscellaneous characteristics. All subjects provided their written informed consent, and the study was approved by the Ethical Committees of the First Affiliated Hospital of the Xi'an Jiaotong University College of Medicine.

Platelet measurement

A blood sample was obtained before breakfast 3 d prior to the surgery by a peripheral venous puncture. A complete blood count was performed regularly for each patient.

Follow-up assessments

All of the patients were followed by telephone interviews. The date of surgery marked the beginning of the follow-up period, which ended at the last follow-up visit (October 2014) or death.

Statistical analysis

The statistical evaluation was conducted with SPSS 19.0 (SPSS Inc., Chicago, IL, United States). The mean values are presented as the mean ± SD. An independent *t*-test was used to compare the groups of continuous, normally distributed variables. Pearson's χ^2 test was used to determine the significance of the differences for the dichotomous variables. A receiver receiver operating characteristic (ROC) curve was plotted to verify the

Table 1 Association of platelet count with the parameters of 223 gallbladder cancer patients *n* (%)

Parameter	Cases	PLT				
		mean ± SD	*P* value	≤178	>178	*P* value
Gender			0.921			0.985
Men	67 (30.0)	219 ± 91		25%	42%	
Women	156 (70.0)	224 ± 91		58%	98%	
Age			0.573			0.379
> 65	99 (44.4)	226 ± 90		40%	59%	
≤ 65	124 (55.6)	217 ± 92		43%	81%	
Comorbidity			0.250			0.101
Yes	84 (37.7)	214 ± 97		37%	47%	
No	139 (62.3)	227 ± 87		46%	93%	
Gallstone history			0.358			0.361
Yes	119 (53.4)	231 ± 95		41%	78%	
No	104 (46.6)	212 ± 85		42%	62%	
ABO blood group			0.713			0.189
A	59 (26.4)	211 ± 95		26%	33%	
B	82 (36.8)	228 ± 84		23%	59%	
O	27 (12.1)	224 ± 98		11%	16%	
AB	55 (24.7)	224 ± 93		23%	32%	
Tumor location			0.422			< 0.001
Neck	90 (40.4)	279 ± 83		9%	81%	
Other	133 (59.6)	184 ± 75		74%	59%	
TNM stage			0.006			< 0.001
0-Ⅱ	49 (22.0)	161 ± 72		34%	15%	
Ⅲ-Ⅳ	174 (78.0)	239 ± 88		49%	125%	
Nevin stage			0.011			< 0.001
Ⅰ-Ⅲ	70 (31.4)	160 ± 69		49%	21%	
Ⅳ-Ⅴ	153 (68.6)	251 ± 85		35%	119%	
Tumor differentiation			0.771			< 0.001
Well and moderately	108 (48.4)	187 ± 84		60%	48%	
Poorly and undifferentiated	115 (51.6)	255 ± 85		23%	92%	
Lymph node metastasis			0.013			< 0.001
Yes	149 (66.8)	251 ± 86		33%	116%	
No	74 (33.2)	163 ± 69		50%	24%	
Pathological type			0.049			0.027
Adenocarcinoma	183 (82.1)	226 ± 88		62%	121%	
Other types	40 (17.9)	205 ± 104		21%	19%	

GBC: Gallbladder cancer; PLT: Platelet count.

optimum cutoff point for PLT. OS was calculated as the time from the curative surgery to the time of mortality or censoring. The OS was calculated by the Kaplan-Meier method, and the difference was assessed by the log-rank test. Univariate analysis and multivariate analysis using the Cox regression proportional hazard model were performed to evaluate the prognostic parameters for survival. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The characteristics of the patients are summarized in Table 1. Among the 223 patients, there were 156 (70.0%) women and 67 (30.0%) men. Ninety-nine (44.4%) of the patients were > 65 years, and 124 (55.6%) were ≤ 65 years. The mean age was 59.1 ± 8.1 years. There were 119 (53.36%) patients with a history of gallstones before the surgery. The entire cohort was comprised of 183 adenocarcinoma carcinomas, 40 carcinomas of other pathology types, including squamous cell carcinomas, adeno-squamous cell carcinomas and undifferentiated carcinomas (21, 13, and 6, respectively). The majority of the patients had relatively poor differentiation [17 (7.6%) with good differentiation, 90 (40.36%) with moderate differentiation, 115 (51.57%) with poor differentiation and 1 (0.45%) undifferentiated].

