Pretreatment fibrinogen levels are associated with survival outcome in patients with cancer using immunotherapy as a second-line treatment

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Received December 4, 2022; Accepted April 4, 2023

DOI: 10.3892/ol.2023.13855

Abstract. The present study aimed to investigate the predictive value of pretreatment fibrinogen (FIB) levels in patients with cancer who received immunotherapy as a second-line treatment. A total of 61 patients with stage III-IV cancer were included. The cut-off value of FIB for predicting overall survival (OS) was determined by receiver operating characteristic curve analysis. The prognostic value of pretreatment FIB on progression-free survival (PFS) and OS was determined by univariate and multivariate analyses. Based on a cut-off point of 3.47 g/l, patients were divided into low pretreatment FIB (<3.47 g/l) and high pretreatment FIB (≥3.47 g/l) groups. A high pretreatment FIB level was more common in older patients (P=0.03). Kaplan-Meier analysis showed that patients with high pretreatment FIB levels had shorter PFS and OS times than patients with low FIB levels (P<0.05). In multivariate analysis, pretreatment FIB was an independent prognostic factor for OS [hazard ratio (HR), 6.06; 95% CI, 2.01-18.28; P<0.01] and OS from the initiation of second-line treatment (HR, 3.69; 95% CI, 1.28-10.63; P=0.02). Overall, FIB is associated with survival outcome in patients with cancer who are administered immunotherapy as a second-line treatment.

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Abbreviations: FIB, fibrinogen; PFS, progression-free survival; OS, overall survival; ICIs, immune checkpoint inhibitors; dMMR, deficient mismatch repair; TMB, tumor mutation burden; ORR, objective response rate; HR, hazard ratio; DCR, disease control rate; FGF-2, fibroblast growth factor-2; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte-activation gene-3

Key words: immune checkpoint inhibitors, immunotherapy, pan-cancer, fibrinogen, prognostic factor

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized treatment strategies for multiple cancer types, such as lung cancer (1-4), head and neck squamous cell carcinoma (5,6), esophageal cancer (7) and metastatic renal cell cancer (8). Available predictive immunotherapy biomarkers for treatment responses include programmed death-ligand 1 (PD-L1) expression, tumor mutation burden (TMB) and microsatellite instability-high/deficient mismatch repair (dMMR). Studies have shown that nivolumab, pembrolizumab and atezolizumab are recommended for the second-line treatment of patients with non-small cell lung cancer (NSCLC) and PD-L1 expression ≥1% (tumor proportion score) (9-11), but that the objective response rate (ORR) is <21.2%. Pembrolizumab is recommended as a second-line treatment for patients with dMMR/TMB-high gastric cancer, with an ORR of ~46.7%. However, no additional markers are available to predict prognosis, and the positive rate of the aforementioned markers is low (12). In addition, immunotherapy is less effective in patients who have not been tested for immunotherapy biomarkers. The clinical application of PD-L1 and genetic testing are limited by unusable specimens and high cost. No other reliable biomarker for effectively selecting responsive patients has been identified to date, especially effective markers for pan-cancer survival. Identifying new, reliable and clinically accessible biomarkers for patients with cancer treated with ICIs as second-line therapy is essential for an improved response.

It has been recognized that hypercoagulability is relevant to the poor prognosis of patients with cancer (13). Fibrinogen (FIB) is an important member of the coagulation system, and also plays an important role in the inflammatory response and tumor progression (14,15). Several studies have shown that elevated pretreatment or preoperative FIB levels are associated with poor outcomes in numerous types of cancer, such as breast, lung, colorectal and gastric cancer (16-19). The cut-off values of FIB in these studies were determined to be 2.83, 4.0, 3.64 and 4.0 g/l, respectively. However, only a few studies have indicated the relationship between FIB and prognosis

in patients with cancer treated with ICIs. Some studies have applied the combination of FIB and other clinical factors, such as the FIB-albumin ratio (FAR), for predicting immunotherapy prognosis and obtained positive outcomes (20,21), but the results of the different studies were not consistent. Yuan *et al* (20) showed that an increased FAR (≥0.145) was an independent prognostic factor of progression-free survival (PFS) and overall survival (OS) for patients with NSCLC treated with ICIs as first-line therapy, but Guo and Liang (21) showed that FAR could not be an independent prognostic factor of OS for patients with cancer, indicating that FAR was not an accurate predictor of OS/DFS. In addition, the prognostic value of FIB and albumin were not analyzed individually in either of the two aforementioned research studies.

