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A novel scoring system based on hemostatic parameters predicts the prognosis of patients with advanced pancreatic cancer

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ABSTRACT

Objective: The aim of this study was to evaluate the prognostic value of pre-treatment plasma hemostatic parameters in patients with advanced pancreatic cancer.
Methods: A total of 320 patients diagnosed with advanced pancreatic cancer between January 1, 2011 to December 31, 2015 were enrolled in this retrospective study. The prognostic significance of hemostatic parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FBG), platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) was determined by univariate and multivariate Cox hazard models. Then, Kaplan-Meier methods and log-rank tests were performed to compare the survival of patients in different risk groups.
Result: Univariate and multivariate analyses showed that prolonged PT, high FBG, and high MPV were independent prognostic factors for poor overall survival (PT > 11.3 s, HR = 1.46, 95%CI = 1.10–1.94, p = 0.009; FBG>2.5 g/L, HR = 1.41, 95%CI = 1.08–1.84, p = 0.011; MPV>12.2 fL, HR = 1.52, 95%CI = 1.13–2.04, p = 0.005). Moreover, all the patients were stratified into three groups by a scoring system based on these three hemostatic markers. The median survival time of the three groups was 8.8 months, 6.3 months and 4.3 months (P < 0.001).
Conclusion: PT, FBG and MPV were independent prognostic factors in advanced pancreatic cancer. A novel scoring system based on these hemostatic parameters could be used to predict the survival of patients with advanced pancreatic cancer.

Introduction

Pancreatic cancer is one of the most malignant tumors and the fourth leading cause of cancer-related mortality in the United State [1]. In China, pancreatic cancer has the ninth highest cancer incidence and is ranked sixth in cancer-related mortality [2]. Approximately 80–85% patients present with locally advanced or metastatic disease when diagnosed, which precludes them from the opportunity for curative surgery [3]. Chemotherapy is currently the standard treatment for these patients. Despite the continuous progression of various therapies, the 5-year survival remains <5% [4]. However, we found the survival of patients with advanced pancreatic cancer varies significantly. Therefore, it is crucial to identify a predictive system that may help to guide optimal therapy and predict the prognosis for the individual patient with advanced pancreatic cancer.

Changes in the hemostatic system and evidence of chronic hemostatic activation are frequently observed in patients with cancer [5,6]. Studies showed that hemostatic system and tumor cells are connected by multiple mechanisms [7]. Cancer-induced activation of hemostatic system has been shown to promote tumor progression, invasion, angiogenesis, and metastasis [8,9]. In addition, thromboembolic disease is a common complication of pancreatic cancer [10,11] and predicts poor prognosis [12]. Therefore, the clinical outcome of hyper-hemostasis may be serious, with a negative impact on survival. Actually, previous studies have reported that hemostatic parameters such as prothrombin time (PT), fibrinogen (FBG), platelet count (PLT), platelet distribution width

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(PDW) and mean platelet volume (MPV) were associated with decreased overall survival (OS) in various cancers [13–18].

The goal of this study was to investigate whether the regular hemostatic parameters are associated with survival in patients with advanced pancreatic cancer.

Materials and methods

Patient characteristics

A retrospective cohort study consisting of 320 patients diagnosed with advanced pancreatic adenocarcinoma from January 1, 2011, to December 31, 2015, was conducted. All patients received primary treatment at Fudan University Shanghai Cancer Center. Patients who met the following criteria were enrolled in this study. 1) The patients' diagnosis of pancreatic adenocarcinoma was histologically or cytologically confirmed. 2) The tumors were staged according to the 8th edition of the American Joint Committee on Cancer (Chicago, IL, USA) [19]. Patients with stage III and IV tumors were recruited. 3) No other primary malignant tumors were found during treatment. The exclusion criteria included a lack of complete clinicopathological and follow-up data, tumors not originating from the pancreas, acute inflammatory diseases, a history of thrombosis or treatment with drugs that might influence the hemostatic system.

