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Characteristics, risk factors and a risk prediction model of tocilizumab-induced hypofibrinogenemia: a retrospective real-world study of inpatients

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Abstract

Objective The occurrence of hypofibrinogenemia after tocilizumab treatment has attracted increasing attention, which may cause bleeding and even life-threatening. This study aims to explore the risk factors for tocilizumab-induced hypofibrinogenemia (T-HFIB) and construct a risk prediction model.

Methods A total of 221 inpatients that received tocilizumab from 2015 to 2023 were retrospectively collected and divided into T-HFIB group or control group. The risk factors for T-HFIB were obtained by logistic regression equation and used to establish the nomogram.

Results T-HFIB was observed in 121 of 221 patients (54.75%). Multifactorial logistic regression analysis revealed that infection (OR = 2.002, 95%CI:1.018 ~ 3.935), COVID-19 (OR = 3.752, 95%CI:1.264 ~ 11.139), CAR-T therapy (OR = 4.409, 95%CI:2.017 ~ 0.894), and concomitant glucocorticoids (OR = 5.303, 95%CI:0.227 ~ 0.894) were identified as independent risk factors for T-HFIB, while high baseline fibrinogen level (OR = 0.813, 95%CI:0.670 ~ 0.988) and concomitant antirheumatic drugs (OR = 0.451, 95%CI:0.227 ~ 0.894) were identified as protective factors. A nomogram was established, and area under the curve (AUC) of prediction model was 0.772 (95%CI:0.709 ~ 0.836). Calibration curve showed a good prediction accuracy for the occurrence of T-HFIB.

Conclusion The infection, COVID-19, CAR-T therapy, and concomitant glucocorticoids were independent risk factors for T-HFIB, while high baseline fibrinogen and concomitant antirheumatic drugs were protective factors. This nomogram can help early identify the patients at potential high risk of developing T-HFIB.

Keywords Tocilizumab, Hypofibrinogenemia, Risk factors, Risk prediction model

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Introduction

IL-6 is a pleiotropic cytokine and implicated in various diseases, known to influence numerous cell types with several biologic activities, including hematopoiesis, bone metabolism, immune response and inflammation. Tocilizumab, a recombinant humanized monoclonal antibody targeting both soluble and membrane-bound IL-6 receptors [1], has been use in the treatment of several rheumatic diseases, cytokine release syndrome, giant cell arteritis and refractory adult-onset Still disease [2–5]. After the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), tocilizumab has shown potential therapeutic value and is recommended for the treatment of severe COVID-19 patients with significantly elevated IL-6 levels [6]. With the wide application of tocilizumab, its uncommon adverse reactions (ADRs), including hypofibrinogenemia, have gradually attracted attention [1, 7].

Fibrinogen is a glycoprotein coagulation factor synthesized and secreted into the blood by liver cells. As the precursor of fibrin, fibrinogen plays a crucial role in the clotting process. Under normal circumstances, fibrinogen levels in human plasma range from 2 g/L to 4 g/L, and hypofibrinogenemia is diagnosed when the level is below 2 g/L [8]. Once hypofibrinogenemia occurs, it may cause bleeding and even life-threatening. Currently, studies of tocilizumab-induced hypofibrinogenemia (T-HFIB) are mostly case reports and small sample studies [7, 9–12], and its clinical characteristics and related risk factors still unclear. This study aimed to retrospectively analyzes cases of hypofibrinogenemia in patients after tocilizumab treatment to explore their clinical characteristics and risk factors, and constructs a predictive model to provide reference for the clinical safe and rational use of tocilizumab. The prediction model will helpful to identify the patients with high-risk of T-HFIB and provide data support for improving patient treatment safety.

Materials and methods

Subjects

All hospitalized patients treated tocilizumab injection (80 mg/4 ml) from January 2015 to December 2023 were analyzed retrospectively, based on the adverse drug events active surveillance and assessment system-II (ADE-ASAS-II) developed by our team [13]. Inclusion criteria: (1) hospitalized patients receiving tocilizumab treatment; (2) fibrinogen ≥ 2.0 g/L before tocilizumab treatment; (3) patients with fibrinogen < 2.0 g/L after tocilizumab treatment were considered as the case group, and patients with fibrinogen > 2.0 g/L were the control group [14, 15]. Exclusion criteria: (1) fibrinogen < 2.0 g/L before treatment; (2) lack of fibrinogen levels before or after tocilizumab treatment within 15 days; (3) lack of hospital medical record information. This retrospective study was approved by the Ethics Committee of Chinese PLA General Hospital and individual consent was waived (S2024-247-01). All patient data were kept strictly confidential.

