ORIGINAL RESEARCH

NEUTROPHIL COUNTS HELP PREDICT FREE WALL RUPTURE FOLLOWING ST-ELEVATION MYOCARDIAL INFARCTION

VOL 44 NO 2 JUNE 2021

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Submitted 21st September 2020, Accepted 1st April 2021

Clin Invest Med 2021;44(2):E62-70; DOI: 10.25011/cim.v44i2.36273

ABSTRACT

Purpose: Free wall rupture (FWR) is a lethal complication after acute myocardial infarction; however, the underlying mechanisms of FWR are unclear. This study analyzes the relationship between neutrophil counts and FWR following ST-elevation myocardial infarction (STEMI).

Methods: The case group was STEMI patients with FWR and the control group was STEMI patients without FWR (case-control ratio was 1:4). The demographic data, clinical manifestation and laboratory test results were retrospectively collected and analyzed.

Results: Of a total of 6,712 consecutive STEMI patients, 78 patients (1.2%) had FWR. Compared with STEMI patients, patients with FWR were older and more likely to be female with an anterior infarct. White blood cell (WBC) counts were significantly higher in the FWR group. Moreover, we found that the elevated neutrophil counts mainly accounted for the elevated WBC counts. There was also a correlation between the age and neutrophil counts ($P=0.0109$); as patient age increased, neutrophil counts decreased ($P=0.0387$). We also found no correlation between neutrophil counts and the time between myocardial infarction attack and FWR; however, when dividing these patients into FWR ≤ 48 h after admission to hospital for STEMI and FWR >48 h, there was a significant difference in neutrophil counts ($P=0.0196$). Furthermore, the results of logistic regression analysis showed that increased neutrophil was an independent risk factor for FWR (odds ratio: 2.404, confidence interval: 1.055-5.477).

Conclusion: Elevated neutrophil counts were found to be the main cause of differences in WBC counts between FWR and STEMI. Elevated neutrophil was an independent risk factor for FWR. This study provided clues for further research and development of therapeutics for the prevention of FWR.

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INTRODUCTION

Before implementation of reperfusion therapy, the incidence of free wall rupture (FWR) following ST-elevation myocardial infarction (STEMI) was about 6% [1]. With the progressive improvements in medical treatment and reperfusion strategies, especially percutaneous coronary intervention (PCI), FWR following STEMI has declined to approximately 2% [2-4]. Nevertheless, as a catastrophic complication after STEMI, due to dangerous onset, difficulty in diagnosis, poor prognosis, and lack of effective prevention and treatment measures, the hospital mortality of FWR is still extremely high (75%-91%) [5,6].

According to the clinical features of FWR, we anticipated being able to identify the predictors of FWR after STEMI, and thereby to provide a basis for exploring the pathogenesis and for developing prevention and treatment strategies.

Previous animal studies suggested post-infarct rupture was associated with inflammatory response. Gao et al. demonstrated accumulation of inflammatory cells appeared to be dominating in the myocardium of mice with ligation of left coronary artery, especially in the border zone [7]. In an ischemia-reperfusion animal model, inhibition of leukocyte-mediated inflammation

was found to reduce the infarcted size and to alleviate myocardial injury [8,9]. Specifically, excessive inflammatory response was found to be an important pathophysiological mechanism of cardiac rupture following acute myocardial infarction (AMI). Acute cardiomyocyte necrosis in the infarcted heart can activate nuclear factor (NF)- κ B system, toll-like receptor (TLR)-mediated pathways, complement cascade and reactive oxygen species (ROS); triggering the post-infarction inflammatory response [10,11]. Abundant infiltration of inflammatory cells, high expression of inflammatory cytokines and plentiful secretion of matrix metalloproteinases were found to result in degradation of extracellular matrix, leading to post-infarct rupture [12].

Most of the previous clinical studies discussed the possible predictors, such as age, gender, infarct site, smoke, hypertension in cardiac rupture (including FWR, ventricular septal perforation and papillary muscle rupture) after STEMI. Several studies have explored the relationship between white blood cell (WBC) count and cardiac rupture. Qian et al. found the incidence of cardiac rupture witnessed an upward trend with the increase of WBC count in STEMI [4,13]. Ipek et al. found that an increased neutrophil-to-lymphocyte ratio was an independent risk factor related to left ventricular FWR in STEMI patients, but neutrophil count had no statistical significance between FWR and non-FWR groups [14]. The role of elevated WBC counts in development of FWR after STEMI still needs to be explored further.