The primary endpoint was OS, which was calculated from the date of diagnosis to the date of either death or the last follow-up time in the study. An independent researcher performed the follow-up work by conducting telephone interviews or reviewing medical records. The last follow-up date was December 31, 2017. Written informed consent was obtained from all patients. This study was approved by the Ethics Board of the Fudan University Shanghai Cancer Center.

Laboratory measurements

All laboratory parameters, including hemostatic parameters, were assayed during routine workups before cancer diagnostic interventions. Data was extracted from the Electronic Medical Record System of Fudan University Shanghai Cancer Center.

Statistical analysis

Patient characteristics before diagnosis or first treatment were reported using descriptive statistics. The optimal cut-off levels of continuous variables were calculated by X-tile software [20]. Survival curves were calculated using the Kaplan–Meier method, and the log-rank test was used to estimate the significance of differences in survival. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model in SPSS version 21.0 (IBM Corp, Armonk, NY, USA). Variables with $p < 0.05$ in the univariate analysis were included as candidates in a multivariate Cox regression model. A p-value <0.05 was considered significant.

Results

Patient characteristics

We retrospectively collected data from 320 patients treated at Fudan University Shanghai Cancer Center between January 1, 2011, and December 31, 2015. The last follow-up date was December 31, 2017. At the time of last follow-up, 1 patient was alive. The basic characteristics of the patients are listed in Table 1. Among the 320 patients enrolled, 204 (63.8%) were male, and 116 (36.2%) were female. The median age was 60 (range from 30 to 81). Additionally, 88 patients (27.5%) were diagnosed with locally advanced disease and classified as stage III, and the remaining 232 (72.5%) were diagnosed with metastatic disease and classified as stage IV. The median survival times are shown in Table 2. The median overall survival time was 7.7 months with a 1-year survival of 28.4%.

Table 1
Basic population characteristics of patients with advanced PDAC.

Characteristics	Parameter	Number	Percentage
Gender	Male	204	63.8%
	Female	116	36.2%
Age	≤60	165	51.6%
	>60	155	48.4%
TNM Stage	III	88	27.5%
	IV	232	72.5%
CA19-9 (U/L)	≤1000	175	54.7%
	>1000	145	45.3%
PT (s)	≤11.3	63	19.7%
	>11.3	257	80.3%
APTT (s)	≤32.6	285	89.1%
	>32.6	35	10.9%
INR	≤1.0	122	38.1%
	>1.0	198	61.9%
FBG (g/L)	≤2.5	77	24.1%
	>2.5	243	75.9%
PLT	≤142	100	31.3%
	>142	220	68.7%
MPV (fL)	≤12.2	262	81.9%
	>12.2	58	18.1%
PCT	≤0.3	297	92.8%
	>0.3	23	7.2%
PDW	≤11.0	45	14.1%
	>11.0	275	85.9%

Association between hemostatic parameters and overall survival

To determine the prognostic value of the hemostatic system in advanced pancreatic cancer, clinical characteristics including gender, age, TNM stage, and CA19-9 as well as hemostatic system parameters including PT, APTT, INR, FBG, PLT, MPV, PCT, and PDW were subjected to the univariate and multivariate analyses using

Table 2
Median survival according to different subsets.

Characteristics	Parameter	Median survival time	95% CI
Gender	Male	8.4	7.5–9.3
	Female	6.4	5.4–7.5
Age	≤60	7.9	6.8–9.0
	>60	7.6	6.3–8.9
TNM Stage	III	10.1	7.8–12.4
	IV	7.0	6.1–7.9
CA19-9 (U/L)	≤1000	8.5	7.5–9.4
	>1000	6.8	5.4–8.2
PT (s)	≤11.3	10.4	8.2–12.6
	>11.3	7.4	6.4–8.5
APTT (s)	≤32.6	7.7	6.8–8.6
	>32.6	8.7	5.5–11.9
INR	≤1.0	8.8	7.5–10.1
	>1.0	7.4	6.4–8.4
FBG (g/L)	≤2.5	9.0	8.0–10.0
	>2.5	7.4	6.5–8.3
PLT	≤142	7.7	6.6–8.8
	>142	7.7	6.6–8.8
MPV (fL)	≤12.2	8.2	7.4–9.0
	>12.2	5.9	3.6–8.2
PCT	≤0.3	8.2	7.5–8.9
	>0.3	4.2	3.4–5.0
PDW	≤11.0	9.6	6.9–12.4
	>11.0	7.6	6.6–8.6