Evaluation methods of adverse reactions

The correlation of hypofibrinogenemia to tocilizumab was evaluated based on Naranjo's scale [16]. The ADR was assigned to a probability category from the total score as follows: definite ≥ 9, probable 5 to 8, possible 1 to 4, and doubtful ≤ 0. Patients with scores ≥ 1 were defined as T-HFIB. The controls were selected through manual chart review from patients eligible for inclusion and exclusion, who didn't develop hypofibrinogenemia disorders after tocilizumab therapy. According to the Common Terminology Criteria for Adverse Events (CTCAE5.0), the severity of hypofibrinogenemia was graded as follows: grade 1 (mild): 1.5 g/L ≤ fibrinogen < 2.0 g/L; Grade 2 (moderate): 1.0 g/L ≤ fibrinogen < 1.5 g/L; Grade 3 (severe): 0.5 g/L ≤ fibrinogen < 1.0 g/L; Grade 4 (life-threatening): < 0.5 g/L. Two researchers performed a blind evaluation to confirm the alarm results, and the cases with inconsistent evaluation results were referred to the experts for final decision.

Data collection

All the information of patients from January 2015 to December 2023 was monitored and extracted from the hospital information system (HIS) using the ADE-ASAS-II, including demographic data (age, gender, body mass index (BMI) and hospital stay), clinical manifestation (combined with malignant solid tumor, chronic liver disease, infection, COVID-19 and chimeric antigen receptor (CAR-) T cell therapy), concomitant drugs (anticoagulants, antiplatelet drugs, antirheumatic drugs, glucocorticoids, cytotoxic chemotherapies, other drugs that may cause hypofibrinogenemia (tigecycline, snake venom hemagglutinin, valproic acid, etc.)) and laboratory indexes (baseline fibrinogen level, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (TBIL), thrombin time (TT), plasma prothrombin time (PT), international normalized ratio (INR), plasma D-Dimer). Other relevant monitoring information including the cumulative dose of tocilizumab, bleeding after treatment, and fibrinogen reduction level.

Statistical analysis

SPSS statistical software (version 24.0; SPSS, IBM Corporation, USA) and R software (version 4.0.3, the R Core Team, USA) was used for data statistical analyze. Kolmogorov-Smirnov (K-S) test was used to test the normality of continuous variables. Quantitative data were expressed as mean and standard deviation (with normal distribution) or median (interquartile range, IQR) (with

non-normal distribution), and compared by Student *t* test and Mann-Whitney *U* test, respectively. Qualitative data were displayed as number and percentage, and compared by χ^2 test. $P < 0.05$ was considered statistically significant.

Univariate and multivariate binary logistic regression analyses were used to determine the independent risk factors for T-HFIB. Variables with significant differences in univariate analysis were included in multivariate analysis. Estimates of odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors were obtained. A nomogram was constructed according to the results of multivariable logistic regression and prediction equation using the "rms package" in R software. The discrimination was tested by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The value of AUC ranges from 0.5 to 1. The closer the AUC value is to 1, the better discrimination capacity the prediction model has. Generally, a prediction model that performs with an AUC of 0.5–0.75 is considered acceptable, and AUC > 0.75 indicates the model shows excellent discrimination [17]. The calibration of the model was evaluated by calibration curve, and the goodness of fit was calculated by Hosmer-Lemeshow test, reflecting the consistency of model prediction probability and actual probability. The nomogram, ROC curve, and calibration curve were drawn by R software.

