D-dimer and outcomes in hospitalized heart failure patients across the ejection fraction phenotypes

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Abstract

Aims The prognostic significance of D-dimer in hospitalized heart failure (HF) patients is incompletely characterized. We aimed to assess the association of D-dimer levels on admission with adverse events at follow-up in patients hospitalized with HF across all ejection fraction (EF) phenotypes.

Methods and results Consecutive patients hospitalized from December 2006 to December 2017 for HF with D-dimer and EF values available (n = 1795) were enrolled. Associations between D-dimer and all-cause death were examined at 1-year follow-up. Median age was 57 years, 73.4% were male, and the majority (72.1%) were in New York Heart Association Classes III–IV. EF was reduced in 53.3% (HFrEF), mildly reduced in 16.3% (HFmrEF), and preserved in 30.4% (HFpEF). Median (interquartile range) D-dimer on admission was 0.56 (0.27–1.295) μg/mL FEU (fibrinogen-equivalent unit) in the whole cohort, 0.64 (0.28–1.48) μg/mL FEU in HFrEF, 0.50 (0.27–1.03) μg/mL FEU in HFmrEF, and 0.495 (0.25–1.10) μg/mL FEU in HFpEF (P = 0.001). At 1-year follow-up, higher D-dimer (D-dimer ≥0.56 μg/mL FEU) independently predicted all-cause death in total cohort [hazard ratio (HR) 1.55; 95% confidence interval (CI), 1.15–2.1], in HFrEF (HR, 1.49; P = 0.039), and in HFpEF (HR, 2.06; P = 0.033). However, no relationship was found for HFrEF or HFmrEF when D-dimer was treated as quartiles. In sensitivity analysis, quantitatively similar but more pronounced association between D-dimer and all-cause death was observed in total cohort and HFpEF cohort.

Conclusions In hospitalized HF patients, higher D-dimer concentration was a significant and independent predictor of 1-year all-cause mortality. Across all HF phenotypes, this effect was most evident in HFpEF patients.

Keywords D-dimer; Heart failure; Prognosis; HFrEF; HFmrEF; HFpEF

Introduction

Heart failure (HF) is a life-threatening and highly prevalent disease. Despite establishment of novel therapeutic methods, long-term prognosis associated with HF remains poor,1,2 causing a major strain on healthcare systems.

HF is associated with an increased risk of thrombosis, leading to sudden death, cardio-embolic stroke, systemic thromboembolism, and venous thromboembolism, which poses serious adverse effects on quality of life and prognosis of patients.3 This is true of HF patients in sinus rhythm, and even more so in the many HF patients with concomitant atrial fibrillation.4,5

D-dimer, a specific degradation product of XIIIa-crosslinked fibrin, is an early marker of in vivo coagulation activation and thrombogenesis.6 Measurement of D-dimer plasma concentration is commonly used in the diagnosis of pulmonary embolism,7 deep vein thromboembolism,8 acute coronary syndrome,9 and acute aortic dissection.10 With respect to HF, increased D-dimer concentrations have been found in
acute HF, and in outpatients\cite{11,12}; however, the prognostic significance of this finding has been scarcely investigated. In particular, unexplored is the possible prognostic role of D-dimer measurements in HF patients with different phenotypes.

Given the heterogeneity of HF syndrome with respect to the degree of cardiac contractile impairment as manifest by left ventricular ejection fraction (LVEF)—the simplest and most widely used tool to ‘phenotype’ HF patients—it is relevant to investigate the prognostic value of D-dimer across EF phenotypes within HF, spanning from HF with reduced LVEF (HFrEF), mildly reduced LVEF (HFmrEF), to HF with preserved LVEF (HFpEF). This differentiation of HF patients based on LVEF is important, as it may entail different characteristics with respect to aetiology, demographics, co-morbidities, and response to therapy.\cite{13–19}

Accordingly, we performed a retrospective study aiming to assess the association of D-dimer levels on admission with adverse events at 1-year follow-up in patients hospitalized with HF across all HF phenotypes.

Materials and methods

Study population

In this single-centre study, data were prospectively collected and retrospectively analysed. We analysed a total of 1795 consecutive patients who were admitted to the Heart Failure Care Unit of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS&UM), with a clinical diagnosis of HF from December 2006 to December 2017 and in whom D-dimer and LVEF values were available. Diagnosis of HF was based on the Framingham study\cite{20} and Chinese guidelines for the diagnosis and treatment of heart failure, and confirmed by two cardiologists.