Cox proportional hazards regression. Table 3 shows the results of univariate and multivariable analyses. The results showed that tumor stage, CA19-9, PLT, PT, FBG, MPV and PDW were associated with OS. The multivariate analysis revealed that several hemostatic parameters, including PT (HR = 1.43, 95% CI = 1.08–1.90, p = 0.014), FBG (HR = 1.39, 95% CI = 1.06–1.81, p = 0.016) and MPV (HR = 1.42, 95% CI = 1.06–1.90, p = 0.020) were independent prognostic factors for OS. Kaplan-Meier curves for the estimated OS are presented in Fig. 1.

Combining PT, FBG, and MPV as a scoring system to predict prognosis

In the present study, we identified that PT, FBG, and MPV as independent prognostic factors of advanced pancreatic cancer. Furthermore, we combined these three factors to develop a novel scoring system. The score was calculated according to the following formula: 1 point for high PT (>1.3), high FBG (>2.5), or high MPV (>12.2) and 0 points for low PT (≤11.3), low FBG (≤2.5), or low MPV (≤12.2). The total score was the sum of three factors and ranged from 0 to 3. Consequently, 13 patients were assigned a score of 0, 93 patients a score of 1, 180 patients a score of 2, and 34 patients a score of 3. To optimize the scoring system, we defined scores of 0 and 1 as the low-risk group (N = 106, 33.1%), score of 2 as the median-risk group (N = 180, 56.5%) and score of 3 as the high-risk group (N = 34, 10.6%). The median survival time of patients in the low-risk, median-risk group and high-risk groups were 8.8 months (95% CI = 6.8–10.9), 6.3 months (95% CI = 5.3–7.3) and 4.3 months (95% CI = 2.6–5.9), respectively (P < 0.001). Fig. 2 shows that there is no significant difference in distribution of risk groups between stage III and IV. As shown in Table 4 and Fig. 3, patients of different risk groups had significantly different survival not only in the whole cohort but also in each TNM stage. These results confirmed that the scoring system can be used in the whole cohort, or in stage III and stage IV separately. Moreover, the patients in the high-risk group had a greater hazard ratio than those in the median-risk group and low-risk group (high-risk, HR = 2.08, 95% CI = 1.40–3.08, p < 0.001; median-risk, HR = 1.46, 95% CI = 1.15–1.87, p = 0.002). Therefore, the combination of these three hemostatic parameters might serve as a novel method for predicting the OS and showed greater predictive power than that of each single factor.

Discussion

Recently, mounting evidence suggests that the hemostatic system and cancer are closely linked by multiple mechanisms [21,22]. The process of hemostasis involves vasoconstriction, the activation, adhesion, and aggregation of platelets in addition to the deposition and maturation of fibrin. Cancer cells secrete various factors such as cytokines (e.g., interleukin-6, tumor necrosis factor-α), hemostatic factors (e.g., tissue factor, microparticles, fibrinolysis proteins) and adhesion molecules (e.g., vWF, GPII/IIIa, fibronectin) [23]. Thus, cancer cells may interact with any step of the hemostatic process. Pancreatic cancer also induces a prothrombotic and hypercoagulable state by secreting procoagulant factors [e.g., tissue factor (TF), platelet factor 4 (PF4), plasminogen activator inhibitor type 1 (PAI-1)] [24]. We also found that patients with increased hemostatic parameters were more likely to develop thrombosis and have poor survival in clinical practice. Therefore, we would like to explore the relation between hemostatic system parameters and the prognosis of advanced pancreatic cancer.