Results

The occurrence and severity of T-HFIB

A total of 1314 patients admitted during 2015 to 2023 were monitored by the ADE-ASAS-II. After screening by ADE-ASAS-II and manual independent revaluation by two clinical pharmacists, 221 cases were included. Among them, 121 patients were identified as T-HFIB (case group) and 100 patients were negative cases (control group). In the case group, 22 cases (18.18%) were evaluated as "probable" and 99 cases (81.82%) as "possible". The median onset time of hypofibrinogenemia after tocilizumab treatment was 6 days (interquartile range: 3.0–10.0 days), and 110 cases (90.91%) occurred within 30 days of administration (Fig. 1a).

For the severity of hypofibrinogenemia, grade 1 (mild): 60 cases (49.59%); grade 2 (moderate): 44 cases (36.36%); grade 3 (severe): 16 cases (13.22%); grade 4 (life-threatening): one case (0.83%) (Fig. 1b). Bleeding occurred in 21 cases (20.19%) of mild and moderate hypofibrinogenemia patients, and in 9 cases (52.94%) of severe and life-threatening hypofibrinogenemia patients (Fig. 1c). The bleeding risk of severe and life-threatening hypofibrinogenemia patients was higher than that of mild and moderate patients, and the difference was statistically significant ($\chi^2 = 6.74$, $p = 0.009$).

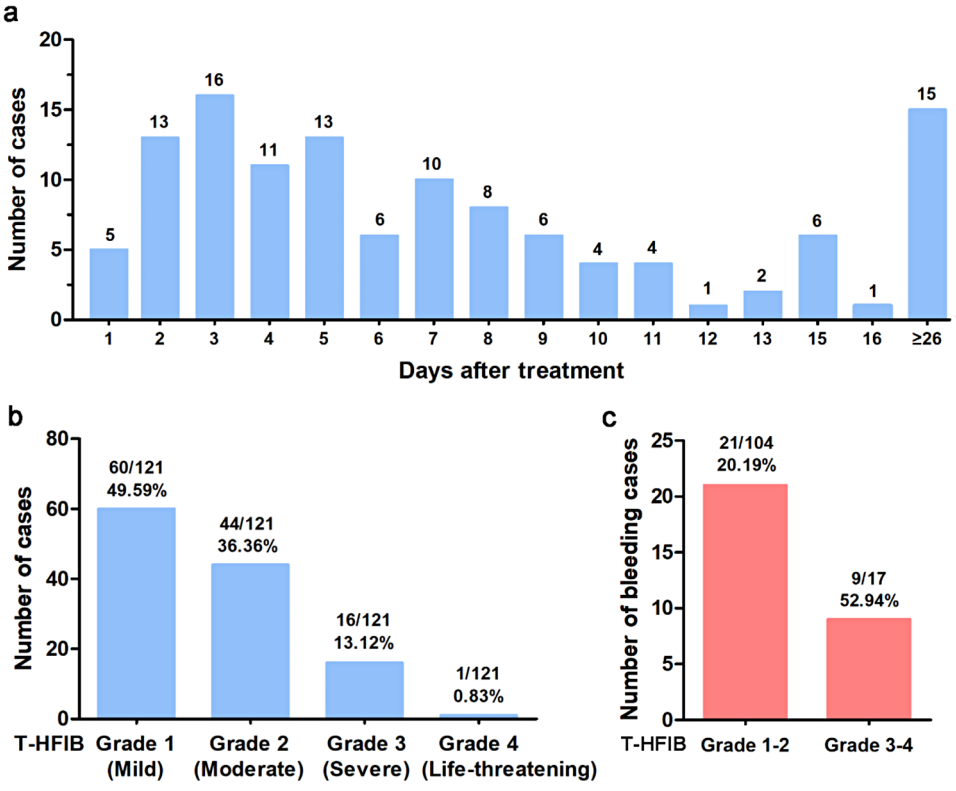

Fig. 1 The number of tocilizumab-induced hypofibrinogenemia. **a** Number of hypofibrinogenemia cases after tocilizumab treatment. **b** Number of hypofibrinogenemia cases in grade 1–4. **c** Number of bleeding cases

Table 1 The clinical characteristics, medication and laboratory indexes of patients

