Prognostic value of D-dimer in acute myocardial infarction complicated by heart failure with preserved ejection fraction

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Abstract

Aims The prevalence of heart failure (HF) after acute myocardial infarction (AMI) is common. Contemporary data are lacking on the prognostic utility of the measurement of biomarker for patients with AMI complicated by HF according to preserved (HFP EF) and reduced ejection fraction (HFrEF). We aim to assess the association between D-dimer levels and all-cause mortality in patients with AMI complicated by different HF subtypes during hospitalization in the context of other risk factors.

Methods and results We enrolled 4495 patients with AMI with complete clinical and laboratory variable assessments in this cohort. D-dimer levels were measured on admission immediately at baseline. We used Cox proportional hazards analysis to assess this association accounting for 18 relevant clinical variables. During the index hospitalization, 589 patients with AMI developed HFP EF, 513 patients with AMI developed HFrEF, and 3393 patients with AMI did not develop HF. The patients were divided into HFpEF, HFrEF, and non-HF groups accordingly. The median length of follow-up was 1 year (range: 1 to 24 months). During the whole follow-up, 58 (15.5%), 107 (27.9%), and 96 (4.2%) of the patients experienced death event in HFpEF, HFrEF, and non-HF groups, respectively. In each group, the patients were divided into high or low D-dimer levels according to D-dimer concentration (145 ng/mL). In the fully adjusted model, the risk of all-cause mortality of those patients with high D-dimer levels was 2.09 [95% confidence intervals (CI): 1.08 to 4.02, \( P = 0.02 \)] times as high as the risk of patients with low D-dimer levels in HFpEF group. When analysing D-dimer as a continuous variable, this associations still existed. But there was no significant association between D-dimer concentration and all-cause mortality in HFrEF [hazard ratio (HR): 1.25, CI: 0.76 to 2.04, \( P = 0.37 \)] or non-HF [HR: 1.56, CI: 0.98 to 2.47, \( P = 0.06 \)], respectively, after fully adjustment for other key clinical variables.

Conclusions High D-dimer levels on admission were found to be strongly associated with the subsequent cumulative incidence of all-cause mortality in patients with AMI complicated by HFpEF.

Keywords D-dimer; Acute myocardial infarction; Heart failure with preserved ejection fraction; Mortality; Survival

Introduction

Heart failure (HF) is common after acute myocardial infarction (AMI)¹,² which is considered to be one of its major precursors (contributing to more than 50% of HF in patients).³,⁴ The occurrence of acute HF in patients with AMI is recognized as a significant predictor of increased morbidity and mortality.⁵,⁶ However, important changes in the epidemiology of HF after AMI have taken place over the last few decades, characterized by a decline in its incidence¹ and a change in the case mix according to left ventricular dysfunction, characterized by an increasing
proportion of HF cases presenting with preserved ejection fraction, for which treatment benefits are less established and its mortality rate is comparable to that of patients with reduced EF. Heart failure with preserved ejection fraction (HFrEF) and heart failure with reduced ejection fraction (HFrEF) are two distinct HF phenotypes with different etiologic factors and pathophysiologic mechanism and need different treatments as well. Contemporary data are lacking on the prognostic utility of the measurement of biomarker for AMI patients complicated by HF according to preserved/reduced ejection fraction. Thus, a measurement of biomarker that identifies high-risk patients could potentially be applied to identify those patients who may benefit from greater clinical monitoring and alterations in available therapies.

D-dimer, a degradation product of cross-linked fibrin, have been found to be associated with a risk of subsequent thrombotic events, all-cause mortality, and risk of cardiovascular disease, particularly in patients with vascular disease or coronary heart disease. Our previous study also showed that D-dimer was associated with the incidence of HF and all-cause mortality in patients with AMI. In this study, we aim to focus on the prognostic utility of D-dimer assessment in patients with AMI complicated by different HF subtypes during the index hospitalization.