HF phenotypes were determined according to LVEF. Those with a significant reduction in LVEF (LVEF <40%) were designated as HFrEF. Patients with an LVEF between 40 and 49% were designated as HFmrEF, and those with an LVEF ≥50% were designated as HFpEF.

We excluded patients in whom no follow-up data were available; other exclusion criteria were (i) acute coronary syndrome; (ii) suspected or confirmed pulmonary thromboembolism identified in CT scans of the chest or pulmonary ventilation/perfusion imaging; (iii) deep vein thromboembolism or thromboembolic events in other organs identified in imaging reports (e.g. CT scans of the head/abdomen, lower extremity ultrasound, and echocardiography); (iv) cancer; (v) acute aortic dissection; (vi) recent trauma; and (vii) severe renal dysfunction. Patients <14 years were also excluded (Figure S1).

Informed consent was obtained from all patients, the study complied with the Declaration of Helsinki, and it was approved by the institutional ethics committee of Fuwai Hospital.

Study endpoint

Patients were followed up at 1, 6, and 12 months through outpatient visits or telephone communication. Primary endpoint was all-cause mortality at 1-year follow-up. All-cause mortality was defined as death from any cause (including heart transplantation and left ventricular assist device requirement) during follow-up.

Clinical and laboratory assessments

Blood samples were collected within 24 h of admission. Whole-blood samples were collected into tubes that were then centrifuged. Haematologic tests were performed in the clinical laboratory of Fuwai Hospital. D-dimer was measured by the PATHFAST™ D-Dimer assay (Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan) based on chemiluminescence immune assay (CLEIA) and MAGTRATION® methodology. Alkaline phosphatase-labelled anti-D-dimer monoclonal antibody and anti-D-dimer monoclonal antibody-coated magnetic particles are mixed with the sample. D-dimer binds to the anti-D-dimer antibodies forming an immunocomplex with enzyme-labelled antibody and antibody coated with magnetic particles. After removing the unbound enzyme-labelled antibody, a chemiluminescent substrate is added. After incubation, the intensity of the measured luminescence generated by the enzyme reaction is proportional to the D-dimer concentration of the sample and expressed as FEU (fibrinogen-equivalent unit).

Baseline data such as demographics, clinical characteristics, medical treatments, and laboratory examination values were collected from medical records, prior medication, and self-reports. Cardiac function data were collected from the first transthoracic echocardiography performed after admission. LVEF was calculated by modified Simpson’s method, left atrium diameter (LAD), and left ventricular end-diastolic diameter (LVEDD) were obtained by M-mode echocardiography.

Co-morbidities (e.g. hypertension and diabetes mellitus) were diagnosed according to the World Health Organization International Classification of Disease. Severe renal dysfunction was defined as an estimated glomerular rate of less than 30 mL/min/1.73m². The estimated glomerular rate was calculated using baseline serum creatinine concentration.\cite{22}

Statistical analysis

Continuous variables are expressed as means and standard deviations (normal distribution) or medians and interquartile
ranges (skewed distribution); categorical variables were presented as frequencies and percentages. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was log transformed because of its right-skewed distribution.

D-dimer levels of the whole population were grouped into quartiles [bottom quartile (Q1): D-dimer < 0.27 μg/mL FEU; second quartile (Q2): 0.27 μg/mL FEU ≤ D-dimer < 0.56 μg/mL FEU; third quartile (Q3): 0.56 μg/mL FEU ≤ D-dimer < 1.295 μg/mL FEU; top quartile (Q4) D-dimer ≥ 1.295 μg/mL FEU]. We also grouped D-dimer levels of the whole population into higher D-dimer (≥0.56 μg/mL FEU) and lower D-dimer (<0.56 μg/mL FEU), based on median value of D-dimer.

The differences of baseline characteristics were analysed based on dichotomized D-dimer and HF phenotypes. Student’s t-test (Wilcoxon rank-sum test for skewed variables) was used for continuous variables, and chi-square test or Fisher’s exact test was used for categorical variables.

To visually assess non-linear relationships between log-transformed D-dimer levels and mortality risk, restricted cubic spline curves before and after adjustment were performed. A thousand-fold D-dimer was log transformed, and the value corresponding to 0.56 was set as hazard ratio (HR) = 1.

The cumulative incidence of all-cause death was estimated by the Kaplan–Meier method among D-dimer quartiles and compared with log-rank test.