Variables	T-HFIB(n = 121)	Control(n = 100)	*p* value
Clinical characteristics			
Male, n (%)	62(51.2)	48(48.0)	0.632
Age ≥ 60 years, n (%)	47(38.8)	20(20.0)	0.002*
Bleeding, n (%)	30(24.8)	6(6.0)	<0.001*
Solid malignancies, n (%)	48(39.7)	37(37.0)	0.685
Chronic hepatopathy, n (%)	35(28.9)	28(28.0)	0.879
Infection, n (%)	60(49.6)	27(27.0)	0.001*
COVID-19, n (%)	28(23.1)	6(6.0)	<0.001*
CAR-T therapy, n (%)	47(38.8)	23(23.0)	0.012*
Cumulative dose mg, (IQR)	400(240 ~ 680)	400(160 ~ 700)	0.929
Blood transfusion, n (%)	41(33.9)	19(19.0)	0.013*
Drug combinations, n (%)			
Anticoagulants	76(62.8)	42(42.0)	0.002*
Antiplatelet drugs	13(10.7)	13(13.0)	0.604
Antirheumatic drugs	28(23.1)	44(44.0)	0.001*
Glucocorticoids	112(92.6)	82(82.0)	0.017*
Cytotoxic chemotherapeutics	50(41.3)	29(29.0)	0.057
Other drugs associated with HFIB	21(17.4)	5(5.0)	0.005*
Laboratory indexes			
Baseline fibrinogen g/L, (IQR)	4.05(2.97 ~ 5.19)	4.60(3.32 ~ 5.67)	0.051
CRP mg/dL, (IQR)	4.74(0.89 ~ 10.06)	3.69(0.71 ~ 7.51)	0.419
ALT U/L, (IQR)	19.20(11.65 ~ 39.55)	17.20(11.08 ~ 30.00)	0.274
AST U/L, (IQR)	21.90(14.30 ~ 41.40)	18.25(13.00 ~ 32.65)	0.140
ALB g/L, (x ± s)	34.26 ± 5.73	35.25 ± 5.18	0.182
TBIL μmol/L, (IQR)	9.10(6.70 ~ 14.40)	8.05(4.98 ~ 12.70)	0.019*
TT s, (IQR)	15.90(14.75 ~ 16.95)	15.80(15.03 ~ 16.98)	0.512
PT s, (IQR)	13.90(13.00 ~ 15.00)	13.45(12.50 ~ 14.40)	0.011*
INR (IQR)	1.08(1.00 ~ 1.20)	1.03(0.95 ~ 1.13)	0.007*
D-Dimer μg/mL, (IQR)	2.04(0.62 ~ 5.39)	1.49(0.64 ~ 3.59)	0.156

HFIB: hypofibrinogenemia; T-HFIB: tocilizumab-induced hypofibrinogenemia; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: serum albumin; TBIL: total bilirubin; TT: thrombin time; PT: plasma prothrombin time; INR: international normalized ratio; D-Dimer: plasma D-Dimer; IQR: interquartile range

Clinical characteristics of the patients

Among the 221 patients, there were 110 males (49.8%) and 111 females (50.2%). The age composition (≥ 60 years) between the T-HFIB group and the control group has a significant difference ($p = 0.002$). The clinical characteristics, medication and laboratory indexes were analyzed by univariate regression. As shown in Table 1, there were statistically significant differences between the two groups in bleeding, infection, COVID-19, CAR-T therapy, blood transfusion (before the onset of hypofibrinogenemia during tocilizumab treatment), use of anticoagulants, antirheumatic drugs, glucocorticoids and other drugs associated with hypofibrinogenemia, TBIL, PT, and INR ($p < 0.05$).

Table 2 Risk factors for tocilizumab-induced hypofibrinogenemia

Variables	Univariate regression analysis		multivariable regression analysis	
	OR(95%CI)	*p* value	OR(95%CI)	*p* value
Age ≥ 60 years	2.541(1.379 ~ 4.682)	0.003		
Infection	2.659(1.508 ~ 4.690)	0.001	2.002(1.018 ~ 3.935)	0.044
COVID-19	4.717(1.866 ~ 11.921)	0.001	3.752(1.264 ~ 11.139)	0.017
CAR-T therapy	2.126(1.176 ~ 3.844)	0.013	4.409(2.017 ~ 9.635)	0.000
Blood transfusion	2.185(1.169 ~ 4.084)	0.014		
Anticoagulants	2.332(1.357 ~ 4.010)	0.002		
Antirheumatics	0.383(0.215 ~ 0.683)	0.001	0.451(0.227 ~ 0.894)	0.023
Glucocorticoids	2.732(1.168 ~ 6.387)	0.020	5.303(1.837 ~ 15.305)	0.002
Other drugs associated with HFIB	3.990(1.446 ~ 11.009)	0.008		
Baseline fibrinogen	0.822(0.695 ~ 0.974)	0.023	0.813(0.670 ~ 0.988)	0.037
PT	1.152(1.001 ~ 1.326)	0.048		

