Risk factors for in-hospital systemic thromboembolism in myocardial infarction patients with left-ventricular thrombus
A multicenter retrospective study

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Abstract
Left-ventricular thrombus (LVT) is a potentially life-threatening disease. However, few studies have explored the risk factors of in-hospital systemic thromboembolism (ST) in LVT patients. In this multicenter retrospective study, we enrolled myocardial infarction patients with LVT from January 2008 to September 2021. Multivariable logistic regression analysis was applied to identify the independent risk factors for ST in LVT patients. A total number of 160 hospitalized LVT patients [median follow-up period 50 months (18.3–82.5 months)] were subjected to analysis. Of them, 54 (33.8%) patients developed acute myocardial infarction, 16 (10%) had ST, and 33 (20.6%) died. Comparable baseline characteristics were established between the ST and non-ST groups, except for the heart failure classification ($P = .014$). We obtained the following results from our multivariable analysis, based on the use of HFpEF as a reference: HFpEF [odds ratio (OR), 6.2; 95% confidence interval (CI), 1.4–26.3; $P = .014$] and HFmrEF (OR, 5.0; 95% CI, 1.1–22.2; $P = .033$). In conclusion, HFpEF, and HFmrEF may be independent risk factors for in-hospital ST development.

Keywords: HFmrEF, HFpEF, left-ventricular thrombus, retrospective study, risk factors, systemic thromboembolism

1. Introduction

Left-ventricular thrombus (LVT) is a potentially life-threatening condition that may predispose to systemic thromboembolism (ST), that is, emboli in the arterial circulation.\textsuperscript{[1]} ST was reported to be associated with an acute mesenteric ischemia, stroke, limb ischemia and renal emboli.\textsuperscript{[2]} According to previous studies, the occurrence rate of ST in LVT patients ranged from 7% to 16%.\textsuperscript{[3,4]} Therefore, early prevention of ST development in clinics is critically essential.

As known, LVT might complicate ischemic cardiomyopathy or other severe left-ventricular systolic dysfunction.\textsuperscript{[3]} Previous study suggested that deteriorated ejection fraction (EF), severe regional wall motion abnormalities, and left ventricular aneurysm were independent risk factors of LVT after myocardial infarction.\textsuperscript{[4]} Thanks to the widespread application of emergent primary percutaneous coronary intervention, the incidence of LVT post- anterior myocardial infarction was dramatically decreased from 57% to 3% dramatically. It was acknowledged that anticoagulation regimens including vitamin K antagonists, parenteral heparins, and direct oral anticoagulants were associated with LVT regression. Post-diagnosis, the standard anti-coagulation treatment was effective with a 33% absolute risk reduction.\textsuperscript{[5]} Therefore, identification and management of risk factors for LVT is of vital importance for this disease prevention and treatment.

Previous studies have evaluated the predictors for thrombus genesis,\textsuperscript{[6–9]} but most of the published data were obtained from case reports.\textsuperscript{[10–16]} For example, Paolo Rubartelli et al reported that hypercoagulable state and myocardial dysfunction contributed to LVT formation in COVID-19 patients. Additionally, a recent meta-analysis showed anticoagulation and triple therapy were independent predictors of lower rates of embolic events in LVT. However, due to limited clinical data, evaluation of the predictors are not sufficient. Therefore, the evaluation of the risk factors based on clinical characteristics of LVT for in-hospital ST may be a valuable strategy for ST prevention at the early stage.

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Therefore, in the present study, we aimed to explore the potential independent risk factors for in-hospital ST development.