Cox proportional hazards regression models assessed the relationship between D-dimer and all-cause mortality in total cohort and different HF phenotype cohorts. Established prognosticators were included in multivariate Cox proportional hazards model. The regression results were reported according to dichotomized D-dimer using the lower range group as the reference and D-dimer quartiles using the bottom quartile as the reference. Trend tests were based on D-dimer level quartiles as a continuous variable. Testing for interaction between D-dimer and ejection fraction groups on outcome was conducted through the use of likelihood ratio tests. The adjusted HRs with their respective 95% confidence intervals (CIs) were calculated. Proportionality assumptions were assessed using graphical approach based on Schoenfeld residuals.

As a sensitivity analysis to test the robustness of the relationship, an inverse propensity of treatment weighting (IPTW) was used. What is more, we conducted multiple imputation to maximize statistical power and minimize bias that might occur if patients with missing data were excluded from analysis. Cox proportional hazards regression models were again constructed based on cohorts after imputation.

All statistical tests were two-tailed, and \( P < 0.05 \) was considered to be statistically significant. All analyses were performed using R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Patient population**

The final cohort consisted of 1795 patients. Characteristics of the study population are shown in Tables 1 and S1. Patients were classified according to dichotomized D-dimer and HF phenotypes. The median age was 57 (47–67.5) years, and 73.4% were male. Overall, 1188 patients (72.1%) were in New York Heart Association (NYHA) functional Class III or IV. Ischaemic aetiology was present in 778 (43.3%) of patients. HFrEF was found in 947 (53.3%) patients, HFmrEF in 289 (16.3%), and HFpEF in 540 (30.4%).

Overall, patients with higher D-dimer tended to be older, have lower body mass index (BMI), higher NYHA functional class, higher levels of NT-proBNP, and lower LVEF. They were more frequently complicated by dyslipidaemia and impaired liver and renal function (Table 1).

**Impact of dichotomized D-dimer and D-dimer quartiles on adverse events in the total cohort**

The median (interquartile range) D-dimer concentrations in the whole cohort was 0.56 (0.27–1.295) μg/mL FEU. All-cause mortality at 1-year follow-up occurred in 324 (18.1%) patients.

The restricted cubic spline curves showed that log-transformed D-dimer has an S-shaped relationship with all-cause mortality over 1-year follow-up period (Figure S2A), even after adjustment of age, sex, and BMI (Figure S2B).

Kaplan–Meier survival analysis for quartiles of D-dimer yielded diverging curves, with the comparison showing pronounced risk stratification (log-rank test \( P < 0.0001 \)) (Figure 1A).

Results of the univariate and multivariate Cox proportional hazards analysis for all-cause death are depicted in Table 2. We simultaneously extracted the results from two adjusted models: Model 1 was adjusted for age, sex, and BMI; Model 2 was further adjusted for other well-established prognosticators such as systolic blood pressure, heart rate, serum creatine, serum sodium, total bilirubin, total cholesterol, haemoglobin, log-transformed NT-proBNP, LVEF, CHD, NYHA functional Class III or IV, diagnosis of diabetes, renin–angiotensin system inhibitor (RASI) prescription, beta-blocker prescription, and aldosterone antagonist prescription. Higher D-dimer remained markedly associated with all-cause death at 1-year follow-up after adjustment (HR, 1.55; 95% CI 1.15–2.1); a similar trend was seen when higher quartiles were compared with lower quartiles.
Table 1: Characteristics of the study participants dichotomized according to D-dimer concentrations at baseline