Nevertheless, the association between FIB and its prognostic role in patients with cancer treated with immunotherapy remains unknown. The aim of the present retrospective clinical study was to investigate the association between FIB and the prognosis of patients with cancer treated with ICIs as second-line therapy.

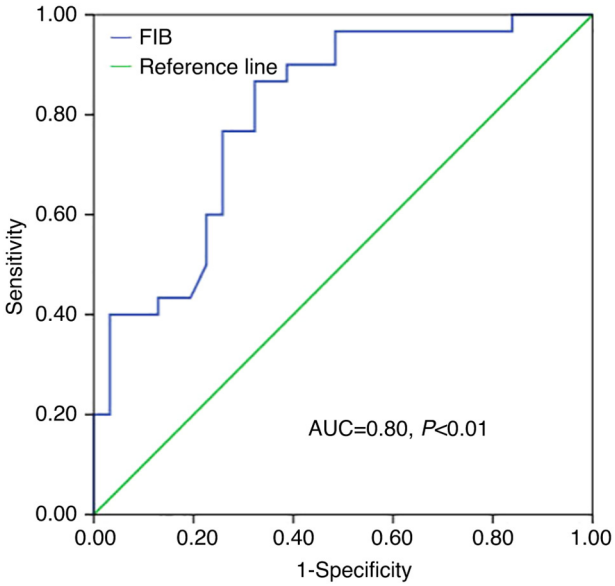

Figure 1. Receiver operating characteristic curve analysis of overall survival based on pretreatment FIB levels. FIB, fibrinogen.

Materials and methods

Patients. From February 2015 to February 2022, a total of 61 patients with various types of stage III-IV malignant tumors (according to the 8th edition of the American Joint Committee on Cancer Staging) (22) treated with ICIs as a second-line treatment in Hainan Hospital of the Chinese People's Liberation Army (PLA) General Hospital (Sanya, China) were studied retrospectively. Among them, 2 patients had received systemic therapy that included ICIs as first-line treatment. The inclusion criteria for the patients were as follows: i) Age >18 years; ii) stage IV or unresectable stage III malignancy confirmed by histology and imaging; iii) available laboratory assays before and after immunotherapy; and iv) anti-programmed cell death protein 1 (PD-1) monotherapy or combination therapy with chemotherapy or targeted therapies as second-line treatment. Patients meeting any of the following criteria were excluded: i) Other malignant tumors; ii) chronic inflammatory diseases; iii) current treatment with glucocorticoids; iv) acute infection; v) vein thrombosis; and vi) disseminated intravascular coagulation or treatment with anticoagulant or procoagulant drugs within 1 month of second-line treatment.

Clinicopathological parameters of the patients included sex, age (<60 or ≥60 years old), smoking history, Eastern Cooperative Oncology Group performance status (23), pathological histology, surgical history, number of metastatic sites, PD-L1 testing results and the administration of locoregional therapy (radiotherapy or interventional therapy) during second-line therapy. The study was approved by the Ethics Committee of Hainan Hospital of the Chinese PLA General Hospital (approval no. 301HLFYLS15). Written informed consent was waived by the committee due to the retrospective nature of the study.

Determination of pretreatment FIB levels. The baseline coagulation (normal FIB range, 2.38-4.98 g/l) of the patients was assessed before the second-line treatment (on the day before receiving immunotherapy or within 7 days before the start of immunotherapy). The samples (5 ml venous blood) were collected in tubes with sodium citrate in and were processed in the hospital laboratory within 6 h to detect FIB.