2. Methods

2.1. Study design and population

This multicenter retrospective study included hospitalized patients with LVT in four centers from January 2008 to September 2021. LVT was confirmed by transthoracic echocardiography. Additionally, some of the patients underwent concurrent cardiac computed tomography and left-ventricular 3-D reconstruction to reconfirm the LVT diagnosis (Fig. 1). The following inclusion criteria were applied: patients with acute myocardial infarction or a history of acute myocardial infarction; in-hospital thrombus genesis; ≥18 years old. The exclusion criteria were as follows: history of atrial fibrillation or atrial flutter; malignant diseases such as leukemia, connective tissue disease, or solid tumors; thrombus in cardiac chambers other than the left ventricle; Patent foramen ovale or valve disease. This study was conducted in compliance with the Declaration of Helsinki and was approved by the Research Ethics Board of Changzhou No. 2 People’s Hospital, Yixing People’s Hospital, Nanjing First Hospital, and Changzhou People’s Hospital No. 1.

2.2. Data collection and definition

Clinical characteristics data, including age, gender, diabetes, acute ischemic phase, myocardial infarction history, cerebral infarction history, hypertension, renal function, liver function, chronic obstructive pulmonary disease, LVT characteristics (diameter, mobility, density, lobe number, and echo characteristics), left ventricular end-diastolic diameter, heart failure classification, and D-dimer levels were extracted from medical records. The follow-up results were also obtained from medical records.

LVT was defined as the presence of a well-defined echogenic left-ventricular mass with an echo texture different from that of the underlying endocardium, identifiable in at least two different views. Considering the false-positive value of TTE, we excluded data with spontaneous echo contrast, which could indicate the presence of a local hypercoagulable or even pre-thrombotic state. The average diameter of the thrombus was defined as the average of the long and short diameters. All echocardiogram findings were confirmed by two independent echocardiologists. According to the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, reduced EF, which is designated as HFrEF, is defined as EF ≤40%, mildly reduced EF, denoted as HFmrEF, is defined as EF between 41% and 49%, and heart failure with preserved EF, indicated as HFrEF, is defined as EF ≥50%.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software (version 20, IBM, Armonk, NY). Data for normally distributed continuous variables were expressed as mean ± standard deviation, whereas variables with a skewed distribution were expressed as median (interquartile range, IQR). Continuous variables were analyzed using the Student’s t test. Categorical variables were presented as counts and percentages, and the differences between groups were analyzed using the chi-squared test and the Fisher’s exact test where appropriate. Univariable logistic regression analysis was performed, and variables with P values <.15 were retained in the multivariable logistic regression analysis (enter mode). A two-tailed P value <.05 was considered to indicate statistically significant differences.

3. Results

A total number of 204 LVT patients were included, 23 patients were excluded for dilated cardiomyopathy or other non-ischemic diseases. Sixteen patients were excluded due to atrial fibrillation, and five patients were excluded for unreliable study site data. Finally, 160 LVT patients hospitalized at Changzhou People’s Hospital No. 2 (n = 59, 36.9%), Yixing People’s Hospital (n = 25, 15.6%), Nanjing First Hospital (n = 38, 23.8%), and Changzhou People’s Hospital No. 1 (n = 38, 23.8%) were included for analysis (Fig. 2). Of them, 140 were male, 54 had acute myocardial infarction, and 16 developed ST. The patients underwent a median follow-up period of 50 months (18.3–82.5 months).

The baseline characteristics of non-ST and ST patients were comparable, except for the heart failure classification data (P = .014) (Table 1). Univariable analysis was applied to identify potential ST-associated variables. Multivariable analysis yielded the following results: HFrEF [odd ratio (OR), 6.2; 95% confidence interval (CI), 1.4–26.3; P = .014] and HFmrEF (OR, 5.0; 95% CI, 1.1–22.2; P = .033) when using HFrEF as a reference (Table 2).

4. Discussion

The findings of the present case-control study suggested that HFmrEF and HFrEF were potential risk factors for ST occurrence, which may lead to change in the prevention and treatment strategies implemented in patients with LVT without atrial fibrillation.