HFIB: hypofibrinogenemia; PT: plasma prothrombin time

Investigation the risk factors for T-HFIB

All potential risk factors ($p < 0.05$ in the univariable analysis) were evaluated in the univariate and multivariable regression analysis. The results showed that the independent risk factors for T-HFIB included infection, COVID-19, CAR-T therapy, blood transfusion, use of antirheumatic drugs, glucocorticoids, and baseline fibrinogen level ($p < 0.05$, Table 2).

Establishment and validation of nomogram for predicting the probability of T-HFIB

As shown in Fig. 2, a nomogram was constructed based on independent predictors from multivariate logistics regression analysis for the prediction of T-HFIB. Using this nomogram model, clinicians can score different indicators and predict the probability of hypofibrinogenemia based on the scoring results. In nomogram, baseline fibrinogen level is a continuous variable, and other

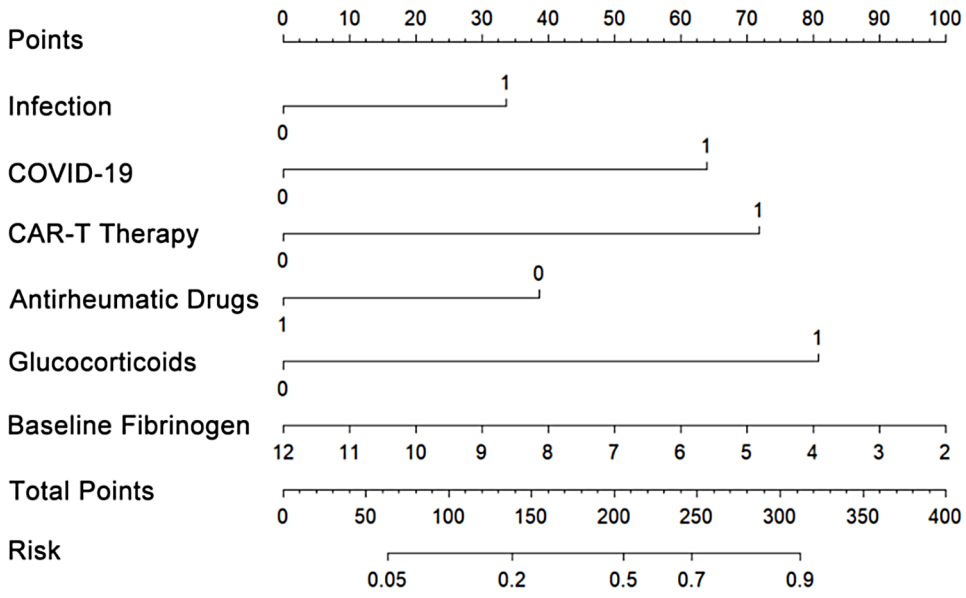

Fig. 2 Nomogram for the prediction of tocilizumab-induced hypofibrinogenemia

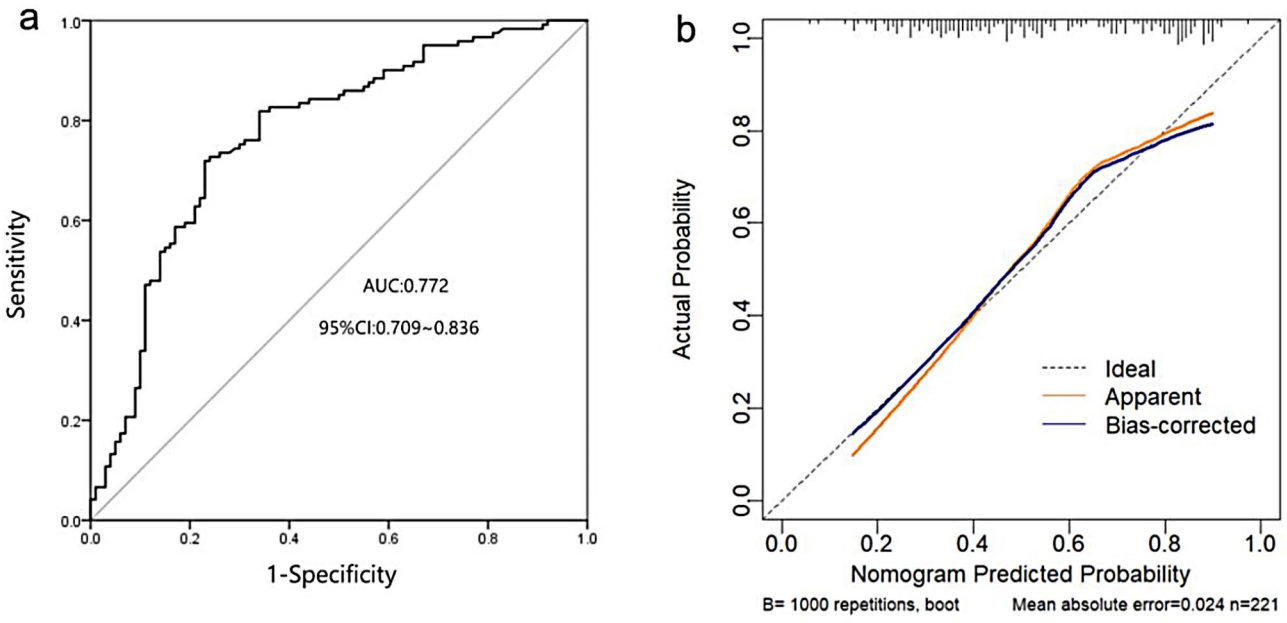

Fig. 3 The receiver operating characteristic curve and calibration curve of nomogram. **a** The receiver operating characteristic curve. **b** The calibration curve

predictors are categorical variables, including infection, COVID-19, CAR-T therapy, use of antirheumatic drugs and glucocorticoids. The total score is the sum of the scores of each risk factor, and its corresponding probability is the predicted probability of T-HFIB.

The prediction model was evaluated by discrimination and calibration. The model discrimination was evaluated by ROC curve, and the maximum Youden index (0.524) was taken as the optimal critical value of the prediction model. The AUC of ROC was 0.772 (95%CI:0.709 ~ 0.836, $p < 0.001$, Fig. 3a). The predicted values and actual values were consistent, indicating good predictive accuracy ($\chi^2 = 13.68$, $p = 0.09$, Fig. 3b).