Our team has been working on cardiac rupture following AMI since 2001. We have already assembled a database that includes 6,712 consecutive patients with STEMI and includes 78 patients with FWR. We found that FWR typically occurred within the first week after AMI. Early-phase FWR (within 48 hours after STEMI) patients had higher random glucose levels and larger percentage of anterior myocardial infarction than in patients with late-phase FWR (more than 48 hours after STEMI). Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), β -blockers and dual antiplatelet therapy may be protective factors in early-phase FWR patients. Defecation, transport, acute emotional upset, diet and invasive treatment may be the main triggers for FWR. We have previously shown that age, β -blocker coverage and primary PCI were related to survival after FWR [15]. The objective of the present study was to further analyze the relationship between the change in neutrophil counts and FWR following STEMI.

METHODS

Study population

Through retrospectively reviewing the medical record system, consecutive patients who presented with STEMI

admitted to Beijing Anzhen Hospital (Beijing, China), from January 2010 to November 2017, were analyzed. We performed a case-control study at a 1:4 ratio. The case group were STEMI patients with FWR, and the control group were STEMI patients without FWR.

The definition of STEMI was based on the guideline of STEMI in 2017 from European Society of Cardiology, following the following criteria: ongoing ischemic symptoms; typical rise or fall in cardiac biomarkers; and a new ST elevation in two or more contiguous leads with leads V1, V2, and V3 measuring at least 0.2 mV or at least 0.1 mV in the remaining leads, or new developed left bundle-branch block pattern [16]. The diagnosis of FWR was based on clinical manifestations or examination results (echocardiography showed massive pericardial effusion and diagnostic pericardiocentesis showed bloody fluid) or surgery results or necropsy.

The study was approved by the ethics committee of Beijing Anzhen Hospital (Beijing, China). All the procedures we followed were in line with the Helsinki Declaration of 1975, as amended in 2008.

Data collection

Baseline demographic, clinical characteristics and medical history of patients were collected from the medical records of the recruited patients. The parameters of peripheral blood samples were provided from the first blood routines and biochemistry examination results of the patients after admission.

Statistical analysis

The expression of variables following a normal distribution were mean $\pm$ standard deviations (SD). As non-normally distributed variables, which were expressed as median (interquartile range). Variables following a normal distribution were compared by using the Student's t-test. The skewed data was compared by the means of the Mann-Whitney U test. For comparison of the distributions of variables between groups, Chi-square or Fisher exact tests was used. The logistic regression analyses were used to calculate the association between FWR and variables. $P < 0.05$ was regarded as statistically significant. IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA) was used to be the statistical analysis.

RESULTS

Baseline patient characteristics

In the 6,712 consecutive patients with STEMI, 78 patients were identified FWR (1.2%) and 28 patients were identified ventricular septal rupture. Sixty-five cases were diagnosed with instantaneous circulatory collapse, with massive pericardial effusion and cardiac tamponade.

Thirteen patients were characterized by sudden clinical condition changes (such as syncope, transient EMD, etc.) or hypotension with moderate/massive pericardial effusion and pericardiocentesis showing bloody fluid. The in-hospital mortality of FWR was 92.3%. FWR typically occurred within the first week after the infarct. Sudden rupture with massive hemorrhage into the pericardial cavity, followed by circulatory collapse was seen in 83.3% of FWR. Among all FWR patients, 79.5% had electromechanical dissociation at the time of FWR onset. Baseline demographic, medical history, clinical characteristics, routine and biochemistry examination results and drug or reperfusion treatment strategies of patients were demonstrated in Table 1.

The proportion of patients with higher age, female and non-smoking was significantly higher in the FWR group than in the STEMI group ($P<0.001$). The proportion of patients taking ACEI/ARB or β -blockers or receiving primary PCI were significantly higher in the STEMI group ($P<0.001$). Similarly, there was also a parallel trend in the intake of aspirin combined with thienopyridine or statin. The FWR group had lower systolic blood pressure, faster heart rate and Killip class III or IV were more frequently compared with the STEMI group. More patients with lower hemoglobin counts were found in the FWR group ($P<0.001$). The WBC count was $(11.3\pm 3.2) \times 10^9/L$ in the FWR group: significantly higher than those of the STEMI group which was $(10.4\pm 3.0) \times 10^9/L$ ($P=0.025$).

