Determinants of Elevated D-Dimer Levels and Long-Term Outcome in Elderly Patients With End-Stage Heart Failure

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Abstract

Background

Previous studies have shown that heart failure is associated with hemostatic abnormalities and hypercoagulable state. Plasma D-dimer levels reflect both fibrin formation and degradation, and elevated D-dimer levels have been associated with poor prognosis in patients with heart failure. However, little is known about their roles in elderly patients with end-stage HF. In present study, we aimed to explore the clinical significance and determinants of plasma D-dimer in elderly patients with end-stage heart failure.

Methods

A total of 177 patients with heart failure at Beijing Geriatric Hospital from November 1, 2015 to December 30, 2018 were enrolled. All hospitalized patients were obtained D-dimer levels within the first 24 h following admission after obtaining informed consent. Primary endpoint was all-cause mortality.

Results

A total of 60 patients had elevated D-dimer levels. Blood urea nitrogen (β = 1.106, 95% CI: 1.029–1.190, p = 0.006), NYHA functional class (β = 2.179, 95% CI: 1.170–4.056, p = 0.014) and white blood cell counts (β = 1.188, 95% CI: 1.040–1.358, p = 0.011) were independent risk factors for elevated D-dimer in elderly patients with end-stage heart failure. Albumin (β = 0.803, 95% CI: 0.728–0.885, P 0.001) was negative risk factor for elevated D-dimer in elderly patients with end-stage heart failure. Elevated D-dimer level was independently associated with increased risk of long-term all-cause mortality (P = 0.048).

Conclusions

For elderly patients with end-stage heart failure, D-dimer levels were associated with white blood cell counts, blood urea nitrogen, albumin and NYHA functional class and elevated D-dimer level was independently associated with poor long-term outcome.

Background

Epidemiologic and clinical data from the last 2 decades have led to the recognition that heart failure (HF) is the major contributor to cardiovascular morbidity and mortality, resulting in reduced longevity [1]. In particular, HF now has become one of the most common reasons for hospitalizations in people over 65 years[2] because of increased survival after improved treatment of coronary artery disease, valvular disease, and hypertension [3].

Patients with heart failure often die of pump failure late in life, nevertheless the causes of death are not studied in detail. Several studies have suggested that thrombosis may serve as significant contributors of poor prognosis and mortality in patients with chronic heart failure (CHF) [4]. As a biomarker of fibrin formation and degradation, D-dimer is related to the pathology of the cardiovascular system [5] and is a useful parameter for clinical evaluation of the degree of hypercoagulability and thrombotic disease [6]. D-dimer levels were found to be significantly higher in 22–65 year old HF patients than in healthy patients [7]. Furthermore, in a study with a mean follow up of 8 ± 5 months (up to 34 months), elevated D-dimer levels were found to predict cardiovascular mortality and the development of atrial fibrillation (AF) in hospitalized patients with end-stage heart failure [6]. However, there are scarce data concerning the D-dimer levels in elderly patients with end-stage heart failure with a long follow up (up to 2 years), which account for the majority form of HF.

Therefore, in this study, we aimed to determine the clinical significance and determinants of plasma D-dimer in elderly patients with end-stage HF. Furthermore, we sought evidence to evaluate the value of the D-dimer baseline level to predict subsequent clinical outcome in patients with end-stage HF for an average of 21 months follow up.

Patients and Methods

Study population

This was a retrospective observational follow-up study. The patients with chronic heart failure (CHF) were included in the cardiovascular medicine unit at Beijing Geriatric Hospital (Beijing, China) from November 1, 2015 to December 30, 2018. The patients were either admitted for the first time or were repeat hospitalization for CHF. The diagnosis of heart failure was according to the Guideline for the diagnosis and treatment of heart failure in China 2018. We defined end-stage HF as New York Heart Association class III-IV, despite of optimal medical therapy, such as beta blockers, angiotensin converting enzyme inhibitors (ACEIs). The causes of CHF included ischemic heart disease, valvular heart disease, hypertension, various cardiomyopathy et al. The patients were excluded if they had presented with HF due to acute coronary syndromes or accelerated hypertension or were in cardiogenic shock or suffered from any serious illness. Additionally, subjects who had a history of malignancy, pregnancy, aortic dissection, trauma or lie in bed were also excluded. Patients with deep vein thrombosis (DVT) and/or pulmonary thromboembolism (PTE) were also excluded from the study. Totally, 177 patients were included in the study. Data including the demographic, clinical, laboratory findings and medications were collected through electronic medical record system. We conducted telephonic interviews with the participants with respect to their survival (see supplementary interview items).

Laboratory Evaluation

For measurement, blood samples were collected in fasting or nonfasting state within 24 hours of hospitalization and measured within 4 hours as routine sample analysis in our hospital laboratory. The concentration of each biomarker was assayed using commercially available assay kits according to

manufacturer protocol and using standard curves and software. Plasma D-dimer was analyzed with immunoassays turbidimetry (Instrumantation Labroatory Company, Spain) as recommended by the manufacturer. The intra-assay coefficient of variation was 8.3% and the inter-assay coefficient of variation was 11.0%, respectively. A plasma D-dimer level would be reexamined if it was not consistent with clinical manifestations. The new results of D-dimer examination were used for analysis. The concetrations of biochemical biomarkers included blood urea nitrogen, serum creatinine, total protein, prealbumin, serum albumin and β2-microglobulin were measured by using a lactate dehydrogenase assay kit (Siemens Healthcare Diagnostics Inc, USA). The blood gas analysis was performed only once using the blood gas analyzer with the arterial blood immediately drawn within 2 hours of admission. PO2, Lac and SO2 were measured. Carbohydrate antigen-125 (CA-125) was obtained using CA125 assay kit (Siemens Healthcare Diagnostics Inc, USA). The FT3 and TT3 were quantitatively determined by free thyroxine assay kit with direct chemiluminescence (Siemens Healthcare Diagnostics Inc, USA).

Echocardiography

Transthoracic echocardiography was performed using an iE33 Color Doppler Ultrasound System (Philips Healthcare, EPIQ7, USA) in ultrasonic department in accordance with American Society of Echocardiography (ASE) guidelines, by dedicated analysts blinded to clinical information. LVEF were derived according to the modified biplane Simpson's rule.

Follow up

We followed up the patients by telephone interview at 6, 12, and 24 months after discharge and the median follow-up period was 21 months (interquartile range of 11 to 30 months). We collected data on all-cause death from the hospital medical records and telephone follow up. All-cause mortality was defined as death from any cause during the follow up period.