Methods

Study design and data collection

With the support of National Key R&D Program of China, this prospective, hospital-based AMI cohort study has been established since 2017 in the 2nd affiliated hospital of Harbin Medical University. A total of 5041 consecutive patients with diagnosed AMI and written consents on admission, including ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), admitted to the cardiac care unit of the 2nd affiliated hospital of Harbin Medical University were recruited between February 2017 and April 2019. As 195 patients who had prior HF as well as heart valve disease and pericardial constriction, liver disease, infection, uremia, malignancy, deep venous thrombosis or other thrombotic diseases, or had received thrombolysis therapy before admission, and a further 28 patients who had not D-dimer assessment during hospitalization were excluded, then a total of 4818 potentially eligible patients were enrolled.

As a further 314 patients had missing data and 9 patients developed HF with unknown type on admission, in the final count, there were 4495 patients with complete clinical and laboratory variable assessments enrolled in this complete data cohort for all-cause mortality analysis.

Follow up

A total of 4423 patients alive at discharge consented to an additional 1 to 24 months follow-up. All participants were followed up for the occurrence of death through their complete inpatient and outpatient community medical records from the admission to the occurrence of death or date of the last follow-up or 28 May 2020. The regular follow-up visits were at 1, 3, 6, 12, 18, and 24 months. To ensure data quality, the diagnosis of all events was further validated through reviewing medical records by two cardiac doctors. The reconciliation between the two doctors was made if they had a disagreement in the diagnosis. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Harbin Medical University.

Definitions

Acute myocardial infarction was diagnosed if a patient had a rise and/or fall of cardiac troponin I (cTNI) with at least one value exceeding the 99th percentile of a normal reference population with one of the following criteria: chest pain lasting 20 min or longer, diagnostic serial electrocardiographic changes consisting of new pathologic Q waves, or ST-segment and T-wave changes, or new left bundle branch block.

The definition of HF was made mainly based on the Framingham study and 2016 ESC guideline. Patients with HF post-AMI were defined as symptoms of dyspnoea with one or more of the following but without non-cardiac causes of breathlessness: pulmonary rales, oedema of lower limbs, radiographic evidence of pulmonary congestion, third heart sound together with persistent sinus tachycardia, and treatment with diuretic or intravenous vasodilator therapy for HF. Each incident HF event was categorized as HFrEF (LVEF ≥50%), HFrEF (LVEF <50%), or unclassified HF (no LV function assessment available and would be excluded from this study). HFrEF diagnosis was established in AMI patients with the above typical symptoms or signs of HF, NT-proBNP > 300 pg/mL, LVEF ≥ 50%, or other evidences of diastolic dysfunction as evaluated using echocardiography. The key functional alterations are left atrial volume index (LAVI) > 34 mL/m² or increased left ventricular mass index (LVMI) ≥ 95 g/m² in women and ≥115 g/m² in men, plus an E/e' ≥ 13 and a mean e' septal and lateral wall <9 cm/s.

Endpoint

The endpoint was all-cause mortality in patients with AMI complicated by HFrEF, HFrEF, or non-HF, respectively.
Common clinical and laboratory assessments

The blood samples were collected on initial presentation to hospital and prior to administration of anticoagulant or antiplatelet use and PCI and were sent to the laboratory for testing immediately. Baseline population characteristics were collected from medical records, prior medication, and self-reports. Routine blood test, myocardial injury assessment, coagulation function test, liver and nephric function tests, and echocardiography were performed on admission and reviewed when needed. Multivessel disease was defined as at least two major vessels (≥2 mm diameter) with >70% stenosis of the diameter measured by quantitative coronary angiography. Uraemia was defined as a glomerular filtration rate (GFR) of less than 15 mL/min/1.73 m², or the need for treatment with dialysis or transplantation. The estimated GFR (eGFR) was calculated using baseline serum creatinine concentrations. The management of all data and quality control was performed with an electronic data capture system (Thinvent Technology Ltd, Nanchang, China).

Statistical analysis

Continuous variables were presented as median (25th and 75th percentile) and compared using Mann–Whitney U test. Categorical variables were presented as number (percentages) compared using χ² test or Fisher exact test. Normality of continuous variables was assessed by the Kolmogorov–Smirnov test.