Discussion

Clinical characteristics of T-HFIB

In present study, 221 patients treated with tocilizumab were included for analysis, and 54.75% (121/221) of patients developed T-HFIB. It is reported that the probability of T-HFIB ranges from 29 to 76.47% [10, 12, 18, 19]. In present study, the median time of T-HFIB was 6 days, 90.91% (110/121) occurred within 30 days after

tocilizumab administration, and most of them were mild or moderate hypofibrinogenemia patients (85.6%, 104/121).

An et al. [19] and Souri et al. [20] did not observe bleeding symptoms in rheumatoid arthritis patients with T-HFIB. However, Imamura et al. [9] pointed out that rheumatoid arthritis patients treated with tocilizumab had lower fibrinogen levels compared to those without treatment, and had higher blood loss after total knee arthroplasty operation. Our study found that 9 patients (52.9%, 9/17) with severe and life-threating hypofibrinogenemia had bleeding, which was significantly higher than that in mild and moderate hypofibrinogenemia patients (20.2%, 21/104). Therefore, it is necessary to monitor the serum fibrinogen levels and other coagulation markers during clinical administration of tocilizumab to prevent fatal bleeding event. In addition, 11.6% (153/1314) of patients were excluded since baseline fibrinogen below 2 g/L, and 71.5% (940/1314) due to fibrinogen levels data missing. This suggested that the drug-induced hypofibrinogenemia has not been fully recognized in clinical practice and it is necessary to strengthen the routine monitoring of serum fibrinogen levels.