Statistical analysis

We used a threshold of 0.5 mg/L to define a positive plasma D-dimer result because this value is widely used in clinic, an age-adjusted D-dimer cut-off model has recently decreased false-positive results without additional false-negative findings in patients and therefore we applied this cut-off to our study. D-dimer values were compared to the current cut-off of 0.5 mg/L and to the suggested age-adjusted cut-off (age/100 mg/L) [8, 9]. Before analysis, normal distribution was tested for continuous variables. Value of D-dimer was logarithm transformed to normalize its distribution. Continuous variables are expressed as mean ± SD, and categorical variables are expressed as percentages. Comparisons between two groups of continuous variables were performed using Student's t-test or Mann-Whitney *U* test. A chi-squared test was used to compare the difference between categorical variables. We used Spearman's correlation test or Pearson's correlation test to examine correlations between two continuous variables (as appropriate). Stepwise multiple linear regression analysis was performed to identify independent variables that might determine plasma D-dimer levels (p value threshold to enter ≤ 0.05, ≥ 0.1 to remove). Forward LR method of multivariate logistic regression analysis was used to detect independent predictors of the elevated D-dimer levels. For multiple linear regression analysis and multivariate logistic regression analysis, we

included variables based on the results of univariate analysis and professional knowledge. Event-free survival curves were constructed using the Kaplan-Meier methods and compared using log-rank test. A P value < 0.05 was considered statistically significant. All analyses were performed with the statistical package SPSS 21.0 (SPSS Inc, Chicago, Illinois). A 2-tailed p value < 0.05 was considered statistically significant.

Results

Baseline Data

The median plasma D-dimer levels was 0.95 mg/L (0.03–31.97). The frequency distribution of D-dimer levels was showed in Fig. 1A, and normal distribution of D-dimer was obtained from logarithmic transformation in Fig. 1B. Totally, one hundred seventy-seven patients were included in the present study. The baseline demographic, clinical characteristics, laboratory findings and drug treatments were summarized according to the cut off value of plasma D-dimer levels in Table 1A and Table 1B. The mean age of recruited patients was 73.7 ± 11.7 years (range 28 to 96), and 91 (51.4%) of the patients were older than 75 years, 83 (46.9%) were female. Almost all of them (99.4%) had dyspnea symptoms, the majority of them (91%) had severe dyspnea (New York Heart Association functional class NYHA III/IV). One hundred thirty-one patients (74%) were complicated with chronic artery disease. Paroxysmal or chronic atrial fibrillation was documented in 73 (41.2%) of the patients. Smoking was present in 79 patients (44.6%). Among them, 118 patients (66.7%) taken Antiplatelet agent.

Table 1

A. Baseline characteristics of 177 heart failure patients with and without elevated D-dimer (≥ 0.5 mg/L).

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		<0.50 (n = 117)	≥ 0.50 (n = 60)	
Demographic				
Age (years)	73.7 ± 11.7	72.79 ± 12.21	75.42 ± 10.39	0.158
Age ≥ 75 (years)	91 (51.4%)	57 (48.7%)	34 (56.7%)	0.344
Female	83 (46.9%%)	53 (45.3%)	30 (50.0%)	0.634
Smokers	79 (44.6%)	46 (39.3%)	33 (55.0%)	0.056
Dyspnea	176 (99.4%)	117 (100%)	59 (98.3%)	0.339
Admission vital signs				
SBP (mmHg)	127.38 ± 20.82	126.32 ± 19.70	129.47 ± 22.92	0.343
DBP (mmHg)	70.68 ± 13.92	70.97 ± 14.73	70.08 ± 12.26	0.690
HR (b.p.m.)	85.80 ± 20.40	85.88 ± 22.02	85.64 ± 20.29	0.945
Heart function parameters				
NT-proBNP (pg/mL)	7537.61 ± 9229.13	7031.31 ± 9385.65	8565.57 ± 8955.60	0.437
LVEF (%)	46.09 ± 14.16	45.92 ± 14.19	46.49 ± 14.27	0.830
LVEDD (mm)	52.31 ± 11.31	51.79 ± 11.27	53.40 ± 11.52	0.525
NYHA functional class				**0.001**
II	16 (9%)	13 (11.1%)	3 (5.0%)	
III	88 (49.7%)	67 (57.3%)	21 (35.0%)	
IV	73 (41.2%)	37 (31.6%)	36 (60.0%)	
LAD (mm)	42.10 ± 8.41	42.69 ± 9.19	40.59 ± 5.83	0.274
Lab examination				
PO2 (mmHg)	91.80 ± 28.78	91.26 ± 26.90	92.71 ± 32.06	0.805
Blood lactic acid (mmol/L)	1.83 ± 1.28	1.63 ± 0.72	2.17 ± 1.83	0.083

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; TT3, Total triiodothyonine protophan; FT3, Free triiodothyonine protophan; CA-125, Carbohydrate antigen-125; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		<0.50 (n = 117)	≥ 0.50 (n = 60)	
Oxygen saturation (%)	93.39 ± 9.73	93.69 ± 10.06	92.89 ± 9.25	0.687
White blood cell (*10^9/L)	7.15 ± 2.95	6.77 ± 2.60	7.88 ± 3.44	**0.017**
Red blood cell (*10^12/L)	3.96 ± 0.84	4.06 ± 0.76	3.75 ± 0.95	**0.021**
Hemoglobin (g/L)	119.33 ± 25.19	122.61 ± 22.94	112.95 ± 28.21	**0.015**
Hematocrit (%)	35.99 ± 7.24	36.89 ± 6.22	34.23 ± 8.67	**0.020**
Platelet (*10^9/L)	189.21 ± 84.28	195.65 ± 86.71	176.75 ± 78.57	0.159
D-dimer (mg/L)	0.95 ± 2.74	0.25 ± 0.12	2.33 ± 4.40	**<0.001**
Sodium (mmol/L)	139.62 ± 3.54	140.10 ± 2.88	138.66 ± 4.45	**0.026**
TT3 (ngl/mL)	3.26 ± 6.92	3.60 ± 6.78	2.67 ± 7.18	0.488
FT3 (pg/mL)	4.08 ± 6.53	4.22 ± 5.68	3.86 ± 7.73	0.780
CA-125 (U/L)	55.48 ± 95.49	34.55 ± 58.41	91.51 ± 130.96	**0.009**
Blood urea nitrogen (mmol/L)	10.43 ± 5.41	9.49 ± 4.60	12.26 ± 6.38	**0.004**
Serum creatinine (μmol/L)	147.04 ± 150.02	130.97 ± 100.07	178.40 ± 214.31	0.108
Total protein (g/L)	65.23 ± 7.70	66.31 ± 6.47	63.14 ± 9.33	**0.009**
Albumin (g/L)	36.44 ± 4.60	37.86 ± 3.17	33.72 ± 4.92	**<0.001**
Prealbumin (mg/L)	181.57 ± 72.70	196.07 ± 66.14	153.30 ± 77.04	**<0.001**
β2-microglobulin (mg/L)	7.02 ± 6.75	6.35 ± 5.94	8.29 ± 7.96	**0.043**
Co-morbidities				
Atrial fibrillation	73 (41.2%)	52 (44.4%)	21 (35.0%)	0.261
Diabetes mellitus	81 (45.8%)	50 (42.7%)	31 (51.7%)	0.259
Hypertension	129 (72.9%)	82 (70.1%)	47 (78.3%)	0.286
Chronic artery disease	131 (74.0%)	84 (71.8%)	47 (78.3%)	0.372