Follow-up procedure and definition of response. Patient information was obtained through electronic medical records or by telephone. Imaging review was performed every 6-8 weeks to assess the response to treatment. The evaluation criteria were based on those outlined in The Response Evaluation Criteria in Solid Tumors (version 1.1) (24). The ORR included complete response (CR) and partial response (PR). Disease control rate (DCR) included CR, PR and stable disease (SD). PFS time was defined as the time from the beginning of second-line treatment to disease progression, death or last follow-up. OS time was calculated as the time from initial diagnosis to death or censoring. OS2 time was defined as the time from the beginning of second-line treatment to death or last follow-up. The last follow-up date was March 1, 2022, and the median follow-up time (from the beginning of second-line treatment) was 17 months (range, 2-51 months).

Statistical analysis. Statistical analyses were performed using SPSS (version 21.0; IBM Corp.). Receiver operating characteristic curve analysis was used to determine the optimal cut-off value for FIB. The relationship between pretreatment FIB and other clinicopathological parameters was calculated using the χ^2 test or Fisher's exact test when appropriate. Kaplan-Meier plots show PFS and OS survival curves, and the log-rank test was used to compare survival outcomes of patients with cancer separated by FIB. Univariate and multivariate analyses were conducted using Cox's regression test. All P-values were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline patient characteristics and the treatment response. The clinicopathological characteristics of the 61 patients with cancer included in this study are listed in Table I. In total,

Table I. Differences in pretreatment FIB among different clinicopathological parameters in 61 patients.

Variables	Patients, n (%)	Pretreatment FIB level, n		P-value
		Low	High	
Sex				
Female	15 (24.59)	6	9	0.93
Male	46 (75.41)	19	27	
Age, years				
<60	31 (50.82)	17	14	0.03[a]
≥60	30 (49.18)	8	22	
Smoking history				
Yes	29 (47.54)	12	17	0.95
No	32 (52.46)	13	19	
ECOG score				
0-1	54 (88.52)	22	32	>0.99
≥2	7 (11.48)	3	4	
Surgical history				
Yes	31 (50.82)	11	20	0.38
No	30 (49.18)	14	16	
Metastatic sites, n				
<2	25 (40.98)	11	14	0.69
≥2	36 (59.02)	14	22	
Locoregional therapy				
Yes	9 (14.75)	5	4	0.55
No	52 (85.25)	20	32	
PD-L1 expression				
Positive	7 (11.48)	1	6	0.16
Negative	2 (3.28)	0	2	
Missing	52 (85.25)	24	28	
Pretreatment FIB, g/l[b]		2.84±0.44	4.63±1.06	

[a]P<0.05; [b]data are presented as the mean ± standard deviation. FIB, fibrinogen; programmed death-ligand 1; ECOG, Eastern Cooperative Oncology Group.

15 female and 46 male patients were included. The mean age of the patients was 58.54 years old (range, 25-79 years old). The most common tumor types were lung, head and neck, and esophageal cancer (Table II). The ICIs included atezolizumab, durvalumab, camrelizumab, pembrolizumab, toripalimab, tislelizumab and sintilimab (Table III).

The treatment response was as follows (Table IV): CR, 0 (0%); PR, 16 (26.23%); SD, 23 (37.70%); and PD, 22 (36.07%). The median OS and PFS times were 36.42 months (95% CI, 28.81-44.02) and 6.29 months (95% CI, 5.04-7.54), respectively.

Predictive value of FIB for PFS and OS. The predictive pretreatment FIB cut-off value for OS was 3.47 (area under the curve, 0.80; sensitivity, 0.87; specificity, 0.68; Fig. 1). According to the Kaplan-Meier analysis based on a cut-off point of 3.47 g/l, patients with a low pretreatment FIB exhibited significantly higher PFS and OS times compared with those with a high pretreatment FIB (P<0.05 and P<0.01, respectively) (Figs. 2 and 3).

Univariate and multivariate analyses for PFS, OS and OS2. According to univariate analysis, high pretreatment FIB levels and high FAR were associated with shorter PFS (P=0.03 and P<0.01, respectively) (Table V). Multivariable analysis showed that in contrast to FAR (P=0.02), the pretreatment FIB levels were not an independent predictor of PFS. Male sex and high pretreatment FIB levels were associated with shorter OS time and were also found to be independent prognostic factors of OS (P=0.01 and P=0.04, respectively) (Table VI). Only the pretreatment FIB level was an independent predictor of OS2 (P=0.02) (Table VII). According to the hazard ratios obtained, a lower FIB level was a protective factor for PFS, OS and OS2.