Among the patients, 76.9% (170/221) of them were combined with CAR-T therapy, rheumatic diseases and COVID-19. The rate of T-HFIB in patients with COVID-19 and CAR-T therapy (74/103) was significantly higher than that in patients with rheumatic diseases (25/67) ($\chi^2 = 12.90$, $p < 0.001$). While, there was no significant difference in the ratio of T-HFIB between patients with COVID-19 and CAR-T therapy. Patients both in case group (4.05 (2.97–5.19) g/L) and the control group (4.60 (3.32–5.67) g/L) have a high level of serum baseline fibrinogen, which may be related to the original diseases. The vast majority (95.0%, 114/121) of patients developed hypofibrinogenemia after the 1–3 administration of tocilizumab, consistent with previous reports that T-HFIB mainly occurred during the 1–4 administration [11, 18, 19]. Uskudar Cansu et al. [11] speculated that the occurrence of hypofibrinogenemia may be affected by the cumulative dose of tocilizumab, but we did not observe the difference in the cumulative dose between the T-HFIB group and the controls.

Related risk factors of T-HFIB

We found that combined with infection, COVID-19, CAR-T therapy, antirheumatic drugs, glucocorticoids, and baseline fibrinogen level were the influencing factors of T-HFIB. Clinical studies have reported that patients with severe COVID-19 pneumonia have high serum baseline fibrinogen levels (median 5.20 g/L, IQR 4.36 ~ 7.14), and fibrinogen levels decreased after 10 days of tocilizumab treatment (median 2.17 g/L, IQR 1.50 ~ 2.85) [21]. Consistently, Tomasiewicz et al. [22] found that the serum fibrinogen concentrations of severe COVID-19 patients were decreased significantly after treatment with tocilizumab ($p < 0.001$), but the incidence was not mentioned.

Cytokine release syndrome (CRS), a major complication of CAR-T therapy, is a systemic inflammatory reaction associated with the release of cytokines, such as IL-6, IL-2, IFN-γ and TNF-α [23]. CRS-related coagulopathy is complex. Briefly, inflammation mediated by various cytokines leads to consumption of coagulation factors during CRS, which is compensated by IL-6-dependent upregulation of fibrinogen synthesis. When tocilizumab is used to treat CRS, the IL-6 stimulus for increased fibrinogen synthesis in the liver is diminished. Therefore, the consumption of fibrinogen far exceeds its production, leading to a persistent state of hypofibrinogenemia [24]. In adult hematologic malignancies patients accepting CAR-T therapy, serum fibrinogen levels elevated at early stage of CRS and dropped significantly after administration of tocilizumab in a dose dependent manner ($p = 0.004$), while patients who did not receive tocilizumab had increased fibrinogen levels [25]. The mechanism of T-HFIB still unclear. In acute phase reaction, fibrinogen biosynthesis is positively regulated by IL-6-mediated transcription of the fibrinogen mRNA [26]. As an inhibitor of IL-6R, tocilizumab may inhibit the expression of fibrinogen by blocking the IL-6 signaling pathway and lead to prolonged hypofibrinogenemia. Therefore, for patients with infection, COVID-19, CAR-T therapy, it is necessary to monitor fibrinogen levels during tocilizumab treatment to prevent severe bleeding events.

Glucocorticoid has become a standard pretreatment during the induction therapy of acute lymphocytic leukemia (ALL) [27]. Hypofibrinogenemia, one of the most frequent findings during steroid therapy of ALL [28], being most frequently associated with disseminated intravascular coagulation or primary fibrinolysis [29, 30]. In present study, there were 24 cases suffered ALL and 31 cases suffered non-Hodgkin lymphoma among the patients treated with glucocorticoids in the case group. At diagnosis of B-cell ALL, 5% patients occurred hypofibrinogenemia at grade 1 before the onset of treatment [31, 32]. After a median of 7 days (range 3 to 28) from glucocorticoids initiation, the decreased plasma fibrinogen levels were observed in 64% patients [31]. For these patients, treatment with tocilizumab may exacerbate fibrinogen consumption, making them more prone to bleeding. It is reported that an excess of Annexin II generation enhances the formation of plasmin on the endothelial-cell surface, which may lead to hypofibrinogenemia [33] and hemorrhagic complications in ALL [34]. However, whether tocilizumab causes hypofibrinogenemia via this mechanism is unclear.