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; TT3, Total triiodothyonine protophan; FT3, Free triiodothyonine protophan; CA-125, Carbohydrate antigen-125; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		<0.50 (n = 117)	≥ 0.50 (n = 60)	
Medications				
β-Blockers	127 (71.8%)	85 (72.6%)	42 (70.0%)	0.727
Calcium channel blockers	36 (20.3%)	25 (21.4%)	11 (18.3)	0.697
ACEI or ARB	63 (35.6%)	42 (35.9%)	21 (35.0%)	1.00
Antiplatelet agent	118 (66.7%)	75 (64.1%)	43 (71.1%)	0.400
Statins	95 (53.7%)	62 (53%)	33 (55%)	0.874
Diuretics	174 (98.3%)	116 (99.1%)	58 (96.7%)	0.552
Trimetazidine	66 (37.3%)	48 (41.0%)	18 (30.0%)	0.189
Digoxin	87 (49.2%)	61 (52.1%)	26 (43.3%)	0.341
Spironoactone	110 (62.1%)	79 (67.5%)	31 (51.7%)	**0.050**

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; TT3, Total triiodothyonine protophan; FT3, Free triiodothyonine protophan; CA-125, Carbohydrate antigen-125; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).

Table 1

B. Baseline characteristics of 177 heart failure patients with and without elevated D-dimer(age-adjusted cut-off,>age/100 mg/L).

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		Normal (n = 132)	Elevated (n = 45)	
Demographic				
Age (years)	73.7 ± 11.7	73.13 ± 11.77	75.31 ± 11.32	0.280
Age ≥ 75 (years)	91 (51.4%)	65 (49.2%)	26 (57.8%)	0.389
Female	83 (46.9%)	60 (45.5%)	23 (51.1%)	0.604
Smokers	79 (44.6%)	55 (41.7%)	24 (53.3%)	0.224
Dyspnea	176 (99.4%)	132 (100%)	44 (97.8%)	0.254
Admission vital signs				
SBP (mmHg)	127.38 ± 20.82	127.33 ± 20.15	127.50 ± 22.95	0.963
DBP (mmHg)	70.68 ± 13.92	70.88 ± 14.19	70.07 ± 13.24	0.739
HR (b.p.m.)	85.80 ± 20.40	85.73 ± 21.71	86.00 ± 20.68	0.943
Heart function parameters				
NT-proBNP (pg/mL)	7537.61 ± 9229.13	7003.16 ± 8945.59	9140.99 ± 10052.08	0.350
LVEF (%)	46.09 ± 14.16	45.79 ± 14.42	47.21 ± 13.35	0.633
LVEDD (mm)	52.31 ± 11.31	52.03 ± 11.29	53.23 ± 11.60	0.666
NYHA functional class				**0.001**
II	16 (9%)	14 (10.6%)	2 (4.4%)	
III	88 (49.7%)	75 (56.8%)	13 (28.9%)	
IV	73 (41.2%)	43 (32.6%)	30 (66.7%)	
LAD (mm)	42.10 ± 8.41	42.69 ± 9.19	40.59 ± 5.83	0.266

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; CA-125, Carbohydrate antigen-125; TCHO, Total cholesterol; LDL, Low density lipoprotein; HDL, High density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		Normal (n = 132)	Elevated (n = 45)	
Lab examination				
PO2 (mmHg)	91.80 ± 28.78	91.42 ± 27.92	92.71 ± 31.20	0.836
Blood lactic acid (mmol/L)	1.83 ± 1.28	1.66 ± 0.74	2.24 ± 2.01	0.130
Oxygen saturation (%)	93.39 ± 9.73	93.44 ± 10.48	93.28 ± 7.82	0.929
White blood cell (*10^^{9}/L)	7.15 ± 2.95	6.80 ± 2.77	8.16 ± 3.25	**0.007**
Red blood cell (*10^^{12}/L)	3.96 ± 0.84	4.04 ± 0.79	3.72 ± 0.93	**0.027**
Hemoglobin (g/L)	119.33 ± 25.19	121.79 ± 23.87	112.13 ± 27.78	**0.026**
Hematocrit (%)	35.99 ± 7.24	36.71 ± 6.73	33.88 ± 8.28	**0.023**
Platelet (*10^^{9}/L)	189.21 ± 84.28	195.24 ± 83.56	171.67 ± 84.84	0.106
D-dimer (mg/L)	0.95 ± 2.74	0.28 ± 0.16	2.91 ± 4.96	**<0.001**
Sodium (mmol/L)	139.62 ± 3.54	140.00 ± 2.98	138.49 ± 4.66	**0.045**
CA-125 (U/L)	55.48 ± 95.49	37.36 ± 64.13	105.75 ± 141.60	**0.014**
Blood urea nitrogen (mmol/L)	10.43 ± 5.41	9.46 ± 4.51	13.27 ± 6.76	**0.001**
Serum creatinine (μmol/L)	147.04 ± 150.02	130.78 ± 96.99	194.76 ± 242.68	0.091
Total protein (g/L)	65.23 ± 7.70	66.17 ± 7.62	62.49 ± 7.32	**0.005**
Albumin (g/L)	36.44 ± 4.60	37.49 ± 4.00	33.43 ± 4.91	**<0.001**
Prealbumin (mg/L)	181.57 ± 72.70	190.08 ± 67.11	157.17 ± 82.82	**0.009**
TCHO (mmol/L)	3.79 ± 0.08	3.74 ± 0.91	3.92 ± 1.27	0.322
LDL (mmol/L)	2.35 ± 0.06	2.34 ± 0.78	2.37 ± 0.77	0.786

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; CA-125, Carbohydrate antigen-125; TCHO, Total cholesterol; LDL, Low density lipoprotein; HDL, High density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Variable	Total Cohort (n = 177)	D-dimer (mg/L)		p Value
		Normal (n = 132)	Elevated (n = 45)	
HDL (mmol/L)	0.98 ± 0.02	1.00 ± 0.28	0.90 ± 0.27	**0.031**
Co-morbidities				
Atrial fibrillation	73 (41.2%)	58 (43.9%)	15 (33.3%)	0.225
Diabetes mellitus	81 (45.8%)	63 (47.7%)	18 (40.0%)	0.392
Hypertension	129 (72.9%)	94 (71.2%)	35 (77.8%)	0.443
Chronic artery disease	131 (74.0%)	96 (72.7%)	35 (77.8%)	0.560
Medications				
β-Blockers	127 (71.8%)	97 (73.5%)	30 (66.7%)	0.444
Calcium channel blockers	36 (20.3%)	31 (23.5%)	5 (11.1%)	0.088
ACEI or ARB	63 (35.6%)	47 (35.6%)	16 (35.6%)	1.00
Antiplatelet agent	118 (66.7%)	89 (67.4%)	29 (64.4%)	0.855
Statins	95 (53.7%)	74 (56.1%)	21 (46.7%)	0.302
Diuretics	174 (98.3%)	131 (99.2%)	43 (95.6%)	0.159
Trimetazidine	66 (37.3%)	51 (38.6%)	15 (33.3%)	0.594
Digoxin	87 (49.2%)	66 (50.0%)	21 (46.7%)	0.732
Spironoactone	110 (62.1%)	87 (65.9%)	23 (51.1%)	0.109