According to a previous study, the incidence of LVT was 7 per 10,000 patients, and 8% of them were with ischemic stroke. In addition, LVT was detected by echocardiography in less than 3% of the patients. To the best of our knowledge, the sample size of the present study is the largest of those of the studies reporting outcomes of patients with LVT in ischemic cardiomyopathy without atrial fibrillation.
The incidence of ST in LVT was reported to range from 3.8% (1/26) to 33.3% (5/15),[20] which might have been due to the small sample size. Given the follow-up and diagnostic bias, this research evaluated only in-hospital ST. Because of the low prevalence of LVT, we reviewed data collected at four centers during the last 13 years to identify factors significantly associated with acute ST. Considering the biased nature of this disease diagnosis (i.e., stress-induced cardiomyopathy, isolated left chamber noncompaction cardiomyopathy, peripartum cardiomyopathy, inflammatory bowel disease, Behcet Disease, and leukemia)[21–23] this research focused only on ischemic heart disease without the history of atrial fibrillation. Therefore, we reviewed and assessed variables related to individual characteristics (such as a history of hypertension, diabetes, age, and gender) and thrombus morphology (location, diameter, density, and mobility).

Previous studies showed that LVT formation was significantly associated with lower EF.[13,24,25] However, in this investigation, HFmrEF and HFpEF were found to be independent risk factors for in-hospital ST, which indicated that the thrombus can easily be detached. In patients with HFpEF or HFmrEF, the compensatory motion of the ventricular wall in the non-infarct area is enhanced, and the contradictory motion is more prominent, which may increase the likelihood for thrombus detachment. Several meta-analyses showed that the routine use of warfarin for prophylaxis against LVT formation following an anterior STEMI was not beneficial in the reduction of mortality and stroke rates.[26,27] Therefore, standard anticoagulation was recommended after the LVT genesis.[23] It is commonly accepted that mobile, protruding, pedunculated, and fresh thrombi are more likely to embolize vessels.[29] However, in the present study, none of these features was statistically confirmed. This condition may be partly due to the limited sample size and low LVT incidence; therefore, further hemodynamic analysis might be required.[30]

This study is not without limitations. First, it is retrospective, which might have led to bias. Second, although the sample was the largest among those of the previous ones, the number was still low, which might have diminished its statistical power. Third, in-hospital ST is a complex disease caused by many factors, such as the left-ventricular pressure and the systole duration. In addition, due to the fact that all patients before enrollment did not have had atrial fibrillation and were not anticoagulated prior to diagnosis, they were recommended to administrate low molecular weight heparin/oral anticoagulant drugs. LVT of all patients occurred during hospitalization, thus this study may not be generalized.

5. Conclusions
In conclusion, to prevent ST occurrence, special attention should be paid to atrial fibrillation-free LVT patients with HFmrEF and HFpEF. Further studies with large sample sizes are needed to confirm the results of the present research.

Author contributions
Zhou, Shi, Ye, Ji, Yang, Huang collected the patient data from four centers. Huang reevaluated the TTE images. Zhou and Huang were major contributors in writing the manuscript. All authors read and approved the final version of the manuscript.

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Zhou et al.  •  Medicine (2022) 101:41

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Table 1

Patient characteristics.