Baseline fibrinogen level has been a strong predictor of HFIB in multiple studies [35–37]. Consistently, we found that high baseline fibrinogen level was a protector factor for T-HFIB. Among the patients included in present study, about 50% of baseline serum fibrinogen levels were 3.0–5.4 g/L, the median value of serum fibrinogen was 4.42 g/L. We choose 4.4 g/L as the inflection point to analyze the correlation between bleeding risk and baseline fibrinogen level, and found that patients with baseline level at 2–4.4 g/L were have a significantly higher risk of bleeding than those with baseline above 4.4 g/L (95%CI:1.037 ~ 3.026, $p = 0.036$). It is reported that the median level of baseline fibrinogen was 5.47 (3.32–7.99) g/L in systemic-onset juvenile idiopathic arthritis patients, 5.20 (4.36–7.14) g/L in COVID-19 patients, and higher than 4.0 g/L in patients after CAR-T therapy with grade 3 CRS without tocilizumab treatment [18, 21, 25]. Therefore, for those patients, serum fibrinogen should be closely monitored after tocilizumab treatment even in normal range, since they have a high risk of bleeding.

Combination of disease modifying antirheumatic drugs was identified as a protective factor T-HFIB. Since other rheumatism related indexes were not analyzed in present study, it is unclear that whether T-HFIB was associated with rheumatoid disease activity. According to previous study, in rheumatoid arthritis patients treated with tocilizumab, tender joint count and swollen joint count were independent risk factors for the occurrence of hypofibrinogenemia [19].

The prediction effect of nomogram on the risk of T-HFIB

Taking infection, COVID-19, CAR-T therapy, combined use of antirheumatic drugs and glucocorticoids, and baseline fibrinogen as independent variables, we established a nomogram to predict the risk of hypofibrinogenemia after tocilizumab treatment. The validation results of nomogram showed a good discrimination and accuracy. This predictive model will help identify patients with high risk of hypofibrinogenemia before tocilizumab treatment, which is a prerequisite for determining whether preventive measures are needed, such as weight the benefits and the risks before administration of tocilizumab and supplementation of fibrinogen or coagulation factors timely when fibrinogen reduction via routine monitoring. This study provided data support for reducing the incidence of hypofibrinogenemia and serve bleeding events as well as improving medication safety.

This study still has some limitations. Firstly, it is a single-center retrospective study. Secondly, the sample size included in this study is limited, since only a small percentage of patients receiving tocilizumab were routinely monitored for fibrinogen, which may make the results unrepresentative. Finaly, there were significant differences in the diagnosed diseases of the included patients, including tumor, blood disease, rheumatism, and the combination drugs with tocilizumab were also complex. These comorbidities and concomitant medications are likely to have an impact on fibrinogen levels, which may cause a bias in the characteristics of hypofibrinogenemia and affect the accuracy of the prediction model. In the future, a large-scale, prospective multi-center studies should be conducted to verify the results of this study and provide more reliable data for clinical therapy.

Conclusion

In this retrospective analysis, we found that combination of infection, COVID-19, CAR-T therapy, and glucocorticoids were independent risk factors of T-HFIB, while high baseline fibrinogen level and combined with antirheumatic drugs had a protective effect. More than half of the patients included in present study developed hypofibrinogenemia after tocilizumab treatment, and it is necessary to strengthened the monitoring of fibrinogen levels. To assess the probability of T-HFIB, we established a nomogram and validation results showed that a good discrimination and accuracy. This prediction model will be helpful to initially identify the patients with high-risk of T-HFIB, which provided data support for promoting routinely monitor fibrinogen levels and improving medication safety.

Author contributions

M.Z., L.C. and D.G. designed the study. L.C. analyzed the data. Z.Q. and A.F. assisted in data collection and analysis. L.C. and X.W. wrote the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study involving humans was approved by the Ethics Committee of Chinese PLA General Hospital with a waiver of the requirement for informed consent (S2024-247-01).

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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