In the current study, we retrospectively examined the prognostic value of hemostatic parameters in advanced pancreatic cancer cohort. Our result revealed that PT (HR = 1.43, 95% CI = 1.08–1.90, p = 0.014), FBG (HR = 1.39, 95% CI = 1.06–1.81, p = 0.016) and MPV (HR = 1.42, 95% CI = 1.06–1.90, p = 0.020) were independent prognostic factors for OS in patients with advanced pancreatic cancer. In addition, we established a novel scoring system based on PT, FBG, and MPV to predict the prognosis of patients with advanced pancreatic cancer. The scoring system showed prognostic value in both Stage III (p < 0.001) and Stage IV (p = 0.036) patients. Besides, we observed that in high risk group, patients of Stage III had shorter survival time than the patients of Stage IV in our study. On the one hand, this phenomenon suggests that we should pay special attention to locally advanced patients in high risk group. On the other hand, the number of these patients

Table 3
Univariate and multivariate analyses for overall survival using the Cox proportional hazards model.

Variables	Parameter	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Gender	Male				
	Female	1.22 (0.97–1.54)	0.085		
Age	≤60				
	>60	1.17 (0.93–1.46)	0.175		
Stage	III				
	IV	1.48 (1.15–1.90)	0.002	1.30 (1.01–1.69)	0.046
CA19-9 (U/L)	≤1000				
	>1000	1.45 (1.16–1.82)	0.001	1.31 (1.04–1.66)	0.024
PT (s)	≤11.3				
	>11.3	1.41 (1.07–1.87)	0.016	1.46 (1.10–1.94)	0.009
APTT (s)	≤33.0				
	>33.0	0.76 (0.53–1.08)	0.129		
INR	≤1.0				
	>1.0	1.18 (0.94–1.49)	0.147		
FBG (g/L)	≤2.5				
	>2.5	1.44 (1.10–1.87)	0.007	1.41 (1.08–1.84)	0.011
PLT	≤142				
	>142	0.77 (0.60–0.98)	0.034	0.87 (0.66–1.15)	0.324
MPV (fL)	≤12.2				
	>12.2	1.64 (1.23–2.19)	0.001	1.52 (1.13–2.04)	0.005
PCT	≤0.3				
	>0.3	1.36 (0.87–2.10)	0.175		
PDW	≤11.0				
	>11.0	1.48 (1.07–2.04)	0.018	1.34 (0.96–1.86)	0.087