SBP, Systolic blood pressure;DBP, Diastolic blood pressure;HR, Heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, Left ventricular ejection fraction;LVEDD, Left ventricular end-diastolic diameter; NYHA, New York Heart Association; LAD, Left atrial diameter; PO2, Partrial pressure of blood oxygen; CA-125, Carbohydrate antigen-125; TCHO, Total cholesterol; LDL, Low density lipoprotein; HDL, High density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).

The incidence elevated D-dimer levels in heart failure

D-dimer values were compared to the current cut-off of 0.5 mg/L showed in Table 1A. A total of 60 (33.9%) patients had elevated D-dimer levels. The concentrations of white blood cell ($p < 0.017$), carbohydrate antigen-125 ($p < 0.009$), β2-microglobulin ($p < 0.043$) and blood urea nitrogen ($p < 0.004$) were significantly higher in patients with elevated D-dimer compared with those with normal D-dimer.

However, the inverse relationship of the D-dimer levels with the anemia indicators including red blood cell ($p < 0.021$), hemoglobin ($p < 0.015$) and hematocrit ($p < 0.020$) were found. Correspondingly, patients with elevated D-dimer had a tendency of hypoproteinemia, such as lower total protein ($p = 0.009$), albumin ($p < 0.001$) and prealbumin ($p < 0.001$). In addition, the elevated group had a lower serum sodium levels than that in normal group ($p = 0.026$). Importantly, patients with the higher levels of D-dimer were accompanied by high New York Heart Association functional class (III/IV) ($p = 0.001$) though the left ventricular ejection fraction ($p = 0.830$) and N-terminal probrain natriuretic peptide (NT-proBNP) ($p = 0.437$) did not differ between the two groups. Interestingly, there were less patients with spironoactone

therapy in elevated D-dimer levels ($p = 0.050$). In addition, the percentage of patients with smoking in the elevated D-dimer group had a rising trend than that in normal group ($p = 0.056$). Interestingly, the results of the age-adjusted cut-off D-dimer is consistent with the current cut-off of 0.5 mg/L basically as shown in Table 1B. A total of 45 (25.4%) patients had elevated D-dimer levels. Additionally, elevated D-dimer group had a lower high density lipoprotein ($p = 0.031$).

Plasma D-dimer values according to clinical characteristics of the patients with heart failure were showed in Table 2. Higher D-dimer levels were found in patients more than seventy-five years old compared those less than seventy-five years old ($p = 0.018$). Moreover, plasma D-dimer levels were significantly higher with respect to severe heart failure symptoms, as judged by NYHA functional class ($p < 0.001$). Correspondingly, the presence of course of disease over five years were associated with increasing plasma D-dimer values ($p = 0.014$). In addition, there were a

trend toward higher plasma D-dimer levels in smokers ($p = 0.085$).

Table 2
Plasma D-dimer levels according to clinical variables of 177 patients with heart failure.

Variable	D-dimer (mg/L)				p Value
	Presence of variables		Absence of variables		
Age ≥ 75 (years)	n = 91	1.16 ± 3.42	n = 86	0.74 ± 1.73	**0.018**
Male	n = 94	1.08 ± 3.52	n = 83	0.80 ± 1.40	0.725
Smokers	n = 79	1.21 ± 3.78	n = 98	0.74 ± 1.42	0.085
Dyspnea	n = 176	0.95 ± 2.74	n = 1	1.68	0.226
NYHA functional class IV	n = 73	0.89 ± 1.04	n = 104	1.00 ± 3.47	**<0.001**
Course of disease > 5 years	n = 58	1.03 ± 4.18	n = 119	0.91 ± 1.65	**0.014**
Atrial fibrillation	n = 73	0.67 ± 1.36	n = 104	1.15 ± 3.38	0.379
Diabetes mellitus	n = 81	1.01 ± 3.59	n = 96	0.90 ± 1.74	0.977
Hypertension	n = 129	1.06 ± 3.13	n = 48	0.66 ± 1.09	0.199
Chronic artery disease	n = 131	0.85 ± 1.56	n = 46	1.24 ± 4.71	0.240
β-Blockers	n = 127	0.95 ± 3.02	n = 50	0.95 ± 1.84	0.820
Calcium channel blockers	n = 36	0.52 ± 0.82	n = 141	1.06 ± 3.03	0.353
ACEI or ARB	n = 63	1.44 ± 4.43	n = 114	0.68 ± 0.84	0.299
Antiplatelet agent	n = 118	0.84 ± 1.62	n = 91	1.17 ± 4.17	0.454
Statins	n = 95	0.73 ± 1.30	n = 82	1.20 ± 3.77	0.597
Diuretics	n = 174	0.90 ± 2.65	n = 3	4.18 ± 5.89	0.222
Trimetazidine	n = 66	0.67 ± 0.99	n = 111	1.12 ± 3.37	0.507
Digoxin	n = 87	0.71 ± 1.42	n = 90	1.19 ± 3.57	0.266
Spironoactone	n = 110	0.94 ± 3.25	n = 67	0.97 ± 1.60	0.221
Abbreviations as in Table 1.					

Data are expressed as median (interquartile range).

Linear and logistic regression analysis of elevated D-dimer levels in heart failure

The correlation between variables and D-dimer levels in patients with heart failure was depicted in Table 3. With univariate correlation analysis, D-dimer as a continuous variable, transformed by naturallogarithm. Log D-dimer was positively correlated with age (r = 0.233, p = 0.002), age over seventy-five years (r = 0.177, p = 0.018), white blood cell counts (r = 0.224, p = 0.003), blood lactic acid (r = 0.213, p

= 0.03), blood urea nitrogen (r = 0.242, p = 0.001), serum creatinine (r = 0.157, p = 0.037), uric acid (r = 0.169, p = 0.025), β2-microglobulin (r = 0.182, p = 0.016), but negatively with red blood cell (r = -0.162, p = 0.031), hemoglobin (r = -0.192, p = 0.011), hematocrit (r = -0.176, p = 0.019), TT3 (r = -0.273, p = 0.003), FT3 (r = -0.294, p = 0.001), sodium (r = -0.208, p = 0.006), total protein (r = -0.234, p = 0.002), albumin (r = -0.456, p <0.001), prealbumin (r = -0.321, p <0.001). In addition, a significant correlation was identified between log D-dimer and NYHA functional class (r = 0.271, p <0.001). Particularly, a significant increase of the percentage of patients with severe NYHA functional class (IV) in elevated D-dimer levels was observed (Fig. 2). Correspondingly, log D-dimer correlated positively with NT-proBNP (r = 0.213, p = 0.033) but negatively with the duration of disease (r = -0.156, p = 0.039).