Association of PLT with the patient characteristics

The median PLT was 222 × 10^9/L ± 91 × 10^9/L. The optimum cutoff point for PLT according to a ROC curve was 178 × 10^9/L (Figure 1). The entire cohort was divided into 2 groups for further analysis, group A with PLT > 178 × 10^9/L and group B with PLT ≤ 178 × 10^9/L. There was an obvious difference between the groups in the degree of differentiation, advanced tumor stage, lymph node metastasis ($P < 0.001$) and pathology type ($P = 0.027$); there was no significant difference in the gender, age, comorbidity, gallstone history or ABO blood group ($P > 0.05$) (Table 1).

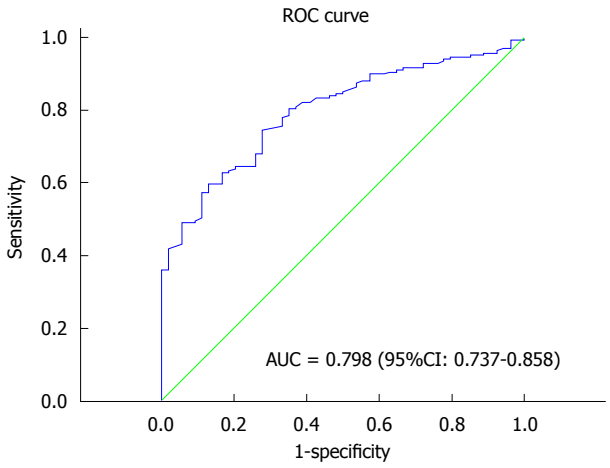

Figure 1 Receiver operating characteristic curve analysis to predict the gallbladder cancer stage. Each point on the receiver operating characteristic (ROC) curve corresponds to a value of platelet count (PLT). A diagonal line at 45°, known as the line of chance, would result from a test that allocated subjects randomly. In general, a good cutoff point produces high sensitivity and high specificity, which could be interpreted as selecting the point on the ROC curve with the largest vertical distance from the line of chance. The area under the ROC curve (AUC) indicates the diagnostic power of PLT. An ROC curve for survival prediction was plotted to verify the optimum cutoff point for PLT, which was 178 × 10^9/L. The AUC for PLT was 79.8% (95%CI: 0.737-0.858), with a sensitivity of 74.6% and a specificity of 72.2% by the Youden index.

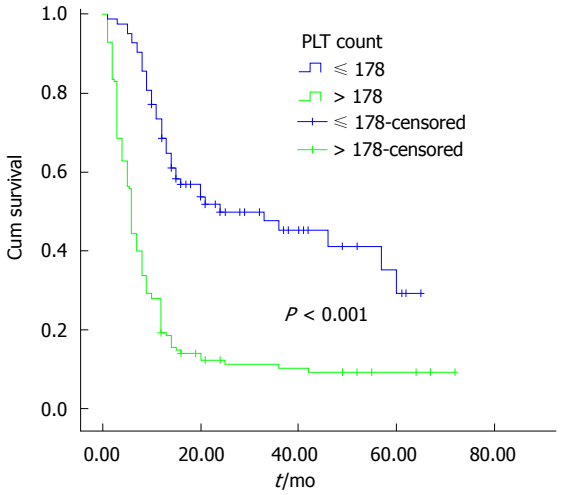

Figure 2 Survival curve according to the presence of platelet count. The patients with a platelet count (PLT) ≤ 178 had a significantly better overall survival than those with a PLT > 178 (P < 0.001).

Analysis of the prognostic factors

The univariate analysis was performed using the Kaplan-Meier method to assess the predictive capability of each variable. Our results showed that tumor location, tumor differentiation, TNM stage, Nevin stage, lymph node metastasis and PLT were predictive factors of OS (P < 0.001) (Table 2). Regarding OS, group B was superior to group A (P < 0.001) (Figure 2). As shown in Figures 3, 4 and 5, different PLR levels play important roles in the prognosis of a subgroup, and group A exhibited a worse prognosis than group B (P < 0.05). The Cox proportional hazards model

Table 2 Univariate analysis of the factors associated with the gallbladder cancer survival rate