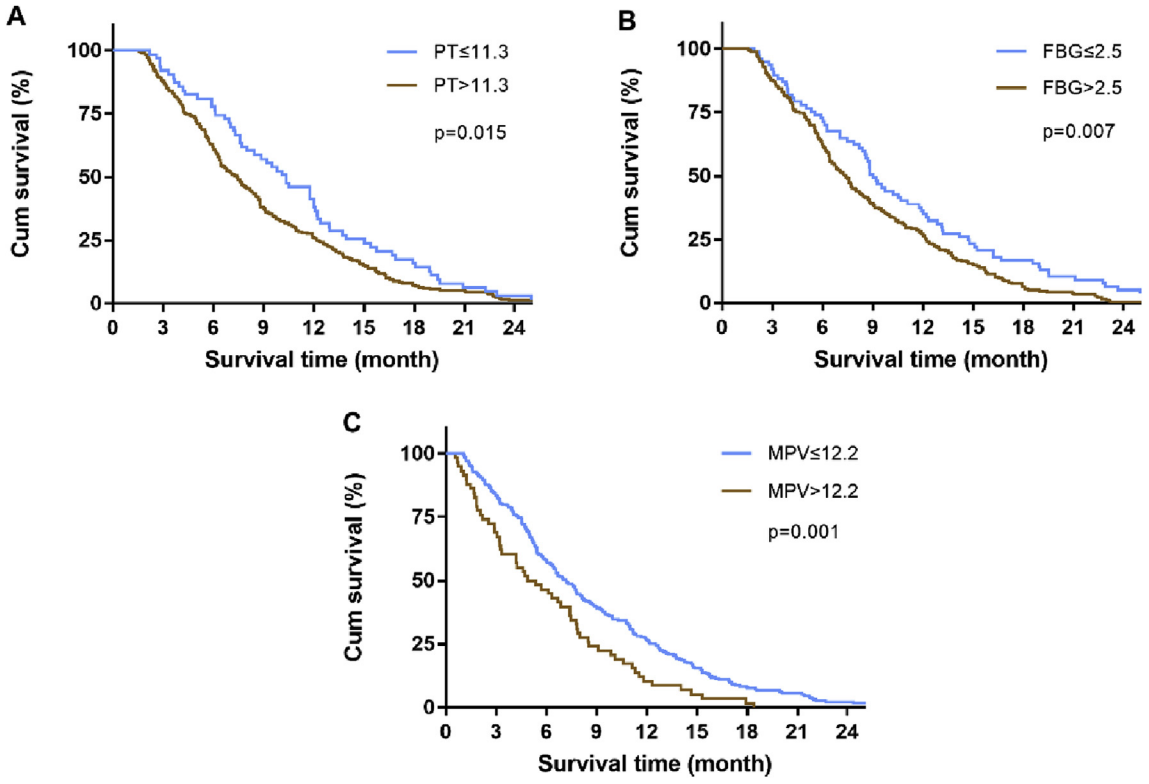

Fig. 1. Kaplan-Meier survival curves estimated on OS. A. PT ≤ 11.3 s or PT > 11.3 s. B. FBG ≤2.5 g/L or > FBG 2.5 g/L. C. MPV ≤12.2 fL or MPV >12.2 fL.

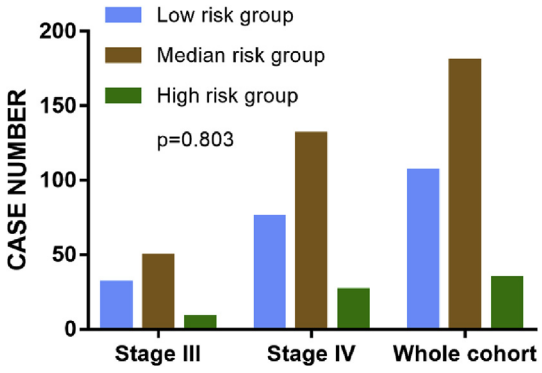

Fig. 2. Distribution of different risk groups in stage III, IV and whole cohort. P value was calculated by Pearson Chi-Square test.

(N = 8) is small, which may account for the result.

Among various hemostatic parameters, prothrombin time (PT) and fibrinogen (FBG) are widely tested in clinical laboratories to demonstrate abnormalities in the coagulation and fibrinolysis systems. PT is the time taken for plasma to clot when exposed to tissue factor (TF) and used to evaluate the extrinsic pathway of coagulation. The potential mechanisms for prolonged PT and cancer may be as follows: first, prolongation of PT indicates a deficiency or depletion of coagulation factors; second, the downregulation of liver biosynthetic capacity and the activation of the coagulation system may contribute this situation. Previous studies also confirmed that prolonged PT is associated with poor prognosis in lung cancer [17], hepatocellular carcinoma [25], and colorectal cancer [15].