Table 3
Correlation between Log (D-dimer level) and other variables in the patients with heart failure.

Variable	Univariate		Multivariate	
	Correlation coefficient(r)	p Value	Standardized coefficients (β)	p Value
Age (years)	0.233	0.002		
Age ≥ 75 (years)	0.177	0.018		
Length of HF diagnosis	-0.156	0.039		
NYHA functional class	0.271	<0.001	0.136	**0.042**
NT-proBNP (pg/mL)	0.213	0.033		
White blood cell (*10^9/L)	0.224	0.003		
Red blood cell (*10^12/L)	-0.162	0.031		
Hemoglobin (g/L)	-0.192	0.011		
Hematocrit (%)	-0.176	0.019		
Blood lactic acid (mmol/L)	0.213	0.03		
TT3 (ng/mL)	-0.273	0.003		
FT3 (pg/mL)	-0.294	0.001		
Sodium (mmol/L)	-0.208	0.006		
Blood urea nitrogen (mmol/L)	0.242	0.001	0.289	**<0.001**
Serum creatinine (μmol/L)	0.157	0.037		
Uric acid (μmol/L)	0.169	0.025		
Total protein (g/L)	-0.234	0.002		
Albumin (g/L)	-0.456	<0.001	-0.293	**<0.001**
Prealbumin (mg/L)	-0.321	<0.001	-0.199	**0.011**
β2- microglobulin (mg/L)	0.182	0.016		
Abbreviations as in Table 1.				

Multiple linear regression analysis showed that blood urea nitrogen (β = 0.289, p <0.001) and NYHA functional class (β = 0.136, p = 0.042) were independently associated with increasing log D-dimer, whereas albumin (β = -0.293, p <0.001) and prealbumin (β = -0.199, p = 0.011) were independently related

to decreasing log D-dimer (Table 3 and Fig. 2). Likewise, multivariable binary logistic regression analysis revealed that blood urea nitrogen (β = 1.106, 95% confidence interval [CI]: 1.029–1.190, p = 0.006) and NYHA functional class (β = 2.179, 95% confidence interval [CI]: 1.170–4.056, p = 0.014) were independent predictors of elevated D-dimer, whereas albumin (β = 0.803, 95% confidence interval [CI]: 0.728–0.885, P <0.001) predicted less likely elevated D-dimer after adjustment for conventional risk factors of heart failure (Table 4A). In addition to, white blood cell counts (β = 1.188, 95% confidence interval [CI]: 1.040–1.358, p = 0.011) was also an independent predictor of elevated D-dimer compared to the suggested age-adjusted cut-off (age/100 mg/L) (Table 4B).

Table 4

A. Association of elevated D-dimer (≥ 0.5 mg/L) levels with clinical variables by logistic regression analysis in the patients with heart failure.

Variable	Univariate		Multivariate	
	Exp (β) (95% CI)	p Value	Exp (β) (95% CI)	p Value
White blood cell (*10^9/L)	1.134 (1.018–1.263)	0.022		
Red blood cell (*10^12/L)	0.637 (0.432–0.939)	0.023		
Hemoglobin (g/L)	0.984 (0.972–0.997)	0.017		
Hematocrit (%)	0.949 (0.907–0.993)	0.023		
CA-125 (U/L)	1.007 (1.002–1.012)	0.006		
Sodium (mmol/L)	0.888 (0.810–0.975)	0.012		
Blood urea nitrogen (mmol/L)	1.098 (1.035–1.165)	0.002	1.106 (1.029–1.190)	**0.006**
Total protein (g/L)	0.944 (0.903–0.987)	0.011		
Albumin (g/L)	0.795 (0.726–0.869)	<0.001	0.803 (0.728–0.885)	**<0.001**
Prealbumin (mg/L)	0.991 (0.986–0.996)	<0.001		
Blood lactic acid (mmol/L)	7.381 (1.001–54.425)	0.050		
NYHA functional class	2.577 (1.482–4.482)	0.001	2.179 (1.170–4.056)	**0.014**
Spironoactone	0.514 (0.272–0.972)	0.041		
smokers	1.886 (1.005–3.540)	0.048		
Abbreviations as in Table 1.				

Table 4

B. Association of elevated D-dimer(age-adjusted cut-off,>age/100 mg/L)levels with clinical variables by logistic regression analysis in the patients with heart failure.

Variable	Univariate		Multivariate	
	Exp (β) (95% CI)	p Value	Exp (β) (95% CI)	p Value
White blood cell (*10^9/L)	1.134 (1.018–1.263)	0.022	1.188 (1.040–1.358)	**0.011**
Red blood cell (*10^12/L)	0.637 (0.432–0.939)	0.023		
Hemoglobin (g/L)	0.984 (0.972–0.997)	0.017		
Hematocrit (%)	0.949 (0.907–0.993)	0.023		
CA-125 (U/L)	1.007 (1.002–1.012)	0.006		
Sodium (mmol/L)	0.888 (0.810–0.975)	0.012		
Blood urea nitrogen (mmol/L)	1.098 (1.035–1.165)	0.002	1.150 (1.062–1.245)	**0.001**
Total protein (g/L)	0.944 (0.903–0.987)	0.011		
Albumin (g/L)	0.795 (0.726–0.869)	<0.001	0.843 (0.764–0.931)	**0.001**
Prealbumin (mg/L)	0.991 (0.986–0.996)	<0.001		
Blood lactic acid (mmol/L)	7.381 (1.001–54.425)	0.050		
NYHA functional class	2.577 (1.482–4.482)	0.001	3.581 (1.651–7.767)	**0.001**
Spironoactone	0.514 (0.272–0.972)	0.041		
smokers	1.886 (1.005–3.540)	0.048		
Abbreviations as in Table 1.				

Clinical Outcomes

The patients of the present study was followed up for a median of 21 months (ranged from 11 to 30 months), 12 patients were lost to follow up. During the follow up, all-cause death occurred in 78 patients (44.1%). Figure 3 showed the Kaplan-Meier curves for cumulative survival stratified by admission D-dimer level. It was found that patients with elevated D-dimer levels had significantly higher cumulative mortality than patients with normal D-dimer levels (log rank $P = 0.048$).