| Characteristics                                  | All population (n = 1795) | D-dimer < 0.56 μg/mL FEU (n = 887) | D-dimer ≥ 0.56 μg/mL FEU (n = 908) | P value |
|--------------------------------------------------|---------------------------|------------------------------------|------------------------------------|---------|
| **Demographic characteristics**                  |                           |                                    |                                    |         |
| Age (years)                                      | 57.00 [47.00, 67.50]      | 57.00 [47.00, 65.00]               | 58.50 [46.00, 70.00]               | 0.001   |
| Sex (male), n (%)                                | 1317 (73.4)               | 676 (76.2)                         | 641 (70.6)                         | 0.008   |
| BMi (kg/m²)                                      | 24.45 [21.93, 27.20]      | 25.02 [22.72, 27.76]              | 23.70 [20.97, 26.55]              | <0.001  |
| Heart rate (bpm)                                 | 78.00 [67.00, 90.00]      | 75.00 [66.00, 86.00]               | 82.00 [70.00, 95.00]               | <0.001  |
| Systolic BP (mmHg)                               | 119.42 [20.14]            | 122.77 [20.36]                     | 116.15 [19.39]                     | <0.001  |
| Diastolic BP (mmHg)                              | 70.00 [63.00, 80.00]      | 72.00 [65.00, 80.00]               | 70.00 [61.00, 80.00]               | <0.001  |
| NYHA functional Class III/IV, n (%)              | 1188 (72.1)               | 517 (63.0)                         | 671 (81.2)                         | <0.001  |
| **Co-morbidities**                               |                           |                                    |                                    |         |
| Coronary heart disease, n (%)                    | 778 (43.3)                | 385 (43.4)                         | 393 (43.4)                         | 0.996   |
| Hypertension, n (%)                              | 842 (46.9)                | 448 (50.5)                         | 394 (43.4)                         | 0.003   |
| Diabetes, n (%)                                  | 527 (29.4)                | 257 (29.0)                         | 270 (29.7)                         | 0.762   |
| Hypertrophic cardiomyopathy, n (%)               | 53 (3.0)                  | 36 (4.1)                           | 17 (1.9)                           | 0.009   |
| Dilated cardiomyopathy, n (%)                    | 575 (32.0)                | 267 (30.1)                         | 308 (33.9)                         | 0.092   |
| OSAS, n (%)                                      | 154 (8.6)                 | 90 (10.1)                          | 64 (7.0)                           | 0.024   |
| COPD, n (%)                                      | 150 (8.4)                 | 61 (6.9)                           | 89 (9.8)                           | 0.031   |
| **Laboratory variables**                         |                           |                                    |                                    |         |
| White blood cell (*10^9/L)                       | 7.02 [5.75, 8.59]         | 6.92 [5.77, 8.33]                  | 7.20 [5.74, 8.84]                  | 0.022   |
| Haemoglobin (g/L)                                | 139.00 (21.77)            | 142.85 (20.27)                     | 135.24 (23.37)                     | <0.001  |
| Haematocrit (%)                                  | 41.35 (6.12)              | 42.15 (5.47)                       | 40.57 (6.61)                       | <0.001  |
| Platelet count (*10^9/L)                         | 194.00 [156.00, 241.00]   | 194.00 [158.00, 238.00]            | 195.00 [153.00, 245.00]            | 0.939   |
| Prothrombin activity (%)                         | 88.00 [75.00, 99.00]      | 94.00 [81.00, 103.00]              | 84.00 [72.00, 93.00]               | <0.001  |
| International normalized ratio (R)               | 1.08 [1.01, 1.20]         | 1.04 [0.98, 1.14]                  | 1.11 [1.04, 1.24]                  | <0.001  |
| Albumin (g/L)                                    | 39.87 (5.27)              | 41.50 (4.75)                       | 38.27 (5.26)                       | <0.001  |
| ALT (IU/L)                                       | 23.00 [14.00, 37.00]      | 23.00 [15.00, 36.00]               | 23.00 [14.00, 40.00]               | 0.805   |
| AST (IU/L)                                       | 24.00 [18.00, 32.00]      | 23.00 [18.00, 30.00]               | 25.00 [19.00, 34.00]               | <0.001  |
| Alkaline phosphatase (IU/L)                      | 66.00 [54.00, 84.00]      | 63.00 [52.00, 77.00]               | 71.00 [56.00, 90.00]               | <0.001  |
| γ-Glutamyl transpeptidase (IU/L)                 | 45.00 [27.50, 85.50]      | 40.00 [26.00, 72.00]               | 50.00 [29.00, 95.00]               | <0.001  |
| Total bilirubin (μmol/L)                         | 20.00 [14.30, 29.79]      | 18.50 [13.50, 25.87]               | 22.20 [15.10, 34.10]               | <0.001  |
| Serum sodium (mmol/L)                            | 138.00 [135.40, 140.00]   | 138.68 [136.00, 140.63]            | 137.52 [135.00, 140.00]            | <0.001  |
| Serum potassium (mmol/L)                         | 3.94 [3.66, 4.26]         | 3.92 [3.67, 4.20]                  | 4.00 [3.65, 4.30]                  | 0.012   |
| Serum creatinine (μmol/L)                        | 90.28 [75.40, 108.15]     | 87.20 [73.54, 103.79]              | 93.84 [77.22, 112.50]              | <0.001  |
| Blood urea nitrogen (mmol/L)                     | 7.20 [5.47, 9.31]         | 6.80 [5.28, 8.80]                  | 7.50 [5.69, 9.86]                  | <0.001  |
| Triglyceride (mmol/L)                            | 1.28 [0.95, 1.83]         | 1.48 [1.05, 2.08]                  | 1.18 [0.89, 1.58]                  | <0.001  |
| Total cholesterol (mmol/L)                       | 3.99 [3.30, 4.74]         | 4.11 [3.43, 4.86]                  | 3.88 [3.17, 4.66]                  | <0.001  |
| High-density lipoprotein (mmol/L)                | 0.95 [0.78, 1.18]         | 0.98 [0.82, 1.23]                  | 0.91 [0.73, 1.13]                  | <0.001  |
| Low-density lipoprotein (mmol/L)                 | 2.45 [1.92, 3.06]         | 2.49 [1.94, 3.12]                  | 2.42 [1.89, 3.02]                  | 0.193   |
| Hs-CRP (mg/L)                                    | 3.32 [1.46, 9.55]         | 2.22 [1.10, 4.92]                  | 5.30 [2.26, 11.66]                 | <0.001  |
| NT-proBNP (pg/mL)                                | 1788.00 [710.00, 4480.00] | 1061.00 [466.50, 2385.50]          | 3101.50 [1297.50, 6581.25]         | <0.001  |
| Log-transformed NT-proBNP                        | 3.22 (0.63)               | 2.99 (0.61)                        | 3.45 (0.57)                        | <0.001  |