Discussion

In this study, it was shown that low pretreatment FIB levels predicted longer PFS and OS times than high pretreatment FIB levels for patients with cancer treated with ICIs as second-line treatment. The ORR and DCR of the low pretreatment FIB

Table II. Tumor types among the entire patient cohort (n=61).

Tumor types	Patients, n (%)
Lung cancer	16 (26.23)
Head and neck cancer	12 (19.67)
Esophageal cancer	6 (9.84)
Gastric cancer	5 (8.20)
Hepatocellular carcinoma	5 (8.20)
Biliary tract carcinoma	5 (8.20)
Urinary system carcinoma	5 (8.20)
Gynecological carcinoma	4 (6.56)
Others	3 (4.92)

Table III. Application of immune checkpoints in the cohort (n=61).

PD-1/PD-L1 inhibitor	Patients, n (%)
Atezolizumab	2 (3.28)
Durvalumab	1 (1.64)
Camrelizumab	8 (13.11)
Tislelizumab	8 (13.11)
Sintilimab	2 (3.28)
Pembrolizumab	21 (34.43)
Toripalimab	19 (31.15)

PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Table IV. Short-term efficacy in the low pretreatment (n=52) and high pretreatment (n=9) groups of patients.

	Pretreatment fibrinogen level	
Response	<3.47 g/l	≥3.47 g/l
CR, n	0	0
PR, n	9	7
SD, n	9	14
PD, n	7	15
ORR, n (%)	9 (36.00)	7 (19.44)
DCR, n (%)	18 (72.00)	21 (58.33)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

group were better than those of the high pretreatment FIB group. Multivariate analysis demonstrated that FIB was independently associated with OS and OS2.

Pretreatment FIB has been reported to play a notable prognostic role in numerous types of cancer. However, only a few studies have shown the relationship between FIB

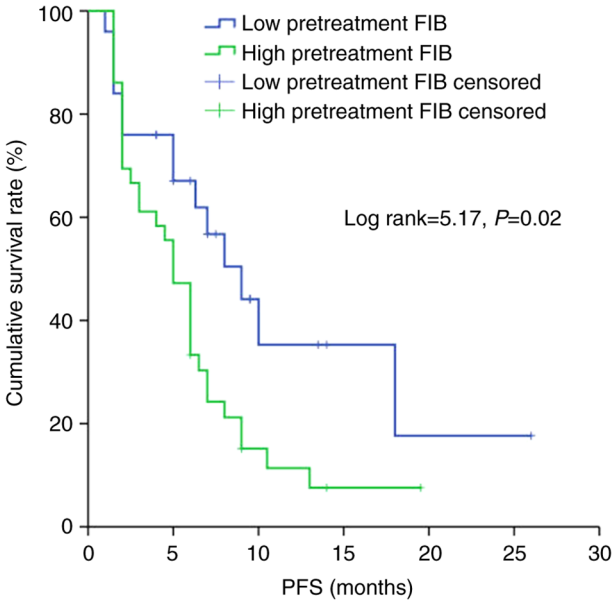

Figure 2. Impact of low or high pretreatment FIB levels on PFS. PFS, progression-free survival; FIB, fibrinogen.

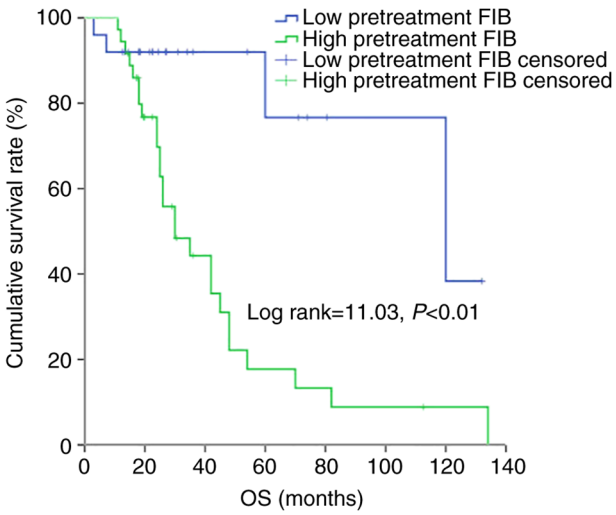

Figure 3. Impact of low or high pretreatment FIB levels on OS. OS, overall survival; FIB, fibrinogen.