Discussion

In recent years, advanced treatment have reduced the mortality and improved the quality of life for patients with heart failure. However, altered hemostasis and abnormalities in endothelial function are thought to be other possible mechanisms that contribute to disease progression, ischemic events, and intracardiac thrombosis in heart failure [10]. HF is associated with an increased risk of venous

thromboembolism (VTE) as a result of vascular abnormalities, increased coagulability, and impaired blood flow [11]. VTE includes two main clinical manifestations, deep vein thrombosis (DVT) and pulmonary embolism (PE), leading to a higher mortality in heart failure [12]. Patients with heart failure have a higher risk of VTE than those without heart failure, and the risk increases with the severity of heart failure. D-dimer is a product of the degradation of cross-linked fibrin and its plasma levels reflect both fibrin formation and degradation, and hence, D-dimer is elevated when there is thrombosis in the whole circulatory system. D-dimer is considered a useful biomarker worthy of continued attention because of its potential to identify patients with hypercoagulability [13]. Alexandre and Theodore E. et al. who evaluated 2593 hospitalized HF patients, observed an positive association between HF severity and both VTE risk and D-dimer concentration [11]. Marcucci et al. found that D-dimer levels increasd significantly in acute decompensated HF patients [14]. In addition, In the study of Ali Zorlu, it was shown that D-dimer was predictive of mortality in patients with systolic HF [4]. In consistent with the previous studies, our data suggested that plasma D-dimer levels were elevated in patients with HF. Importantly, patients with the higher levels of D-dimer were accompanied by high New York Heart Association (NYHA) founctional calss. Furthermore, our study showed that a elevated D-dimer level associated with an increased risk of all-cause death in elderly patients with CHF during 2 years follow up (Fig. 3).

Generally, the patients with HF were often accompanied by a disorder of protein metabolism. Albumin as the most represented plasma protein plays a pivatal role in the maintenance of homeostasis and physiological functions [15]. Serum albumin as a nutritional marker is related to cardiovascular mortality as well as important survival determinants and indicators for hemodialysis patients [16]. Hypoalbuminemia is common in elderly HF patients with a prevalence of 25–42% [17]. Previous studies also showed that hypoalbuminemia was associated with cardiovascular disease in the general population and adverse outcome in patients with HF independent of natriuretic peptides [18]. Arnaud et al studied 546 patients with HF, and found that 64.8% patients with a serum albumin lower 38.7 g/L and hypoalbuminemia (< 34 g/L) yielded the best sensitivity (78.8%) and specificity (75%) for predicting hospital death [19]. A retrospective studies in a real-world cohort of patients with HF performed by Israel et al demonstrated that decreasing albumin levels were directly associated with reduced survival and serum albumin is a significant predictor of a worse outcome in these patients [20]. Another study done in 177 patients with acute decompensated heart failure (ADHF) performed by Megan M et al showed that baseline serum albumin concentration of 30 g/L or less had a value for predicting worsening renal function in patients with ADHF [21]. The finding is consistent with our belief, our data suggested that patients with HF had a less serum albumin level compared to the threshold, 36.44 ± 4.60 g/L and 40 g/L, respectively. And about one hundred thirty-three patients (75%) had a serum albumin value less than 40 g/L. Additionally, our results showed that the serum albumin level were negatively significant associated with both elevated D-dimer and plasma D-dimer levels on univariate analysis. Furthermore, multivariate analysis showed that the serum albumin level was independently related to elevated D-dimer levels. Several mechanisms have been proposed to explain the association between hypoalbuminemia and plasma D-dimer, including hypoalbuminemia-induced hypercoagulability and thrombosis [22, 23]. Data from Bang et al and Iioka Y et al showed negative correlations between serum albumin level and plasma

D-dimer level in patients with nephrotic syndrome [24, 25]. A similar result was obtained by Remuzziet al [26]. Combined with the negative correlations between plasma D-dimer and serum albumin found in this study, which have also been indicated by Soon Bae Kim et al [27], we speculated that elevated plasma D-dimer in HF may be partially related to hypoalbuminemia-induced hypercoagulability.

Prealbumin (PAB) is another indicator of nutritional status, similar to albumin, also known as transthyretin. Compared with albumin, PAB has the advantages of shorter half-life and smaller serum pool. Its main functions are to bind and transport endogenous proteins and small molecules. Thus, PAB is more sensitive to changes in acute protein status [28]. Previous studies have shown that prealbumin is most commonly used as an indicator of malnutrition, and hypoalbuminemia has an adverse effect on disease outcomes because of increase in incidence of infection, length of hospital stay, and risk of death [29]. Andreia et al found that hypoprealbuminemia are more susceptible to early posttransplant thrombotic complications, particularly hepatic artery thrombosis which correlates with high morbidity, in patients with hereditary transthyretin amyloidosis (ATTR) [30]. Patrícia and his colleagues showed that prealbumin is an independent predictor of in-hospital mortality in HF patients [31]. Furthermore, they suggested that prealbumin levels below a cut-off < 15 mg/dL were found to be associated with reduced survival and increased rates of all-cause and HF readmission at 6-month follow up [32]. In consistent with the previous studies, our finding using multivariate linear regression analysis showed that the serum prealbumin level was inversely related to elevated plasma D-dimer levels after adjustment for multiple variables including age, gender, HF risk factors, and medicine treatment. More interestingly, our data showed that elevated D-dimer level was with a lower serum prealbumin level about 15.3 mg/dL.

Blood urea nitrogen (BUN) as a nitrogenous end product of protein metabolism has been observed to be associated with mortality in various diseases [33]. A large body of evidence have demonstrated that elevated BUN levels are associated with adverse outcomes in patients with HF, especially in acute decompensation state [34, 35]. The ACTIV study showed highest BUN quartile had the highest 60-day mortality, more importantly, BUN was a predictor of the composite end point of mortality and 60-day post-discharge death or hospitalization for chronic heart failure [36]. Fonarow et al identified BUN level of 43 mg/dL on admission as the best single indicator between hospital survivors and nonsurvivors by evaluating the Acute Decompensated Heart Failure National Registry (ADHERE) database. Of note, they suggested that BUN may be a stronger predictor of outcomes [37]. In a total of 541 patients with decompensated HF, Aronson et al showed BUN was also a predictor of adverse outcomes after discharge, comparing with the impact of serum creatinine. Moreover, BUN had at least equal role in determining prognosis and predicting mortality compared with N-terminal brain precursor natriuretic peptide (NT-proBNP) [38]. In addition, It has been shown that in patients with stable CHF, elevated BUN levels are still strongly associated with short and long-term mortality [39]. The precise mechanisms underlying the relationship between BUN and HF are that in patients with HF, low cardiac output decreases renal blood flow and GFR which leading to an increase of urea and thus BUN. Meanwhile, BUN may also be affected by intestinal function, nutritional status such as protein intake or systemic catabolism, and neurohumoral factors [40]. As expected, our data suggested that patients with heart failure had a higher BUN levels than that in the general population, of note, the positive relationship between BUN and D-dimer remained

significant even after adjustment for potential confounding factors, in multivariate linear regression analysis. Although we were unable to elucidate the definite causes for this correlation, inflammation might play a role in this regard. It was proposed that BUN increased levels of inflammatory markers and mediators which leading to hypercoagulability and embolism in alcoholic hepatitis patients [41].