In addition, we separately classified patients who underwent primary PCI. The results showed that compared with patients who did not develop FWR and underwent primary PCI, the final TIMI flow of patients who developed FWR decreased significantly (2.737 ± 0.452 vs 2.898 ± 0.3033 , $P=0.0356$), the “door to balloon” time of patients who developed FWR was slightly but not statistically significantly higher (120.8 ± 63.22 vs 115.3 ± 78.25 , $P=0.7679$).

Elevated neutrophil counts mainly attributed to elevated WBC counts

Further analysis of neutrophil, lymphocyte and monocyte revealed a meaningful difference in the proportion of neu-

trophil between the FWR and the STEMI group ($P=0.009$), while lymphocyte and monocyte showed no statistically significant difference. These data are shown in Figure 1. At the same time, the percentage of neutrophil/WBC was statistically different between the two groups ($P<0.05$). However, compared with the FWR group, the monocyte and lymphocyte counts were not significantly different in the STEMI group. When it came to neutrophil/lymphocyte (N/L), the FWR group had more patients with high N/L, whereas the STEMI group had more patients with lower N/L ($P<0.05$).

TABLE 1.
PATIENT CHARACTERISTICS.

Variables	STEMI group* (n=312)	FWR group*	P value
Age, years	57.0 [49.0, 62.0]	73.0 [67.5, 79.0]	<0.001
Male	271 (86.9)	35 (44.9)	<0.001
Smoking	209 (67.0)	24 (30.8)	<0.001
Alcohol	88 (28.2)	14 (17.9)	0.083
Hypertension	166 (53.2)	47 (60.3)	0.309
Diabetes	76 (24.4)	23 (29.5)	0.383
Prior MI	29 (9.3)	6 (7.7)	0.826
Anterior myocardial infarction	157 (50.3)	51 (65.4)	0.022
Time from onset to admission [†] (h)	6.0 [4.0, 12.0]	6.0 [3.0, 11.3]	0.523
SBP (mmHg)	120.0 [110.0, 132.0]	115.0 [103.0, 26.5]	0.010
Heart rate (bpm)	72.0 [65.0, 79.0]	79.5 [65.0, 92.3]	0.006
Killip class III or IV	33 (10.6)	18 (23.1)	0.008
WBC ($10^9/L$)	10.4 ± 3.0	11.3 ± 3.2	0.025
Neutrophils ($10^9/L$)	8.1 ± 3.1	9.1 ± 3.1	0.009
Lymphocytes ($10^9/L$)	1.7 ± 1.1	1.6 ± 2.0	0.753
Monocytes ($10^9/L$)	0.5 ± 0.3	0.6 ± 0.4	0.129
Hemoglobin (g/L)	147.0 [137.0, 158.0]	133.0 [121.0, 140.0]	<0.001
Platelet count ($10^9/L$)	216.0 [189.0, 252.0]	211.5 [170.0, 248.5]	0.217
Aspirin + Thienopyridine	310 (99.4)	72 (92.3)	0.001
Anticoagulants	298 (95.5)	71 (91.0)	0.155
ACEI/ARB	223 (71.5)	24 (30.8)	<0.001
β -blockers	244 (78.2)	41 (52.6)	<0.001
Statin	298 (95.5)	65 (83.3)	0.001
Primary PCI	207 (66.3)	19 (24.3)	<0.001
Thrombolysis	11 (3.5)	6 (7.7)	0.121
Conservative treatment	94 (30.1)	53 (67.9)	<0.001

*Data given as No. (%), mean $\pm$ SD or median [IQR].

[†]Time from onset to admission refers to the time between the onset of STEMI and admission to the hospital.

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell

FIGURE 1.
COMPARISON OF WBC AND ITS SUBTYPES LEVEL BETWEEN STEMI AND FWR GROUPS.

A, B, D, E: WBC, neutrophil, monocyte and lymphocyte counts in the two groups. C: Percentage of neutrophil. F: Ratio of neutrophil/lymphocyte. Abbreviations: FWR, free wall rupture; STEMI, ST-elevated myocardial infarction; WBC, white blood cell. *P < 0.05.