The patients with AMI were divided into HFpEF, HFrEF, and non-HF groups. In each group, the patients were divided into high or low D-dimer levels according to D-dimer concentration (145 ng/mL). The cumulative incidence of death of different groups was estimated using Kaplan–Meier method. Univariable and multivariable Cox proportional hazards analyses were constructed to examine the association between D-dimer levels and all-cause mortality in each group. Multivariable Cox regression model adjusted for risk factors that are known to influence the endpoint including sex, age, body mass index (BMI), smoking status, AMI types and the histories of hypertension, diabetes and myocardial infarction, amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity C reactive protein (hs-CRP), cTNI, eGFR, total cholesterol (TC), percutaneous coronary intervention (PCI), and medical treatment. The regression results are reported by per SD increase in D-dimer (as a continuous variable) and reported according to D-dimer binary levels (as a categorical variable) using the low level as the referent to aid in interpretation. A two-tailed P value of <0.05 was considered statistically significant in this study. All the analyses were performed with EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

Results

Patient population

A total of 4495 patients with AMI with complete data were enrolled in this study. During the index hospitalization, 589 patients developed HFrEF, 513 patients developed HFpEF, and 3393 patients did not develop HF. Characteristics of the study population were shown in Table 1. The median length of follow-up was 1 year (range: 1 to 24 months). Patients complicated by HFrEF seemed to have higher level of D-dimer, NT-proBNP, and hs-CRP or lower level of eGFR than patients complicated by HFpEF and followed by patients without HF. Patients complicated by HFpEF also had a higher prevalence of hypertension than patients with HFrEF and followed by patients without HF.

In each group, the patients were divided into high or low D-dimer levels according to D-dimer concentration (145 ng/mL). Patients with high D-dimer levels in each group were more likely to be older and have a lower eGFR, NT-proBNP, and hs-CRP (Table 2).

All-cause mortality

During the whole follow-up, 107 (27.9%), 58 (15.5%), and 96 (4.2%) of the patients experienced death event in HFrEF, HFpEF, and non-HF groups, respectively (Figure 1). In each group, the incidence of death was higher in patients with high D-dimer levels than patients with low D-dimer levels (Supplemental Table).

Cox regression analysis showed that elevated D-dimer was strongly associated with mortality in the unadjusted model in the total AMI population and the patients in different groups (Table 3). We also observed that the risk of all-cause mortality among patients with high D-dimer levels were 1.61 [95% confidence intervals (CI): 1.20 to 2.17, P = 0.002] times as high as the risk among patients with low D-dimer levels for the total AMI population in the fully adjusted model. When analysing D-dimer as a continuous variable, this association remained with a 20% increased risk of all-cause mortality (95% CI: 1.04 to 1.37) for each SD increase in D-dimer.

When divided the patients with AMI into HFpEF, HFrEF, or non-HF groups, we observed that the risk of all-cause mortality among patients with D-dimer values in high levels was 2.09 (95% CI: 1.08 to 4.02, P = 0.02) times as high as the risk among patients with D-dimer values in low levels in HFpEF group after fully adjustment for other variables. When analysing D-dimer as a continuous variable, this association remained with a 43% increased risk of all-cause mortality (95% CI: 1.05 to 1.94, P = 0.024) for each SD increase in D-dimer. But there was no significant association between D-dimer concentration and all-cause mortality in HFrEF [hazard ratio (HR): 1.25, CI: 0.76 to 2.04, P = 0.37] or non-HF
After AMI, HF strongly increases the risk of mortality independently of key confounders, including MI severity, comorbidity, and acute treatment. Patients with HFrEF and HfP EF after AMI shared a similar prognosis. The prevalence of HfP EF relative to HFrEF was rising at an alarming rate of 1% per year, yet survival improved over time for those with reduced EF but not for those with preserved EF. Hence, there is a strong need to identify patients with HfP EF post-AMI who are at high risk of death and improve prevention strategies in the management. What is more, contemporary data are lacking on the prognostic utility of the measurement of biomarker for AMI patients complicated by HF according to preserved/reduced ejection fraction. To the best of our knowledge, our study is the first to evaluate the prognostic utility of D-dimer assessment in AMI patients complicated by different HF subtypes, and we also assess the association among AMI patients complicated by non-HF in addition.