(Continues)
Table 1 (continued)

|                      | All population | D-dimer < 0.56 μg/mL FEU | D-dimer ≥ 0.56 μg/mL FEU | P value |
|----------------------|----------------|---------------------------|---------------------------|---------|
| **Echocardiographic evaluation** |                |                           |                           |         |
| LAD (mm)             | 44.00 [39.00, 50.00] | 44.00 [38.00, 49.00] | 45.00 [40.00, 51.00] | <0.001  |
| LVEDD (mm)           | 61.51 (12.57)   | 61.29 (12.55)             | 61.73 (12.59)             | 0.461   |
| LVPWT (mm)           | 9.00 [8.00, 10.00] | 9.50 [8.05, 10.00]        | 9.00 [8.00, 10.00]        | 0.183   |
| IVST (mm)            | 10.00 [8.50, 11.00] | 10.00 [8.60, 11.00]       | 9.90 [8.25, 11.00]        | 0.255   |
| LVEF (%)             | 38.00 [29.00, 53.00] | 40.00 [30.00, 55.00]      | 35.00 [27.00, 50.00]      | <0.001  |
| **Medication**       |                |                           |                           |         |
| Digoxin, n (%)       | 899 (50.8)      | 417 (47.3)                | 482 (54.3)                | 0.003   |
| Beta blockers, n (%) | 1524 (86.2)     | 773 (87.6)                | 751 (84.7)                | 0.082   |
| ACEi/ARB, n (%)      | 1036 (58.6)     | 582 (66.0)                | 454 (51.2)                | <0.001  |
| Aldosterone antagonists, n (%) | 1278 (72.2) | 629 (71.3)                | 649 (73.2)                | 0.414   |
| Diuretics, n (%)     | 1520 (86.5)     | 759 (87.0)                | 761 (86.0)                | 0.565   |

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septal thickness; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSAS, obstructive sleep apnoea syndrome.

Continuous variables are presented as mean (SD) or median (interquartile range). Categorical variables are presented as numbers and frequencies [n (%)].
Impact of dichotomized D-dimer and D-dimer quartiles on survival prediction in different HF phenotype cohorts

The median (interquartile range) D-dimer concentrations in the three EF phenotypes were 0.64 (0.28–1.48) μg/mL FEU in HFrEF, 0.50 (0.27–1.03) μg/mL FEU in HFmrEF, and 0.495 (0.25–1.10) μg/mL FEU in HFpEF (P = 0.001).

Disparity exists in D-dimer’s prognostic effects in three HF phenotype cohorts. Though Kaplan–Meier survival analysis for quartiles of D-dimer yielded diverging curves in different HF phenotypes individually (all log-rank test P < 0.05) (Figure 1B–D), prognostic power of D-dimer varied through the whole spectrum of EF phenotypes (Table 2). In HFpEF, at 1-year follow-up, patients with higher D-dimer had 2.06 times higher risk after adjustment (P = 0.033, 95% CI...
## Table 2  Risk of 1-year all-cause death by D-dimer