Younger FWR patients had higher neutrophil counts

By drawing the scatter plot of all FWR patients, we found that there was a correlation between the age and neu-

trophil counts ($P=0.0109$). The neutrophil counts were higher in the ≤ 75 -year-old age group compared with those in the >75 -year-old age group ($P=0.0387$), as shown in Figure 2.

FIGURE 2.
RELATIONSHIP BETWEEN NEUTROPHIL COUNTS AND THE AGE IN FWR PATIENTS.

A: Correlation existed between the age and neutrophil level in FWR patients. B: Comparison of neutrophil count in the ≤ 75 -year-old age group and the >75 -year-old age group. Abbreviation: FWR, free wall rupture. *P < 0.05.

Neutrophil counts related to the time to FWR after STEMI

Among the 78 patients with FWR, accurate rupture times were available for 72 patients. The median time from the onset of STEMI to FWR was 36.50 [14.75, 108.75] hours and for the FWR patients: 55.6% occurred within the first 48 hours after STEMI. As shown in Figure 3A, there was no correlation between the number of neutrophil and the time from myocardial infarction attack to FWR. However, the neutrophil counts in FWR patients decreased while the time from onset of STEMI to FWR increased. Further dividing these patients with cardiac rupture into FWR ≤ 48 h group and FWR >48 h group, we found that there was a significant difference in neutrophil counts between the early rupture and late rupture groups (Figure 3).

FIGURE 3.
RELATIONSHIP BETWEEN NEUTROPHIL COUNTS AND THE TIME TO FWR.

A: Neutrophil counts related to the time to FWR after STEMI. B: Comparison of neutrophil counts in FWR ≤ 48 h and FWR >48 h groups. Abbreviations: FWR, free wall rupture; STEMI, ST-elevated myocardial infarction; * $P < 0.05$.

Increased neutrophil was an independent risk factor for FWR

Logistic regression analysis used data on clinical characteristics on admission (age, gender, smoking, infarction site, blood pressure, heart rate, Killip class, medical and reperfusion treatment, count of neutrophil and hemoglobin level). Complete data were obtained from 78 FWR patients. By logistic regression analysis, the age, gender, heart rate, ACEI/ARB, primary PCI and count of neutrophil had statistical significance. The independent predictors of FWR are as follows: age ≥ 75 years (odds ratio (OR) 52.883, confidence interval (CI) 14.054-198.995); female gender (OR 6.211, CI 2.151-17.857); heart rate ≥ 80 bpm (OR 3.836, CI 1.577-9.332); use of ACEI/ARB in the first 24 h (OR 0.216, CI 0.094-0.493); treatment of primary PCI (OR 0.222, CI 0.098-0.502); and neutrophil counts $\geq 9 \times 10^9/L$ (OR

2.404 CI 1.055-5.477). Data are shown in Table 2.

DISCUSSION

The major finding of our study was that the WBC count was higher in the FWR patients than those in the STEMI group, and these increased neutrophil counts were the main cause of the elevated WBC counts. Elevated neutrophils were found to be an independent risk factor for FWR, and the younger the patients were and the shorter the time between admission and FWR, the higher these neutrophil levels. Neutrophil count may be a direct and convenient predictor of FWR and shows promise as a method for investigating pathogenesis and treatment measures in STEMI patients.

In recent years, cardiac inflammatory response, damage to extracellular matrix and blunted fibrotic healing were considered primary mechanisms of heart rupture and acute ventricular remodeling [17]. Systematic inflammatory response could be activated after AMI, accompanying a mass of inflammatory cells infiltration in the heart [10]. Excessive inflammatory response was an important pathological mechanism of post-infarct rupture. Abundant inflammatory cells infiltration, inflammatory factors expression and matrix metalloproteinases secretion caused the degradation of extracellular matrix, then leading to rupture [12]. Some articles have revealed that inflammatory cells infiltration and hemorrhage were key histopathology by observation of the heart from rupture and non-rupture patients through microscopic pathology [18-20]. Qian et al. indicated that elevated leukocyte

TABLE 2.
LOGISTIC REGRESSION ANALYSIS.