Fibrinogen is a multifunctional protein synthesized by hepatocytes. Previous studies have demonstrated that fibrinogen plays a vital role in tumorigenesis, including stroma formation, angiogenesis, and hematogenous metastasis [26]. Some possible explanations for the pro-tumoral effect of fibrinogen have been postulated. First, it is one of the most common components of the extracellular matrix, providing structure to the tumor stroma [27]. Second, fibrinogen also produces proliferative signals by acting as a scaffold for binding growth factors such as VEGF [28] and FGF-2 [29] to promote cellular adhesion, proliferation and migration during angiogenesis, and tumor cell growth. Third, fibrinogen helps platelets adhere to tumor cells and in turn promote more fibrinogen aggregation around tumor cells [30]. Platelets and fibrinogen facilitate each other to protect tumor cells from natural killer

Table 4
Median survival of different risk groups according to TNM Stages.

Stage	Scoring system	Number (percentage)	Median survival time	95% CI
Stage III	Low risk group	31 (35.2%)	13.1	10.4–15.8
	Median risk group	49 (55.7%)	8.0	7.0–9.0
	High risk group	8 (9.4%)	4.2	0.8–7.7
Stage IV	Low risk group	75 (32.3%)	8.5	7.4–9.7
	Median risk group	131 (56.5%)	6.5	5.5–7.5
	High risk group	26 (10.6%)	5.3	3.2–7.4

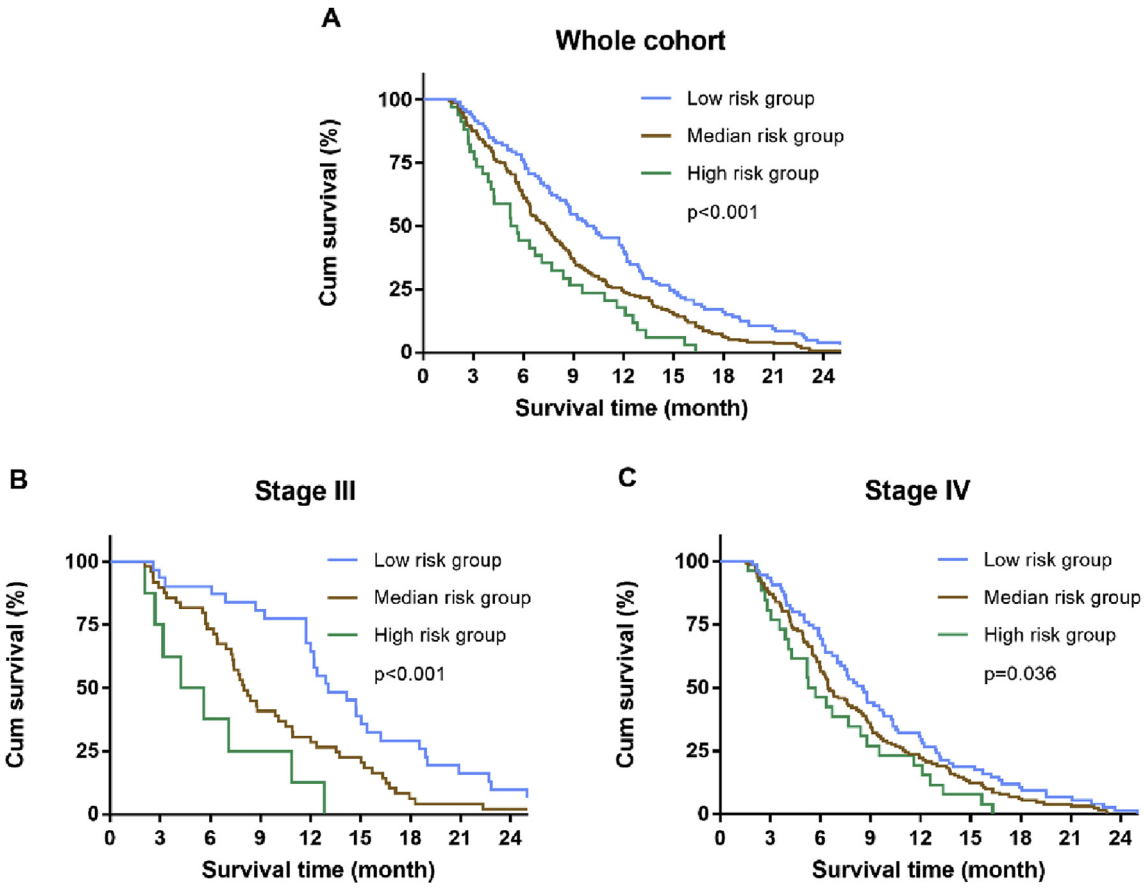

Fig. 3. Kaplan-Meier survival curves estimated on OS of whole cohort and stage III, IV according to the scoring system.