Variable	HR (95%CI)	*P* value
Gender	0.940 (0.677-1.306)	0.712
Male		
Female		
Age (yr)	1.137 (0.840-1.539)	0.408
≤ 65		
> 65		
Gallstone history	1.066 (0.923-1.232)	0.383
Yes		
No		
Comorbidity	0.912 (0.665-1.251)	0.567
Yes		
No		
Tumor location	8.910 (6.236-12.730)	< 0.001
Neck		
Other (body, bottom)		
Tumor differentiation	3.209 (2.325-4.427)	< 0.001
Well and Moderately		
Poorly and undifferentiated		
TNM stage	11.003 (5.896-20.535)	< 0.001
0-Ⅱ		
Ⅲ-Ⅳ		
Nevin stage	10.642 (6.612-17.127)	< 0.001
Ⅰ-Ⅲ		
Ⅳ-Ⅴ		
Lymph node metastasis	9.775 (6.224-15.352)	< 0.001
Yes		
No		
Pathological type	0.708 (0.469-1.070)	0.101
Adenocarcinoma		
Other types		
PLT	3.333 (2.351-4.726)	< 0.001
≤ 178		
> 178		

GBC: Gallbladder cancer; PLT: Platelet count.

Table 3 Multivariate Cox regression analysis of overall survival in gallbladder cancer patients

Variable	Characteristic	HR (95%CI)	*P* value
Lymph node metastasis	Yes	1.795 (1.170-2.755)	0.007
	No		
TNM stage	0-Ⅱ	3.349 (1.436-7.814)	0.005
	Ⅲ-Ⅳ		
PLT	≤ 178	1.541 (1.038-2.287)	0.032
	> 178		
Tumor location	Neck	6.200 (4.120-9.329)	< 0.001
	Other (body, bottom)		

GBC: Gallbladder cancer; PLT: Platelet count.

demonstrated that lymph node metastasis (P = 0.007), TNM stage (P = 0.005), PLT (P = 0.032) and tumor location (P < 0.001) were independent prognostic factors (Table 3).

DISCUSSION

The incidence of GBC appears to be increasing

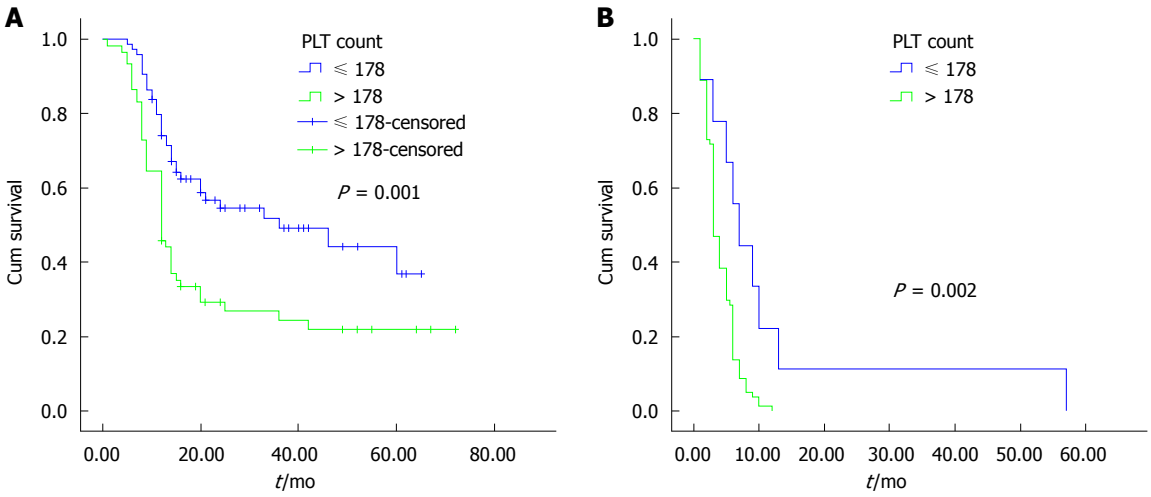

Figure 3 Kaplan-Meier survival curves stratified by platelet count in the gallbladder cancer patients with a tumor located in the neck of the gallbladder (A) and located in other locations (body, bottom) of the gallbladder (B). PLT: Platelet count.