Variables	Univariate analysis		Multivariate analysis	
	OR [95% CI]	P value	OR [95% CI]	P value
Age ≥75 years	33.638 [13.318, 84.961]	<0.001	52.883 [14.054, 98.995]	<0.001
Female	8.130 [4.673, 14.084]	<0.001	6.211 [2.151, 17.857]	0.001
Smoking	0.219 [0.128, 0.374]	<0.001		
Anterior myocardial infarction	1.865 [1.112, 3.126]	0.018		
SBP ≥120 mmHg	0.725 [0.433, 1.212]	0.219		
Heart rate ≥80 bpm	3.105 [1.858, 5.190]	<0.001	3.836 [1.577, 9.332]	0.003
Killip class III or IV	2.536 [1.339, 4.803]	0.004		
Aspirin + Thienopyridine	0.077 [0.015, 0.391]	0.002		
ACEI/ARB	0.177 [0.103, 0.304]	<0.001	0.216 [0.094, 0.493]	<0.001
β-blockers	0.309 [0.184, 0.519]	<0.001		
Statin	0.235 [0.105, 0.523]	<0.001		
Primary PCI	0.163 [0.093, 0.288]	<0.001	0.222 [0.098, 0.502]	<0.001
Neutrophils ≥9 (10 ⁹ /L)	2.175 [1.309, 3.614]	0.003	2.404 [1.055, 5.477]	0.037
Hemoglobin ≤120 g/L	4.443 [2.181, 9.052]	0.001		

Data given as mean ± SD or median [IQR].

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; IQR, interquartile range; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell counts

was a risk factor for FWR after AMI in a retrospective study [21]. Leukocytes were activated in patients with AMI, showing more active transcription of inflammatory genes [22]. Aging, gender and other factors were also associated with heart rupture as they affect inflammatory response and infiltration of inflammatory cells in mice with ligated left anterior descending arteries [23,24]. Inhibition of inflammation, including inhibition of production of inflammatory cytokines or infiltration of inflammatory cells, could significantly reduce the incidence of rupture after AMI [25,26]. The bone morphogenetic protein antagonist Gremlin 2 could limit the magnitude and extent of inflammatory cell infiltration by suppressing canonical bone morphogenetic protein signalling, controlling the adverse effects of excessive inflammation response after AMI, and thereby improving the heart function [27]. Toll-like receptor 7 (TLR7) deficiency could decrease cardiac inflammation, prevent ventricular rupture, attenuate ventricular remodeling and preserve cardiac function after MI [28], whereas toll-like receptor 9 (TLR9) prevented rupture following AMI without inflammation in mice [29]. CD8⁺ T-cells were a double-edged sword: on the one hand, they improved the cardiac physiology and brought a better overall survival; on the other hand, they increased innate inflammation and poor scar formation, leading to higher incidence of cardiac rupture [30].

The number and status of different leukocyte subsets also changed profoundly. In the rupture model of mice, previous studies have proved in the infarct and border zone, neutrophil constituted the main type of infiltrated cells in the first 24–48h, following by a marked accumulation of monocytes/macrophages in 3–4 days. Macrophages and lymphocytes still expressed up to 4 weeks after AMI, but with a transient decrease [7,23,31,32]. Previous studies have shown in the rupture and control group with AMI, the measurement of inflammatory cell infiltration and matrix metalloproteinase-9 (MMP-9) expression, which were indexes of the extent of inflammation, could trend differently [18]. Zidar et al. observed that in autopsy samples of infarcted heart tissue of human, the count of interstitial

neutrophils was higher in the FWR between the 2nd and 7th days than in cases without FWR, but there was no difference in histologic characteristics within 24 hours between the two groups [33]. Indeed, neutrophil was found to be an important constitution of innate immune system; by releasing reactive oxygen species and matrix-degrading enzymes, neutrophil infiltrated coronary artery plaque and infarcted myocardium and mediated tissue injury after AMI [34]. The increase of MMP-9 in myocardium after AMI mainly caused by the infiltration and release of neutrophil, which increased as early as 1 day and peaked at 3–4 days after AMI [23,35]. Heymans et al. confirmed that MMP-9^{-/-} mice significantly reduced the incidence of rupture after AMI (7% vs. 33%) [36]. Gong et al. found that the expression of MMP-9 was reduced in trimetazidine-treated mice after AMI, and the occurrence of post-infarct rupture was decreased, too [37]. Our study also indicated that neutrophil counts were markedly increased in the early stage of myocardial infarction in the peripheral blood samples, and the shorter of the time to occurrence of FWR, the higher the level of neutrophil infiltration.