|                         | Unadjusted |            | Model 1 |            | Model 2 |            |
|-------------------------|------------|------------|----------|------------|----------|------------|
|                         |            |            | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| D-dimer ≥ 0.56 vs. <0.56 μg/mL FEU |            |            |          |        |          |        |          |        |
| Overall                 |            |            | 3.12 (2.41,4.03) | <0.001 | 2.62 (2.3,44) | <0.001 | 1.55 (1.15,2.1) | 0.004  |
| HFrEF                   |            |            | 2.79 (2.02,3.84) | <0.001 | 2.43 (1.74,3.4) | <0.001 | 1.49 (1.02,2.17) | 0.039  |
| HFmrEF                  |            |            | 2.64 (1.25,5.62) | 0.011 | 1.77 (0.76,4.15) | 0.188 | 1.42 (0.87,2.30) | 0.158  |
| HFpEF                   |            |            | 4.18 (2.42,7.21) | <0.001 | 3.65 (2.07,6.42) | <0.001 | 0.55 (0.14,2.21) | 0.400  |
| P value for interaction | 0.419      | 0.686      |          |        |          |        |          |        |
| D-dimer quartiles       |            |            |          |        |          |        |          |        |
| Overall                 |            |            |          |        |          |        |          |        |
| Q1:D-dimer < 0.27 μg/mL FEU | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 |
| Q2:0.27 ≤ D-dimer < 0.56 μg/mL FEU | 1.52 (0.97,2.39) | 0.066 | 1.5 (0.95,2.39) | 0.082 | 0.96 (0.59,1.58) | 0.882 | 0.77 (0.42,1.43) | 0.408 |
| Q3:0.56 ≤ D-dimer < 1.295 μg/mL FEU | 3.31 (2.22,4.93) | <0.001 | 2.85 (1.88,4.31) | <0.001 | 1.53 (0.99,2.37) | 0.054 | 1.5 (0.97,2.33) | 0.068 |
| Q4:D-dimer ≥ 1.295 μg/mL FEU | 4.59 (3.11,6.77) | <0.001 | 3.71 (2.48,5.54) | <0.001 | 1.15 (0.71,1.89) | 0.324 | 1.18 (0.71,1.89) | 0.532 |
| HFrEF                   |            |            |          |        |          |        |          |        |
| Q1:D-dimer < 0.27 μg/mL FEU | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 |
| Q2:0.27 ≤ D-dimer < 0.56 μg/mL FEU | 1.09 (0.63,1.9) | 0.754 | 1.05 (0.59,1.86) | 0.868 | 0.77 (0.42,1.43) | 0.408 | 1.45 (0.87,2.41) | 0.152 |
| Q3:0.56 ≤ D-dimer < 1.295 μg/mL FEU | 2.67 (1.69,4.24) | <0.001 | 2.38 (1.48,3.82) | <0.001 | 1.45 (0.87,2.41) | 0.152 | 1.45 (0.87,2.41) | 0.152 |
| Q4:D-dimer ≥ 1.295 μg/mL FEU | 3.14 (2.01,4.91) | <0.001 | 2.6 (1.63,4.13) | <0.001 | 1.18 (0.71,1.98) | 0.532 | 1.18 (0.71,1.98) | 0.532 |
| HFmrEF                  |            |            |          |        |          |        |          |        |
| Q1:D-dimer < 0.27 μg/mL FEU | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 |
| Q2:0.27 ≤ D-dimer < 0.56 μg/mL FEU | 2.02 (0.52,7.8) | 0.309 | 1.55 (0.39,6.2) | 0.537 | 0.41 (0.06,2.58) | 0.340 | 0.25 (0.04,1.46) | 0.124 |
| Q3:0.56 ≤ D-dimer < 1.295 μg/mL FEU | 2.83 (0.77,10.46) | 0.188 | 1.21 (0.29,5.11) | 0.791 | 0.25 (0.04,1.46) | 0.124 | 0.25 (0.04,1.46) | 0.124 |
| Q4:D-dimer ≥ 1.295 μg/mL FEU | 6.12 (1.73,21.68) | 0.005 | 4.08 (1.11,14.94) | 0.034 | 0.76 (0.14,4.02) | 0.744 | 0.76 (0.14,4.02) | 0.744 |
| HfPEF                  |            |            |          |        |          |        |          |        |
| Q1:D-dimer < 0.27 μg/mL FEU | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 | Reference | P for trend < 0.001 |
| Q2:0.27 ≤ D-dimer < 0.56 μg/mL FEU | 3.4 (1.11,10.42) | 0.032 | 3.67 (1.19,11.32) | 0.024 | 2.91 (0.88,9.65) | 0.081 | 2.91 (0.88,9.65) | 0.081 |
| Q3:0.56 ≤ D-dimer < 1.295 μg/mL FEU | 7.38 (2.56,21.27) | <0.001 | 6.92 (2.36,20.31) | <0.001 | 3.17 (1.01,9.92) | 0.047 | 3.17 (1.01,9.92) | 0.047 |
| Q4:D-dimer ≥ 1.295 μg/mL FEU | 11.13 (3.92,31.61) | <0.001 | 9.86 (3.41,28.54) | <0.001 | 5.61 (1.77,17.81) | 0.003 | 5.61 (1.77,17.81) | 0.003 |

CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.