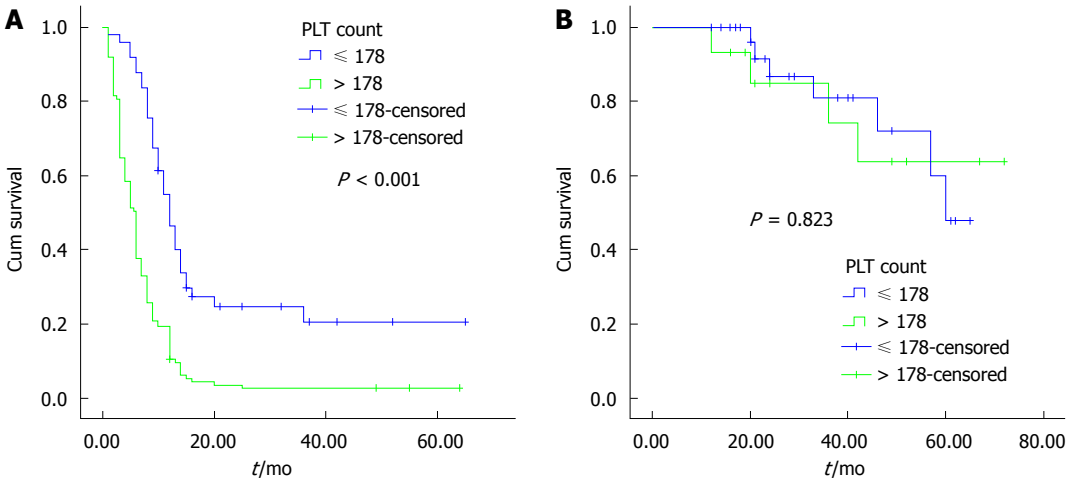

Figure 4 Kaplan-Meier survival curves stratified by platelet count in the pTNM 0-Ⅱ stage (A) and Ⅲ-Ⅳ stage (B) gallbladder cancer patients. PLT: Platelet count.

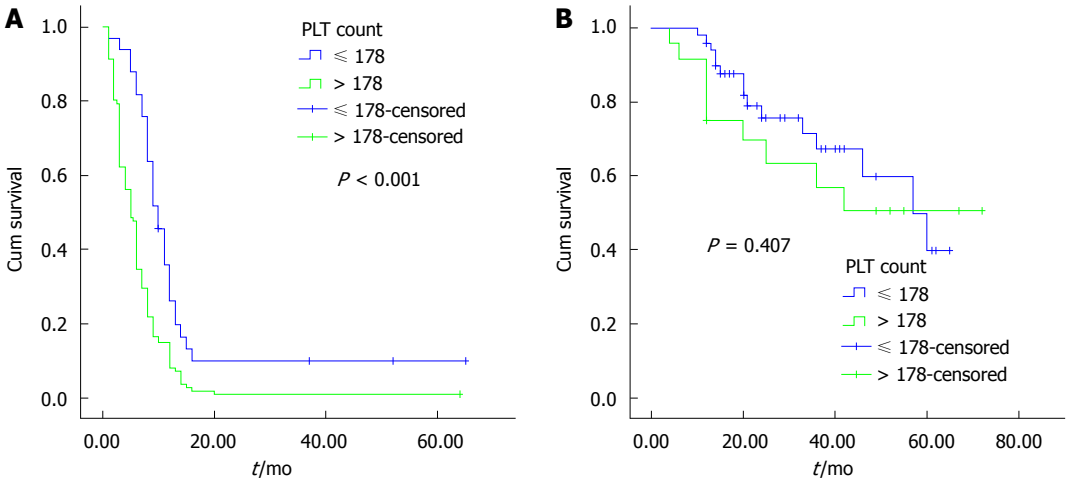

Figure 5 Kaplan-Meier survival curves stratified by platelet count in gallbladder cancer patients with lymph node metastasis (A) and in those without (B). PLT: Platelet count.

worldwide, creating an enormous public health and economic burden. In this study, our results demonstrated that PLT is an important prognostic factor for OS in GBC, and group B showed a better survival than group A. Additionally, we found that similar results exist in different subgroups (tumor location, lymph node metastasis, and TNM staging system). The multivariate analysis showed that tumor location, lymph node metastasis, TNM stage and PLT were independent prognostic factors. To the best of our knowledge, this study is the first to investigate the association between PLT and the prognosis of GBC.

Although PLT is associated with many types of cancers, little is known regarding PLT in GBC. Ong *et al*[16] hypothesized that GBC patients with a PLT > 345 × 10^9/L should not undergo surgical exploration. This hypothesis should be confirmed by investigations with large samples. In this study, a PLT > 178 × 10^9/L was the optimal cutoff value to identify GBC patients with a poorer prognosis. To ensure the credibility of this research, patients without neoadjuvant or adjuvant treatment were selected because systemic chemotherapy or radiation inevitably affects systemic inflammation, which is strongly linked with cancer[7].