|                      | No. of acute ST (N = 16) | No. of non-ST (N = 144) | P value |
|----------------------|--------------------------|-------------------------|---------|
| Clinical characteristics |                          |                         |         |
| Age ≤55              | 3 (7.9%)                 | 35 (92.1%)              | .764    |
| Age >55              | 13 (10.7%)               | 109 (89.3%)             |         |
| Age                  | 64.6 ± 9.4               | 63.7 ± 12.7             | .794    |
| Male                 | 14 (10.0%)               | 126 (90.0%)             | 1.000   |
| Female               | 2 (10.0%)                | 18 (90.0%)              | .058    |
| Chronic phase        | 14 (13.2%)               | 92 (86.8%)              |         |
| Acute phase          | 2 (3.7%)                 | 52 (96.3%)              | .102    |
| Diabetes             | 9 (15.0%)                | 51 (85.0%)              |         |
| Non-diabetes         | 7 (7.0%)                 | 93 (93.0%)              | .792    |
| Hypertension         | 10 (6.6%)                | 90 (93.4%)              |         |
| Non-hypertension     | 7 (9.3%)                 | 68 (90.7%)              |         |
| Chronic renal failure, CRF | 2 (6.5%)              | 29 (93.5%)              | .739    |
| Non-CRF              | 14 (10.9%)               | 115 (89.1%)             |         |
| Thrombus characteristics |                        |                         |         |
| Diameter ≤20 mm      | 9 (10.3%)                | 78 (89.7%)              | .869    |
| Diameter >20 mm      | 6 (9.5%)                 | 57 (90.5%)              |         |
| Diameter (mm)        | 1.7 (1.5, 2.3)           | 1.9 (1.5, 2.4)          | .531    |
| Mobile thrombus      | 3 (23.1%)                | 10 (76.9%)              | .126    |
| Immobile thrombus    | 13 (8.6%)                | 134 (91.4%)             |         |
| Low density          | 12 (11.9%)               | 90 (88.2%)              | .324    |
| Density              | 4 (6.9%)                 | 54 (93.1%)              |         |
| Unilobe              | 16 (10.3%)               | 139 (89.7%)             | 1.000   |
| Multilobe            | 0                       | 5 (100.0%)              |         |
| Echo characteristics |                          |                         |         |
| LVEDD ≤55 mm         | 8 (13.8%)                | 50 (86.2%)              | .263    |
| LVEDD >55 mm         | 6 (5.2%)                 | 90 (91.8%)              |         |
| LVEDD (mm)           | 54.0 (48.3, 59.0)        | 58.0 (52.0, 62.0)       | .096    |
| HF classification    |                          |                         |         |
| HFpEF                | 3 (3.8%)                 | 77 (96.3%)              | .014*   |
| HFmrEF               | 7 (18.9%)                | 30 (81.1%)              |         |
| HFrEF                | 6 (14.6%)                | 35 (85.4%)              |         |
| Laboratory test      |                          |                         |         |
| D-dimer ≥0.5         | 13 (13.1%)               | 86 (86.9%)              | .145    |
| D-dimer <0.5         | 2 (4.3%)                 | 44 (95.7%)              |         |

HFpEF = heart failure with preserved EF (LVEF ≥50%), HFmrEF = heart failure with mid-range EF (LVEF: 41%–49%), HFrEF = heart failure with reduced EF (LVEF ≤40%), LVEDD = left ventricular end-diastolic diameter, LVFW = left-ventricular posterior wall width, ST = systemic thromboembolism.

Table 2

Logistic regression analysis of in-hospital systemic thromboembolism.

|                          | Univariate logistic regression | Multivariate logistic regression |
|--------------------------|--------------------------------|---------------------------------|
|                          | OR                             | P value                         | OR                             | P value                         |
| Age                      | 1.0 (1.0, 1.0)                 | .793                            | 0.3 (0.1, 1.3)                 | .104                            |
| Chronic phase            | 0.3 (0.1, 1.2)                 | .076                            | 0.3 (0.1, 1.3)                 | .144                            |
| Diabetes                 | 0.4 (0.2, 1.2)                 | .110                            | 0.3 (0.1, 1.3)                 | .444                            |
| Mobile thrombus          | 0.3 (0.1, 1.3)                 | .117                            | 0.9 (0.9, 1.0)                 | .136                            |
| LVdD                     | 0.9 (0.9, 1.0)                 | .041                            | 0.6 (1.5, 24.7)                | .013                            |
| HFpEF                    | 6.0 (1.5, 24.7)                | .013                            | 6.2 (1.4, 26.3)                | .014*                           |
| HFmrEF                   | 6.4 (1.0, 18.6)                | .044                            | 5.0 (1.1, 22.2)                | .033*                           |

HFpEF = heart failure with preserved EF (LVEF ≥50%), HFmrEF = heart failure with mid-range EF (LVEF: 41%–49%), HFrEF = heart failure with reduced EF (LVEF ≤40%).


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