Model 1, adjusted for age, sex, and BMI; Model 2, further adjusted for systolic blood pressure, heart rate, serum creatine, serum sodium, total bilirubin, total cholesterol, haemoglobin, log-transformed NT-proBNP, LVEF, CHD, NYHA functional Class III or IV, diagnosis of diabetes, RASi prescription, beta-blocker prescription, and aldosterone antagonist prescription.

*Results of inverse propensity of treatment weighting.*
1.06–4); with regard to quartiles, patients with D-dimer values in Q2, Q3, and Q4 had 2.91 \((P = 0.081, 95\% \text{ CI } 0.88–9.65)\), 3.17 \((P = 0.047, 95\% \text{ CI } 1.01–9.92)\), and 5.61 \((P = 0.003, 95\% \text{ CI } 1.77–17.81)\) higher risk compared with patients in Q1, respectively \((P \text{ for trend } 0.003)\). In HFrEF or HFmrEF patients, higher D-dimer quartiles were not related to increased risk of all-cause death.

**Sensitivity analysis**

IPTW allows a pseudo-population to be created through assigning individuals with weights that corresponded to the inverse of their probability of being allocated to dichotomized D-dimer given observed covariates; it was carried out for sensitivity analysis. In line with previous findings, it showed pronounced prognostic effect of baseline dichotomized D-dimer in whole cohort \((HR, 1.64; \ P = 0.014)\) and in HfPEF \((HR, 2.62; \ P = 0.048)\) (Table 2). In HFrEF, higher D-dimer was prognostic of 1-year mortality \((HR, 1.49; \ P = 0.039)\); however, after IPTW, this effect was attenuated \((HR, 1.42; \ P = 0.158)\). After multiple imputation of missing data, we repeated Cox proportional hazards analysis in the total cohort and HF phenotype cohorts; quantitatively similar but more pronounced results were found as in the prior analysis. When the total cohort was categorized according to D-dimer quartiles, we observed a notable association between D-dimer and 1-year all-cause mortality; patients with D-dimer values in Q2, Q3, and Q4 had 1.16 \((P = 0.524, 95\% \text{ CI } 0.73–1.83)\), 1.7 \((P = 0.012, 95\% \text{ CI } 1.12–2.56)\), and 1.68 \((P = 0.013, 95\% \text{ CI } 1.11–2.55)\) higher risk compared with patients in Q1, respectively \((P \text{ for trend } 0.004)\). Results are shown in Table S2.

What is more, because we excluded 284 patients in whom follow-up data were absent, a comparison of baseline characteristics for patients lost in follow-up and patients included in final analysis was conducted to avoid potential risk of bias (we excluded a total of 82 patients in cohort of patients lost to follow-up according to previously stated exclusion criteria). Obvious difference was not discerned between groups (Table S3).

**Discussion**

This single-centre study evaluated the associations between D-dimer concentrations and 1-year mortality in 1795 consecutive patients hospitalized with HF from 2006 to 2017. It reveals that D-dimer was associated with a higher risk of 1-year mortality in the whole hospitalized HF patient cohort. Across the ejection fraction phenotypes, a more pronounced association was found in patients with HfPE. Sensitivity analyses reinforced the finding.

**Thromboembolism in heart failure**

Thromboembolism is a major complication in hospitalized HF patients.23–26 The ARIC (Atherosclerosis Risk in Communities) cohort found 27% incidence rate of venous thromboembolism in HF outpatients over 22 years follow-up.27 Patients with HF are characterized by ‘Virchow triad’, that is, blood stasis, hypercoagulable state, endocardium, and endothelial dysfunction, all resulting in a pro-thrombotic state.28,29 Patients complicated with thromboembolism have poor prognosis according to the Worcester Venous Thromboembolism Study.30 The disease burden and poor prognosis indicate a significant role of pro-thrombotic biomarkers in HF prognosis.

**D-dimer and its unexplored role in heart failure**

D-dimer is a simple, widely employed biomarker reflecting activation of coagulation and fibrinolysis, and it is applied to the diagnosis of venous thromboembolism, identification of patients at high risk of venous thromboembolism, identification of patients who may benefit from rivaroxaban for stroke reduction, prediction of stroke risk in atrial fibrillation, and independent prediction of cardiovascular disease mortality and other fatal events across multiple diseases.31,32 However, despite abundant evidence of elevated pro-thrombotic biomarkers in HF patients, including D-dimer,11,12 their prognostic value has not been recognized until recent years.33–36 Previous studies on this topic are characterized by limitations, including relatively small sample size,33,34,36 or short follow-up.34 Furthermore, study populations were at times complicated by multiple co-morbidities that may affect D-dimer levels, such as malignancies, aortic dissection, and deep vein thromboembolism.35 Thus, a more accurate assessment is needed.