The location of GBC was an independent prognostic factor in this study. Shindoh *et al*[17] hypothesized that tumor location was a strong predictor of tumor progression and survival in GBC in the T_2 category and that the density of the vascular structures and the length of the drainage route from the tumor to first-echelon lymph nodes or the liver affect the incidence of vascular invasion and metastasis. Because classical studies using staining methods have reported that the hepatic side of the gallbladder is drained by short cystic veins (2-20 in number) directly connecting to intrahepatic portal veins, whereas the peritoneal side is typically drained by 1 or 2 cystic veins terminating into the adjacent liver parenchyma or the venous plexus at the hepatic hilum. We proposed that the anatomical regions adjacent to the neck of the gallbladder bile duct, portal vein, liver, duodenum and colon are vulnerable to damage, and the early radical resection rate is greatly reduced. A cystic tumor in the neck greatly increases the difficulty of surgery and reduces the probability of radical resection.

Platelets are involved in the physiological process of coagulation and in the growth and metastasis of tumors although the mechanism has not been determined. Platelets could adhere to, aggregate and locally release their angiogenic contents in tumors, which was hypothesized to interact with tumor cells and vascular endothelial cells in physiological as well as pathological angiogenesis[9,18]. Platelets are the source of platelet-derived endothelial cell growth factor (TP/PD-ECGF), which has the potential to promote mitogenesis and angiogenesis[19]. They could endocytose and store TP/PD-ECGF in their α-granules, and this molecule is secreted immediately after platelet activation[20]. Yamamoto *et al*[21] found that TP/PD-ECGF, which stimulates the chemotaxis of endothelial cells *in vitro* and possesses angiogenic activity *in vivo*, is produced by cancer cells and infiltrating cells associated with tumor progression in human GBC. Additionally, platelets endocytose and concentrate the plasma protein vascular endothelial growth factor secreted from tumor cells and later transport them into their granules[22-25]. A recent study reported that the interactions between platelets and tumor cells augmented metastasis by promoting epithelial mesenchymal transition through the TGFB/SMAD and NFKB pathways and that inhibition of these two pathways solely in platelets could suppress metastasis *in vivo*[26]. Platelets enhance tumor metastasis by expressing immunoregulatory proteins including the glucocorticoid-induced TNF-related protein to protect tumor cells from the host's immune system[7,27,28]. Intratumoral platelet activation and the subsequent release of thrombopoietin could lead to increased platelets[18]. The thrombopoietic cytokine interleukin-6 has been found to be produced by tumor tissues and was correlated with platelets[29-31]. The interaction between platelets and tumor cells promotes tumor progression.

This study has some limitations. First, this study was a retrospective investigation. Second, the data were obtained from a single institution. Our results should be validated by prospective research and multiple center data.

PLT is an independent prognostic factor for GBC, which facilitates the identification of patients with poorer survival by subgroups (tumor location, lymph node metastasis, and TNM staging system) after surgery. As an inexpensive, simple, reliable and reproducible method, we hypothesize that PLT could be used in clinical practice to determine the GBC prognosis.

COMMENTS

Background

Numerous studies have indicated that platelet count (PLT) is correlated with a variety of cancers. In the clinic, the overall survival (OS) of gallbladder cancer (GBC) is poor, and there are no effective markers that identify the patients with a poorer prognosis.

Research frontiers

In recent decades, the OS of GBC has been far from satisfactory despite rapid technological developments, which might be attributed to the following reasons: (1) although sufficient molecular investigations have been conducted, the specific mechanism is unclear; and (2) effective clinical prognostic markers are lacking. Exploring the novel markers associated with GBC is necessary to improve the OS.

Applications

These data show that PLT is an independent factor and can be used to identify the patients with poorer OS.

Terminology

GBC, originating in the biliary tract system, is characterized by a very poor prognosis. The risk factors for GBC include gallstones, aging, and female gender. The common mechanism of GBC has not been determined. Platelets are bioactive small cytoplasmic cells that originate in the bone marrow of mature megakaryocyte cytoplasmic cleavage and play an important role in hemostasis, wound healing, inflammation, thrombosis, organ transplant rejection, and other

physiological and pathological processes.

Peer-review

The purport of this article is to study the relationship between PLT and the prognosis of patients with primary gallbladder, and the results showed that PLT count is an independent prognostic factor of primary gallbladder, and can be used in the clinical evaluation of the prognosis of primary gallbladder.

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