In line with our results, some previous studies conducted in patients with coronary heart disease or acute coronary syndrome also found that D-dimer was predictive for the occurrence of mortality. With respect to the HF population, a study showed that a plasma concentration of D-dimer >250 ng/mL increased almost threefold risk for all-cause mortality during a follow-up period of 6 years in elderly patients with HF. What was different to us is that D-dimer levels were independent of traditional clinical factors and usual biomarkers. In addition, we observed a non-significant association between D-dimer levels and the incidence of all-cause mortality in patients with AMI complicated by HFrEF or non-HF.
Table 2  Patient characteristics at baseline in different groups divided by HF types and D-dimer levels

|                     | HFrEF (n = 513) | Non-HF (n = 3393) |
|---------------------|-----------------|-------------------|
|                     | <145 ng/mL      | ≥145 ng/mL       | <145 ng/mL       | ≥145 ng/mL       |
|                     | n = 294         | n = 295           | n = 200          | n = 313          | n = 2420         | n = 973          | P value          |
| Age (years)         |                 |                   |                 |                   |                   |                   | <0.001           |
| Male                |                 |                   |                 |                   |                   |                   | 0.972            |
| BMI (kg/m²)         | 24.25 (21.90–26.89) | 23.59 (21.83–26.09) | 24.80 (22.12–27.07) | 23.67 (21.48–25.95) | 25.13 (23.04–27.68) | 24.44 (22.22–26.89) | <0.001           |
| Smoking (current + ex) | 170 (57.82)         | 171 (57.97)       | 123 (61.50)       | 178 (64.54)       | 1643 (67.89)       | 628 (64.54)       | <0.001           |
| Hypertension        |                 |                   |                 |                   |                   |                   | 0.176            |
| Diabetes            |                 |                   |                 |                   |                   |                   | 0.924            |
| MI                  |                 |                   |                 |                   |                   |                   | 0.133            |
| AMI types           |                 |                   |                 |                   |                   |                   | 0.004            |
| STEMI               | 202 (68.71)      | 190 (64.41)       | 144 (72)         | 225 (71.88)       | 1612 (66.61)       | 689 (70.81)       | 0.018            |
| CAG                 | 291 (98.98)      | 288 (97.63)       | 188 (94)         | 298 (95.21)       | 2356 (97.36)       | 924 (94.96)       | <0.001           |
| Multivessel disease | 154 (52.38)      | 162 (54.92)       | 114 (57)         | 195 (62.30)       | 936 (38.68)        | 441 (45.32)       | <0.001           |
| PCI                 | 259 (88.10)      | 246 (83.39)       | 167 (83.50)      | 259 (82.75)       | 2027 (83.76)       | 774 (79.55)       | 0.003            |
| LVEDd (mm)          | 45.60 (42.65–48.10) | 45.20 (42.48–46.65) | 52.85 (48.48–57.60) | 52.50 (47–57)    | 45.60 (42.80–48.40) | 45.30 (42.20–48.10) | 0.001            |
| EF (%)              | 59 (55–62)       | 59 (55–62)        | 40.85 (37–45)    | 40.70 (35–45)    | 62 (58–63)         | 61 (56–62)        | <0.001           |
| Laboratory covariates |              |                   |                 |                   |                   |                   |                  |
| eGFR (mL/min/1.73 m²) | 76.88 (62.45–92.03) | 58.87 (42.70–76.20) | 81.40 (66.46–93.59) | 60.63 (43.38–76.38) | 88.48 (74.67–101.75) | 77.96 (63.49–92.96) | <0.001           |
| cTnI (ng/L)         | 48.77 (14.17–120.47) | 37.81 (11.04–126.67) | 74.51 (17.16–146.01) | 54.19 (12.32–163.93) | 26.59 (7.46–77.44) | 34.36 (9.88–93.26) | <0.001           |
| NT-proBNP (pmol/L)  | 3823 (115–5298.50) | 5407 (3241–8668.50) | 4045.50 (1799–7365.25) | 7060 (3873–14 274) | 559.50 (202–1211) | 1069 (425–203)    | <0.001           |
| Hs-CRP (mg/L)       | 6.36 (2.44–12.62) | 11.74 (5.41–14.11) | 11.16 (4.33–13.95) | 12.83 (8.27–14.26) | 3.96 (1.73–9.57) | 7.17 (2.97–12.40) | <0.001           |
| TG (mmol/L)         | 1.36 (0.97–2.02) | 1.27 (0.91–1.81) | 1.29 (0.98–1.79) | 1.28 (0.94–1.77) | 1.44 (0.99–2.11) | 1.32 (0.96–1.86) | <0.001           |
| TC (mmol/L)         | 4.50 (3.79–5.25) | 4.38 (3.73–5.52) | 4.37 (3.78–5.22) | 4.30 (3.60–5.08) | 4.62 (3.98–5.33) | 4.51 (3.89–5.25) | <0.001           |
| Medical treatment   |                 |                   |                 |                   |                   |                   |                  |
| Aspirin             | 289 (98.30)      | 277 (93.90)       | 190 (95)         | 279 (89.14)       | 2387 (98.64)       | 941 (96.71)       | <0.001           |
| Clopidogrel or ticagrelor | 291 (98.98)      | 280 (94.92)       | 192 (96)         | 278 (88.82)       | 2394 (98.93)       | 947 (97.33)       | <0.001           |
| Statins             | 288 (97.96)      | 275 (93.22)       | 191 (95.50)      | 272 (86.90)       | 2358 (97.44)       | 940 (96.61)       | 0.185            |
| ACEI/ARB            | 231 (78.57)      | 216 (73.22)       | 164 (62)         | 212 (67.73)       | 1821 (75.25)       | 668 (68.65)       | <0.001           |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAG, coronary angiography; cTnI, cardiac troponin I; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hs-CRP, high sensitivity C reactive protein; LVEDd, left ventricular end-diastolic dimension; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride.