As we known, D-dimers are fibrin degradation products released into the bloodstream after blood clot fibrinolysis that have classically been used for the evaluation of venous thromboembolism. However, D-dimers are also serum acute-phase proteins (APP) that show upregulated expression after stress, infection, or worsening disease states [42]. Increasing evidences have showed that inflammatory response played an important role in the development of DVT. Acute DVT causes a systemic inflammatory response characterized by elevated inflammatory factors and temporal accumulation of inflammatory cells including white blood cells [43, 44]. Dawei Liu et al studied 1179 patients of tibial plateau fractures, and found that platelet and neutrophil count were independently associated with elevated D-dimer levels [45]. Moreover, data from 84 patients with lung cancer showed the accumulation of massive neutrophils in the inflammation sites leads to embolism and thrombosis which resulting poor prognosis [46]. One reason D-dimers may be predictive of the outcome is because they serve as a biomarker of inflammation. In consistent with this studies, our data suggested that plasma D-dimer levels were significantly positively associated with white blood cell counts, furthermore, white blood cell counts was an independent predictors for a high D-dimer level.

Our study has several limitations, worthwhile mentioning. Firstly, it was a single centre and observational study with a limited number of patients, and our results may not be extended to patients in other regions due to the heterogeneity in individual. Secondly,we only measured D-dimer levels at admission, and it was therefore not possible to assess changes in D-dimer levels over time and to evaluate the implications of these changes on CHF outcomes. Thirdly, the follow up time was only 2 years, and the more long-term effect of D-dimer on prognosis still needs to be further studied. We're just looking at all causes of death and the exact cause of death was not analyzed. Last but not least, due to the observational study design, the effect of unmeasured confounders may have impacted the results, although we performed statistical adjustments. Despite these limitations, our results still have a potential clinical significance and merit further researches, particularly for elderly patients with end-stage heart failure.

Conclusions

In the present study, we found numbers of elderly patients with end-stage CHF had a significant increase in D-dimer levels. Blood urea nitrogen, NYHA functional class and white blood cell counts were independent risk factors for elevated D-dimer, whereas, albumin and pre albumin were negative risk factor for elevated D-dimer. Moreover, elevated D-dimer level was independently associated with poor long-term outcome in elderly patients with end-stage heart failure. However, more long-term effect of D-dimer on prognosis needed to be further studied.

Abbreviations

HF	Heart Failure
NYHA	New York Heart Association
LVEF	Left Ventricular Ejection Fraction
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
ACEI	Angiotensin-converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker

Declarations

All procedures and methods included in this study were undertaken as part of routine clinical practice and regulations of Beijing Geriatric Hospital (Beijing, China).

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of Beijing Geriatric Hospital. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Consent for publication

Not applicable.

Availability of data and materials

Datasets used during the current study are included in supplementary information files.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Aiju Tian conceived, designed and drafted the project; Shengfeng Weng provided administrative, technical, or material support; Xiaoli Chen and Hong Liu collected the data; Chengzhi Yang conducted the data analysis and suggested revisions of the paper. Zhi Luo conceived and designed the project. All the authors have read and approved the final manuscript.

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Figures

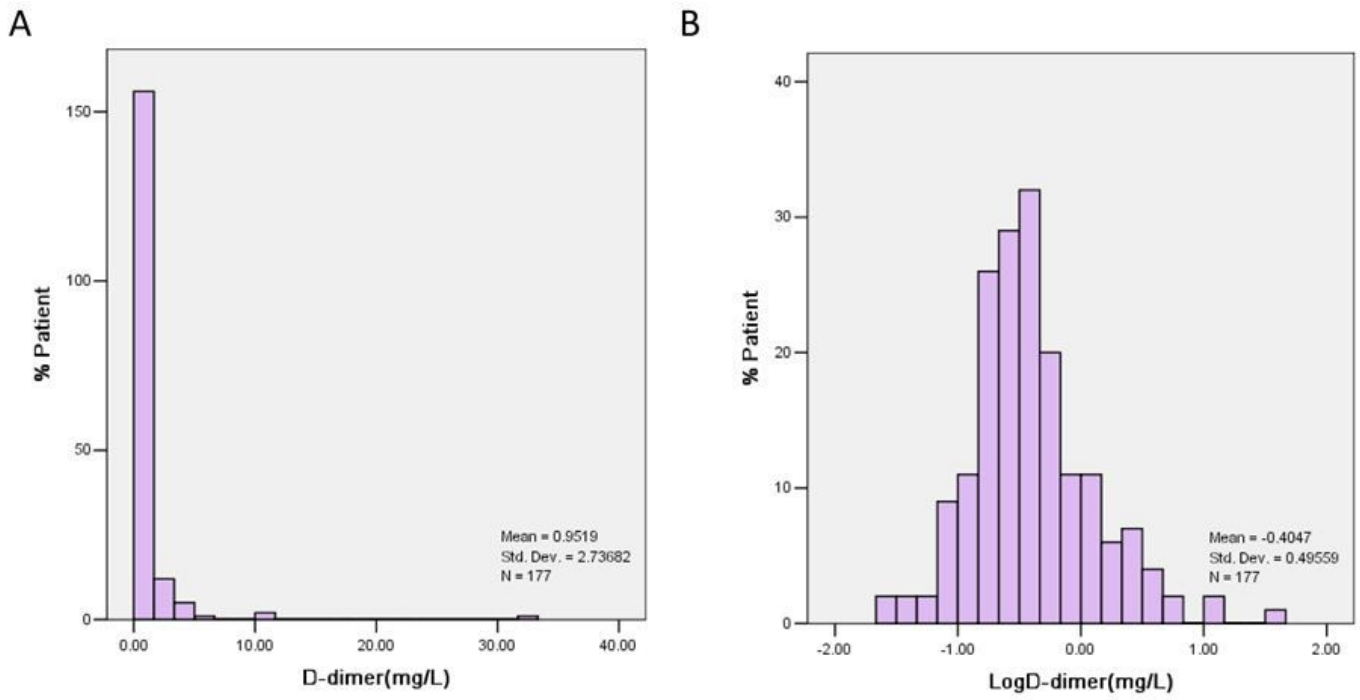

Figure 1

(A) Frequency distribution of plasma D-dimer levels in patients with heart failure. (B) Frequency distribution of plasma D-dimer levels in patients with heart failure after logarithmic transformation.