Different HF phenotypes are distinct in underlying diseases, pathophysiological mechanisms, clinical manifestations, and disease prognosis. In this respect, biomarker-based risk stratification is not only feasible and easily accessible in clinical practice, but it could also prove important for tailoring treatment and long-term management. However, most widely accepted biomarkers, such as NT-proBNP, troponin, soluble suppression of tumorigenicity 2 (sST2), galectin-3, and growth differentiation factor-15 (GDF-15), tend to have prognostic data derived from studies in unselected HF populations, or restricted to HfREF, whereas valuable prognostic biomarkers in hospitalized HfPEF patients, with a few exceptions,37,38 are poorly investigated.
Prognostic importance of D-dimer in hospitalized heart failure patients and across the range of heart failure phenotypes

In the present study, higher D-dimer independently predicted all-cause death at 1-year follow-up. Sensitivity analysis revealed more pronounced prognostic value of D-dimer, underlining D-dimer’s prognostic effects at 1 year. The precise mechanisms of baseline D-dimer’s prognostic effects on 1-year mortality are unclear. D-dimer is a symbol of hypercoagulable state that is, by most reckoning, transient. However, in recent study, it is found that hypercoagulable state can be persistent in medically ill hospitalized patients.39 It is conceivable that, in addition to reversible and correctable pro-thrombotic causes (such as immobilization and hemodynamic alterations in hospitalized HF patients), endothelial injury, chronic systemic inflammatory condition, and persistent hemodynamic abnormalities, may be long-term risk factors of thrombosis in HF patients.

What is more, elevated D-dimer is not merely associated with HF prognosis as frequently noted, that it may be the consequence of haemodynamic alterations and impaired blood flow in HF, reflecting the cardiac functional status and disease severity, and that elevated D-dimer in turn results in inflammatory reactions by inducing synthesis and release of inflammatory cytokines,40 adding to the disease burden.

With respect of different HF phenotypes, the present study shows that D-dimer has particular prognostic value in HfPEF patients. This is not entirely surprising, as over the last decade, our understanding of HfPEF has evolved from a mere left ventricular diastolic dysfunction to a multi-organ syndrome, in which obesity, diabetes, and hypertension may predispose to systemic inflammation and microcirculatory alterations affecting the myocardium.13,41 Cluster analysis of HfPEF based on clinical characteristics and biomarker profiles has been developed to explain heterogeneity in pathophysiology and to identify ‘phenogroups’ with distinctive prognosis.17,18,42–44 However, apart from platelet activation biomarkers, thrombotic biomarkers are under-represented in those studies. A study on SERPINE1 and ageing has pointed out that plasminogen activator inhibitor 1 was associated with HfPEF,45 which indicated that coagulation and fibrinolysis biomarkers might be essential for clustering of HfPEF phenogroups and understanding of pathophysiological pathways, which merits further investigation.

Limitations

This is a single-centre study, performed in a Chinese population; hence, findings should be extrapolated cautiously to populations with different ethnicity. Due to its observational nature, there are possible confounders that we were unable to control. Of note, however, patient enrolment was concluded well before onset of SARS-Cov-2 pandemic, and therefore, potential confounding effects of D-dimer elevation in patients with concomitant COVID-19 and HF can be excluded.46 With respect to different EF phenotypes, in our analysis, HfMR EF patients were substantially fewer, in line with previous reports,14,15,19 and this may have contributed to the inability to detect a significant effect in this sub-group. Finally, patients in this study were enrolled prior to the extensive prescription of ARNI and SGLT-2 inhibitors.

Conclusions

In patients hospitalized with HF, D-dimer was a significant and independent predictor of 1-year all-cause mortality. Across all HF phenotypes, D-dimer was independently associated with all-cause mortality at 1-year follow-up period in HfPEF patients. Future studies exploring treatment with statins and anti-thrombotic agents might be considered in these patients.

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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.

Figure S1. Study Flow Chart.
Figure S2. D-dimer Concentrations and All-Cause Mortality.
Table S1. Characteristics of the Study Participants Categorized by HF Phenotypes and D-dimer Concentrations.
Table S2. Risk of All-Cause Death by D-dimer (After Imputation).

Table S3. Characteristics of the Patients Lost in Follow-up and Patients Included in Final Analysis.

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