As a marker of inflammatory reaction, leukocytosis was a powerful predictor for the death from AMI [38]. A high neutrophil count had been found to be associated with mortality and major clinical adverse outcomes in pa-

tients with acute coronary syndrome [39]. The neutrophil counts were higher than the leukocyte counts. When N/L quintiles were in the fourth (5.51-8.79) and fifth (8.84-67.9) quintile, the incidence of death had increased 2.5- and 4.2-fold versus those in the first (1.09-2.76) quintile [38]. Horne et al. described an elevated risk of myocardial infarction or mortality in 3,227 patients who were in the fourth quartile of N/L compared with those in the first quartile, suggesting that in addition to leukocyte counts, N/L was also related to prognosis [40]. As a main cause of death after AMI, FWR deserves our attention. Neutrophils may be a potential marker for clinical outcomes in patients with STEMI; by measuring the count of neutrophils in the early phase after AMI, we may be able to predict the prognosis.

As an independent risk factor of FWR, high neutrophil counts detected upon admission to hospital could be suggestive of FWR (underlying mechanism shown in Figure 4). The possibility of early identification of patients at high-risk of FWR post STEMI and application of early prevention and treatment measures is of great significance to reducing the incidence of FWR and in-hospital mortality, improving the survival rate and life quality of STEMI patients, and reducing the social and economic burden. In addition, our study suggests that neutrophils played an important role in FWR, providing an important basis for studying the pathogenesis of FWR and exploring prevention and treatment strategies. Previous studies have suggested that systematic inflammatory

response markers could be used as predictors of rupture after STEMI [4]. However, at present, it is still difficult to determine whether FWR occurs in STEMI patients by detecting systematic inflammatory response markers.

In the future, we can integrate scientific scoring methods to accurately predict FWR by studying and evaluating the predictive value of different components of systemic inflammatory response markers. To some extent, β -blockers could reduce the risk of FWR in patients with AMI [41], but studying key factors in the inflammatory response of FWR after STEMI is crucial to choose and design better treatments.

LIMITATIONS

There were several limitations to this study. First, it was a single-center retrospective study; therefore, some data were subject to inherent limitations and potential biases. These included collection of potential biases, incomplete or missing information and non-randomized data. Second, we focused on the in-hospital patients and thus did not include pre-hospital and out-of-hospital patients. Third, for severely ill cases and for cases with short admission times, the weights of many of the FWR patients were missing. Fourth, this study focused on the influence of neutrophils counts. Other factors, such as inflammation response, oxidative stress, matrix metalloproteinase and collagen fibers, which have also been found related to FWR, need to be further explored.

FIGURE 4.
ROLE OF NEUTROPHIL IN CARDIAC RUPTURE.

Abbreviations: ECM, extracellular matrix; ICAM-1, intercellular adhesion molecule-1; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-8, interleukin-8; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; NF- κ B, nuclear factor (NF)- κ B; TLRs, toll-like receptors; TNF- α , tumor necrosis factor- α ; VCAM-1, vascular cell adhesion molecule; PAF, platelet active factor.

CONCLUSIONS

Leukocyte count was significantly higher in the FWR group than the control STEMI group, mainly due to elevated neutrophil counts. Elevated neutrophil counts was an independent risk factor for FWR, and the younger the patient and the earlier the FWR occurred post-hospital admission, the higher the neutrophil counts. Our study suggests that neutrophils played a crucial role in FWR, and this finding provides an important basis for studying the pathogenesis of FWR and for exploring prevention and treatment strategies.

FUNDING

This study was supported by grants from the National Natural Science Foundation of China (81970292, 81600213 and 81670222). Beijing Natural Science Foundation (7191002). Beijing Hospitals Authority Youth Program (QML20190603). Capital's Funds for Health Improvement and Research (2018-1-2061). CS Optimizing Antithrombotic Research Fund (BJUHFCSOARF201901-08). Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201710), Beijing Municipal Administration of Hospitals' Ascent Plan (DFL20180601).

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