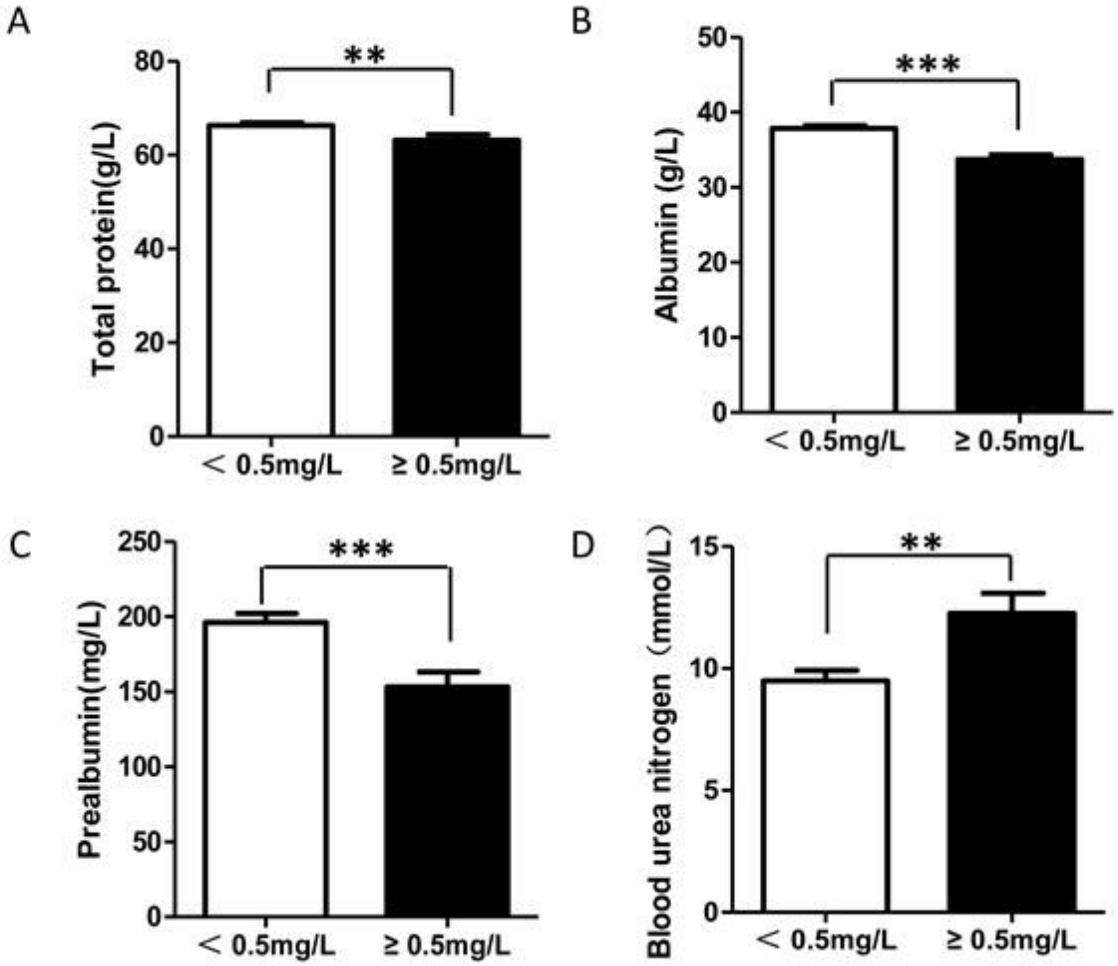

Figure 2

(A) Serum total protein levels in patients with and without elevated plasma D-dimer. (B) Serum albumin levels in patients with and without elevated plasma D-dimer. (C) Serum prealbumin levels in patients with and without elevated plasma D-dimer. (D) Blood urea nitrogen levels in patients with and without elevated plasma D-dimer.

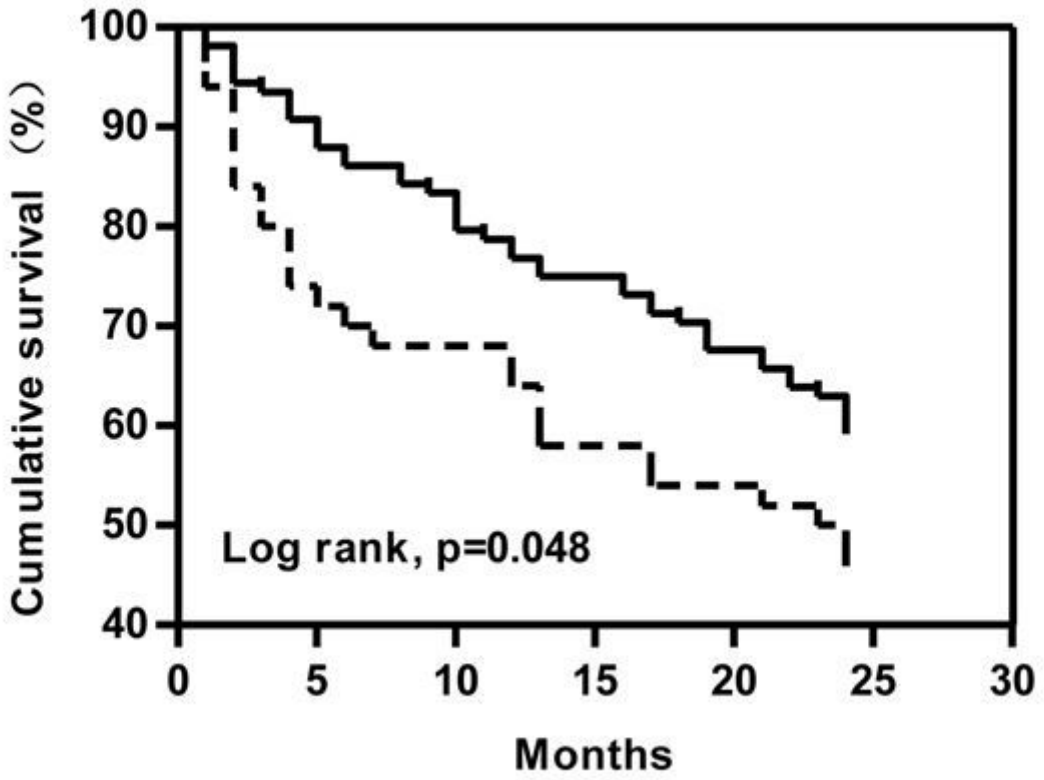

Figure 3

Kaplan-Meier curve for cumulative event-free survival in patients with D-dimer ≥ 0.50 and < 0.50 mg/L. During a median follow up period of 21 (interquartile range, 11 to 30) months, all-cause death occurred in 78 patients (44.1%). All-cause death occurred in 48 patients (42.9%) in D-dimer < 0.50 mg/L group. All-cause death occurred in 30 patients 56.7%) in D-dimer ≥ 0.50 mg/L group. Elevated plasma D-dimer levels were significantly associated with all-cause death (P = 0.048). (¬ -), D-dimer < 0.50 mg/L ; (–), D-dimer ≥ 0.50 mg/L.

Supplementary Files

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