Values are median (25th and 75th percentile) or number (percentages).
associated with an increased risk of all-cause death irrespective of the subtypes of HF including HFrEF and HfPEF. The difference among these results may be that our study was conducted in the AMI population accompanied by HFpEF, HFrEF, or non-HF during the index admission, but the other studies were only conducted in the pure HF population or coronary heart disease population.

HFpEF and HFrEF are two distinct HF phenotypes with different etiologic factors and pathophysiologic mechanism. Myocardial remodelling of HFpEF differs from HFrEF, where remodelling is driven by loss of cardiomyocyte. The size of myocardial infarct, myocyte loss, and myocardial necrosis are the principal causes of HFrEF development after AMI. However, the development of HFpEF in patients with AMI is complex: Ischaemic and necrotic myocardium promotes the process of cardiac systolic and diastolic dysfunction, and the stunned myocardium in surrounding and the surviving cardiomyocytes can present transient impairment of contraction and relaxation, especially affecting the diastolic function which requires consuming oxygen and glucose. The extent of ventricular enlargement after infarction is related to the magnitude of the initial damage to the myocardium, and although an increase in cavity size tends to restore stroke volume despite a persistently reduced ejection fraction, ventricular dilatation has been associated with a reduction in survival. Thus, the mortality of HFrEF group was more than the HFpEF group just as our study showed.