cytotoxicity. Several studies have reported that elevated plasma fibrinogen level is an unfavorable prognostic prediction in non-small-cell lung cancer [31], esophageal cancer [32], gastric cancer [33].

Recent studies have confirmed that the platelet contributes to cancer progression and metastasis [34,35]. In this study, we found that high MPV is an independent predictor for shorter OS in advanced pancreatic cancer. The mean platelet volume (MPV) is the volume of the average circulating platelets in femtoliters and is an indicator of activated platelets [36]. To date, the impact of MPV on survival of has not been fully understood in malignant tumors. Emerging evidence indicates that there is an increase in platelet number and activity in patients with a wide spectrum of malignacies [37]. Active platelet releases secretory factors that promote growth factors, chemokines, proangiogenic regulatory proteins, proteolytic enzymes and microparticles within the microenvironment to promote tumor cell growth and invasion [38]. Previous studies have revealed that high MPV predicts poor prognosis in colorectal cancer [37], non-small-cell lung cancer [39], breast cancer [40].

Consistent with our findings, Qi et al. reported that Hyperfibrinogen is associated with the systemic Inflammatory response and predicts poor prognosis in advanced pancreatic cancer [14]. Yin et al. found that elevated MPV is associated with worse survival outcome in pancreatic cancer patients with synchronous liver metastases [18]. These studies indicated that hemostatic parameter is associated with survival in pancreatic cancer. Each of these studies focused on a single hemostatic marker and provided one aspect of the whole hemostatic system in pancreatic cancer. Our scoring system was established on the three hemostatic markers to offer a more comprehensive overview and predict prognosis.

Clinically, patients with pancreatic cancer are at high risk of venous thromboembolism which is associated with increased in-hospital mortality [10]. Whether our scoring system could predict the incidence of thrombotic events is a valuable question that needs further researches. Anticoagulation therapy, in particular, the low-molecular weight heparins (LMWHs), and antiplatelet therapy hold promise for improving survival in patients with cancer [41,42]. Our findings add to the accumulating evidence that supports the benefit of anticoagulation and antiplatelet therapy. Therefore, our scoring system may be useful in understanding the prognostic value of hemostatic system and guiding treatment in advanced pancreatic cancer.

Several limitations of the present study should be mentioned. Firstly, the study was a retrospective cohort study conducted at a single center. Additional large-scale and multi-center studies may provide stronger data and evidence. Secondly, further studies should be conducted to explore the underlying mechanism between the hemostatic system and cancer. Thirdly, our subjects were advanced stage patients. The application for early stage group needs further research.

In conclusion, this is a retrospective study investigating the prognostic value of hemostatic parameters in advanced pancreatic cancer. Based on the 320 patients, our study found that PT, FBG, and MPV were independent prognostic factors. Furthermore, we combined these three parameters to form a novel scoring system and demonstrated that patients in the low-risk, median-risk, and high-risk groups had significantly different survival. The novel scoring

system might be used to evaluate the prognosis of patients with advanced pancreatic cancer.

Conflicts of interest

No potential conflict of interest is reported by the authors.

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Abbreviations

PDAC	pancreatic ductal adenocarcinoma
AJCC	American Joint Commission on Cancer
OS	overall survival
PT	prothrombin time
APTT	activated partial thromboplastin time
FBG	fibrinogen
PLT	platelet count
MPV	mean platelet volume
PVT	plateletcrit
PDW	platelet distribution width

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