and immunotherapy. Shen *et al* (25) conducted a study on 57 patients with unresectable hepatocellular carcinoma who were treated with lenvatinib and ICI, and showed that high FIB was significantly associated with poor survival (P=0.024), and the cut-off value of FIB was 2.83 g/l. Nenclares *et al* (26) showed that on-treatment FIB level (day 28) was a reliable biomarker to predict both disease progression and mortality for 100 patients with HNSCC treated with immunotherapy (P=0.008). Among them, 55 enrolled patients were treated with ICIs as first-line treatment, and 36 patients were treated with second-line therapy. The cut-off value for on-treatment FIB levels was 4 g/l. The outcome of the current study was consistent with these studies, with the exception of the cut-off levels reported, indicating that there are still limitations that need to be explored in depth in the future. Previous studies indicated that FIB levels were associated with age, and that

Table V. Progression-free survival analysis.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Reference					
Female	1.07	0.55-2.08	0.84			
Age, years						
<60	Reference					
≥60	0.97	0.54-1.74	0.92			
Smoking history						
Yes	1.20	0.67-2.15	0.54			
No	Reference					
Surgery history						
Yes	0.79	0.44-1.42	0.43			
No	Reference					
Metastatic sites						
<2	Reference					
≥2	1.24	0.68-2.25	0.49			
Pretreatment fibrinogen, g/l						
<3.47	Reference					
≥3.47	1.99	1.06-3.74	0.03[a]			
FAR						
<0.09	Reference					
≥0.09	3.15	1.58-6.31	<0.01[a]	3.48	1.22-9.91	0.02[a]

[a]P<0.05. HR, hazard ratio; CI, confidence interval; FAR, fibrinogen-albumin ratio.

Table VI. Overall survival analysis.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Reference					
Female	0.34	0.13-0.93	0.03[a]	0.24	0.08-0.72	0.01[a]
Age, years						
<60	Reference					
≥60	1.74	0.80-3.79	0.16			
Smoking history						
Yes	1.44	0.66-3.15	0.36			
No	Reference					
Surgery history						
Yes	0.66	0.31-1.41	0.28			
No	Reference					
Metastatic sites						
<2	Reference					
≥2	1.79	0.83-3.88	0.14			
Pretreatment fibrinogen, g/l						
<3.47	Reference					
≥3.47	5.02	1.73-14.53	<0.01[a]	4.84	1.09-21.5	0.04[a]
FAR						
<0.09	Reference					
≥0.09	3.23	1.23-8.52	0.02[a]			

[a]P<0.05. HR, hazard ratio; CI, confidence interval; FAR, fibrinogen-albumin ratio.

Table VII. Overall survival2 analysis.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Reference					
Female	0.63	0.27-1.50	0.30			
Age, years						
<60	Reference					
≥60	1.92	0.90-4.12	0.09			
Smoking history						
Yes	0.90	0.43-1.88	0.77			
No	Reference					
Surgery history						
Yes	0.94	0.45-1.97	0.87			
No	Reference					
Metastatic sites						
<2	Reference					
≥2	1.31	0.61-2.82	0.48			
Pretreatment fibrinogen, g/l						
<3.47	Reference					
≥3.47	4.06	1.41-11.67	0.01[a]	3.69	1.28-10.63	0.02[a]
FAR						
<0.09	Reference					
≥0.09	3.27	1.25-8.55	0.02[a]			

HR, hazard ratio; CI, confidence interval; FAR, fibrinogen-albumin ratio.

the FIB level increased with increasing age (18,27), which was consistent with the findings of the present study. Other relevant indicators for FIB include tumor differentiation, tumor location, pathological tumor (pT) category, pathological nodal (pN) status and Tumor-Node-Metastasis stage (18,25,26). An appropriate predictive value of FIB in clinical practice may need to be selected in combination with other indicators for a comprehensive analysis. The results of FAR in the present study showed that it was an independent prognostic factor of PFS, but it could not be independently associated with OS in patients with cancer. Following combination of these results with those from previous studies such as the one carried out by Guo and Liang (21), it is hypothesized that FAR is not a suitable biomarker for evaluating prognosis in patients with cancer treated with ICIs.