D-dimer, acting as a marker of a thrombotic burden and reflecting the turnover of fibrin secondary to plaque rupture at any vascular site and plasmin-mediated fibrin degradation, also a sensitive marker of ongoing thrombosis, may be directly linked to an inflammatory vascular state. There are two points that may explain the association between D-dimer concentration and all-cause mortality in patients with AMI complicated by HFpEF. At one hand, hospitalized HF is often accompanied with vascular abnormalities, increased coagulability, and impaired blood flow. It is reasonable to conceive that early elevation of D-dimer may reflect the development or the severity of several chronic diseases, including cardiovascular disease, cancer, or infectious

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**Table 3** Hazard ratios (95% confidence intervals) associated with D-dimer for outcomes in patients with AMI in different HF groups

|                | D-dimer <145 ng/mL | D-dimer ≥145 ng/mL | P value | 1-SD increase in D-dimer | P value |
|----------------|--------------------|--------------------|---------|--------------------------|---------|
| All patients   |                    |                    |         |                          |         |
| Unadjusted     | 1                  | 3.12 (2.38, 4.10)  | <0.001  | 1.60 (1.44, 1.78)        | <0.001  |
| Adjusted model | 1                  | 1.61 (1.20, 2.17)  | 0.002   | 1.20 (1.04, 1.37)        | 0.01    |
| HFpEF          |                    |                    |         |                          |         |
| Unadjusted     | 1                  | 3.46 (1.89, 6.31)  | <0.001  | 1.79 (1.41, 2.26)        | <0.001  |
| Adjusted model | 1                  | 2.09 (1.08, 4.02)  | 0.02    | 1.43 (1.05, 1.94)        | 0.024   |
| HFrEF          |                    |                    |         |                          |         |
| Unadjusted     | 1                  | 2.27 (1.46, 3.53)  | <0.001  | 1.34 (1.14, 1.58)        | <0.001  |
| Adjusted model | 1                  | 1.25 (0.76, 2.04)  | 0.37    | 0.97 (0.78, 1.21)        | 0.81    |
| Non-HF         |                    |                    |         |                          |         |
| Unadjusted     | 1                  | 3.77 (2.51, 5.66)  | <0.001  | 1.92 (1.62, 2.28)        | <0.001  |
| Adjusted model | 1                  | 1.56 (0.98, 2.47)  | 0.06    | 1.40 (1.10, 1.77)        | 0.001   |

Unadjusted model adjusted for: none. Adjusted model adjusted for: sex, age, BMI, smoking status, AMI-types and the histories of hypertension, diabetes, and myocardial infarction, NT-proBNP, cTNI, hs-CRP, eGFR, TC, PCI, and medical treatments including aspirin, clopidogrel or ticagrelor, and statins.

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**Figure 1** Cumulative incidence of mortality among patients with AMI complicated by HFrEF, HFpEF, or non-HF, respectively.
diseases which lead to augmented mortality. On the other hand, the mechanism behind the association between D-dimer and death may be related to a long-term risk of thrombotic events in association with various pathogenic pathways, including atherosclerosis, inflammatory, and infectious disease processes.29 Hence, the patients with high D-dimer levels may be associated with a cumulative incidence of death just as our study suggested.

However, the association between D-dimer and mortality in patients with HFrEF was not statistically significant in our study, possibly due to the significant increasing levels and remarkable prognostic value of NT-proBNP and cTNI that attenuated the effect of D-dimer. What is more, the association between D-dimer and mortality in patients with non-HF was not significant, possibly due to the overall low levels of D-dimer in this population.

Limitations

Some limitations should be acknowledged in interpreting these data. First, these results emanated from a single-centre study and was performed in a Northeast Chinese population, and thus, they may not be applicable to other populations. Second, we did not conduct serial measurements for D-dimer levels at other time points, particularly the peak levels after the occurrence of AMI; however, the D-dimer levels on admission also gave us strong information for the prognosis of patients with AMI complicated by HFP EF during the index hospitalization. Third, this was an observational cohort study, and the observed differences in clinical outcomes and D-dimer levels may be subject to possible confounders which we were unable to control for. However, our findings were strongly statistically significant and clinically meaningful, and relevant results were shown by viewing the numerical data.

Conclusions

In patients with AMI complicated by HFP EF, a high D-dimer level is an important independent and sustained risk factor for all-cause mortality. It predicts risk independently and in addition to known traditional risk factors and biomarkers, with the potential to guide management decisions.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information

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