As a potentially notably predictor of immunotherapy, the underlying mechanism of FIB has not been thoroughly clarified. Patients with malignant tumors tend to have varying degrees of hypercoagulability (28,29). Based on the recognized mechanisms for FIB and tumor progression, four hypotheses have been proposed. Firstly, FIB can bind or interact with growth factors such as fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) (30,31). Derynck *et al* (32) demonstrated that TGF-β could release immunosuppressive cytokines and generate an immunosuppressive environment, thus weakening the effect of immunotherapy. Binding of FIB with FGF-2 or PDGF can enhance their ability to promote cancer cell proliferation, metastasis and angiogenesis (30,31). Second, FIB is mainly synthesized upon inflammatory stimulation by IL-6 and IL-1β, as well as by cancer cells (33-35). Increased FIB levels promote the migration of cancer cells and protect them from the innate immune surveillance system by promoting platelet binding (36,37). Third, a high concentration of FIB can induce the epithelial-mesenchymal transition (EMT) (38). Zhang *et al* (39) demonstrated that EMT can increase PD-L1 expression in tumors, and the interaction of PD-1 and PD-L1 can decrease cytotoxic T-cell activity, which leads to resistance to immunotherapy in colorectal cancer. Fourth, fibrinogen-like protein 1 (FGL1) belongs to the FIB superfamily, with high amino acid homology to the carboxyl terminus of the FIB β- and γ-subunits (40). FGL1 is a major immune inhibitory ligand of lymphocyte-activation gene-3 (LAG-3), and the FGL1/LAG3 interaction can cause immune suppression (41). Whether high FIB is related to the FGL1/LAG3 interaction needs to be further explored. The aforementioned factors may be the cause of poor immunotherapy effects in patients with high FIB.

A number of studies have reported that high FIB or other coagulation indices are associated with tumor progression, such as that in breast, pancreatic and esophageal cancer (42-44). Izuegbuna *et al* (42) and Wang *et al* (43) showed

that patients with breast cancer and patients with pancreatic cancer with a higher concentration of FIB, had a worse tumor stage. Kołodziejczyk *et al* (45) reported that the products of FIB degradation were associated with disease progression and metastasis. Liu *et al* (46) conducted a study that included 176 patients with metastatic breast cancer and showed that the FIB levels significantly increased after first-line therapy in patients with disease progression. Therefore, we hypothesize that FIB has a higher predictive value for the efficacy of second- or third-line therapy. Further research is needed to provide evidence of this predictive index in first-line therapy.

Although the present study provided evidence to support the prognostic significance of elevated FIB in patients with cancer, there were still limitations. First, this study was a retrospective analysis and included only 61 patients. Consequently, selection bias was unavoidable. Second, only 13 patients underwent genetic testing, and only 9 patients had PD-L1 expression tested in the present study. Thus, the interaction between relevant genetic information and the therapeutic effect of ICIs was not described. Third, due to the nature of this retrospective study, it was not feasible to explore the mechanism of FIB in the context of immunotherapy in depth. Nonetheless, further prospective trials and primary research studies are needed to confirm the predictive value of FIB in patients with immunotherapy.

Overall, to the best of our knowledge, this study is the first observation concerning the prognostic role of FIB across cancer types, particularly in patients treated with ICIs. FIB is a promising prognostic factor for predicting the prognosis of patients undergoing immunotherapy.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81872009).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RX, BY, FL and QZ conceived and designed the study. RX and TY acquired the data and drafted the manuscript. RX and JY analyzed and interpreted the data. BY, JY and FL checked the data, and performed critical revision of the manuscript. QZ supervised the study. RX, TY and QZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hainan Hospital of the Chinese People's Liberation Army (PLA) General Hospital (approval no. 301HLFYLS15), and written informed consent was waived by the Ethics Committee of Hainan Hospital of the PLA General Hospital due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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