HUMAN BIOLOGY
2025, VOL. 95, ISSUE 1
ORIGINAL ARTICLE

OPEN ACCESS

Plasma D-Dimer Concentrations as A Risk Factor in Patients with Acute Heart Failure

Juanjuan Liu[1], Peiwu Li[1], Li Song[1]

ABSTRACT

Background: The aim of this clinical study was to evaluate the risk factors associated with Acute Heart Failure (AHF) patients, classified according to the presence of patients-reported clinical symptoms and signs.

Methods: There were 181 AHF patients of which included in this cross-sectional clinical investigation from 02.09.2022 to 31.03.2023 in the Emergency department of Laanzhou University Second Hospital. Additionally, there are four categories of AHF patients (warm and wet, warm and dry, cold and wet, and cold and dry), and which not only the guidelines of the treatment therapy but also enables the progression of AHF in patients to be assessed. All statistical tests were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM-SPSS, Chicago, IL, USA). A p-value of < 0.05 was assumed to be significant.

Results: Based on the results of the ordinary logistic regression analysis, it can be concluded that individuals with acute heart failure with elevated d-dimer levels were substantially more likely to be "cool and dry" (odds ratio [OR] 1.12, 95% confidence intervals [CI] (0.017;0.212); P=0.022). Additionally, a strong association was identified between the "cold and dry" and the lower patient age (OR 0.95, 95% CI (-0.084;0.011); P=0.011).

Conclusion: According to the results from this clinical study, it can be concluded that the higher d-dimer levels had a significant relationship with the essential circumstances of symptoms and signs in AHF patients. In addition, age was also associated with the progression in patients with AHF based on the clinical assessment.

INTRODUCTION

Dyspnea, lower limb oedema, evidence of decreased cardiac output, and/or elevated intracardiac pressures are all symptoms and signs of heart failure (HF). The latter can be defined as a clinical illness caused by structural and/or functional cardiac abnormalities Ponikowski et al. (2016). HF is commonly recognised as a fatal illness and thus it is a significant global public health concern. Not only does it have a significant impact on patient mortality and morbidity but it also highlights the importance of providing infrastructure that facilitates the care of these patients. Acute decompensated heart failure (ADHF) is the term used to describe acute heart failure (AHF), which is defined as the development of typical heart failure (HF) signs and symptoms for the first time in the presence of pre-existing cardiomyopathy. Emergency care is essential because the disorder poses a significant threat to life. Due to the ageing population and the increasing prevalence of HF, the actual number of HF hospitalizations has significantly worsened in recent times, with more than 80% of hospitalised HF patients being treated in emergency department settings Storrow et al. (2014).

The severity of the initial clinical presentation of the symptoms and signs of AHF patients is employed by the European Society of Cardiology Meade et al. (1986) to diagnose AHF patients Nohria et al. (2003) Patients with AHF are classified as "wet" or "dry" based on their fluid condition, and "cold" or "warm" depending on their perfusion status. The four categories (warm and wet, warm and dry, cold and wet, and cold and dry) will be combined with those clinical assessments and serve as both a progression chart for AHF patients as well as a guide for medical therapy Meade et al. (1986). To evaluate and analyse the risk fators variables in the AHF patients in the Emergency Department, a comprehensive and objective clinical investigation was carried out in this work. This clinical trial is helpful in slowing the progression of AHF and lowering the

[1]The Second hospital of Lanzhou University, Research Center of Emergency, Lanzhou China.

Correspondence to: Li Song, MD, The Second hospital of Lanzhou University, Research Center of the Emergency, Lanzhou, China, Tel ph: 0086-09318942430, E-mail: songli81@yeah.net.

Keywords: Acute Heart Failure, Risk Factor, Plasma D-dimer, Cross-sectional Clinical Study, Emergency Department.

incidence of AHF in general. Moreover, in order to slow the evolution of acute heart failure, we sought to identify the risk factors involved in the advancement of AHF in accordance with the European Society of Cardiology's recommendations Ponikowski et al. (2016). These risk factors might be crucial in the initiation and progression of AHF. By examining these risk factors, AHF can be prevented the development and AHF patients can be given the most appropriate and optimal care based on the clinical literature recommendations.

METHODS

Research Design and Participants

Altogether, there were 181 participants took part in this cross-sectional clinica study, all of whom had been diagnosed with Acute Heart Failure in the Emergency department of the Lanzhou University Second Hospital. To take part in this study, patients had to be over 21 years of age and have experienced a rapid onset of disease. Moreover, their clinical syndrome must have been characterized by various symptoms, including dyspnoea, orthopnoea and lower limb swelling. Moreover, other signs such as elevated jugular venous pressure and pulmonary congestion may be present. In addition, it is important to note that patients who had experienced acute cardiovascular events, congenital heart disease, or chronic kidney disease were excluded from participation in this study. Based on the clinical signs and symptoms presented in the acute heart failure patients, four groups were established, namely warm and wet (group I), warm and dry (group II), cold and wet (group III), and cold and dry (group IV).

In this cross-sectional study, the researchers adhered to the guidelines established in the guildline of Declaration Halsinkin, 2013. Moreover, the study procedures were approved by the ethics committees of the Lanzhou University Second Hospital (the reference number of the ethics vote: 2022A-514). All patients who agreed to participate were asked to sign informed consent forms. Additionally, to maintain patient confidentiality, no identifying information (such as names, addresses or identification numbers) was collected from patients.

Blood was taken in the morning from each AHF patients, after which it was immediately processed in the Central Laboratory of the Lanzhou University Second Hospital under the set established standards. To measure the serum glucose levels, a variety of methods were employed, such as the cholesterol oxidase method, the cholesterol oxidase method for total cholesterol, colourimetry, the chemistry modified enzyme method, the selective melt method, the cholesterol oxidase method for low-density lipoprotein (LDL) cholesterol, the cholesterol oxidase method for high-density lipoprotein (HDL) cholesterol, and the uric acid method. Meanwhile, ionic exchange HPLC (IE-HPLC) was used in the D-10 haemoglobin analysis system to measure the HbA1c level (Bio-Rad). Additionally, the urinary albumin (unit: mg) level was measured through an immunoturbidimetry test (Image 800, Beckman Coulter). Tests were also carried out to determine the creatinine (unit: g) and urinary albumin-to-creatinine ratio (UACR). Baseline plasma D-dimer concentrations were sent to a central laboratory for testing using frozen (−20°C) citrated plasma with Siemens Healthcare Diagnostics INNOVANCE® D-dimer reagents. The intra-assay precision is 1.5-7.8, whilst the variation coefficient was between 2.2% to 7.9%.

Continuous parameters were summarized as mean ± SE. The two measures used to express categorical parameters were absolute and relative frequencies. The homogeneity test of variance was used to determine whether the variance was uniform or equal. P-value is a comparison of the classify in AHF patients. The continuous parameters were employed based on the Kruskal-Wallis test for non-normal distributed values, whilst the values of the AVONA test were found to have a normal distribution. If the Fishers exact test for categorical variables was not employed and 0 cells had expected counts less than 5, the Pearson Chi-square was applied. To measure the relationship between potential risk factors and identify AHF patients based on the clinical assessment, ordinal logistic regression models were applied. SPSS Version 25.0 from IBM-SPSS was used for all statistical analyses (Chicago, IL, USA).

RESULTS

This clinical trial involved 181 particioants in AHF. The baseline clinical characteristics between the four groups of AHF patients are presented in Table 1. Significant age differences were identified between the patients in group 1 (aged 68.52±1.82 years), group II (aged 68.64±1.45 years), group III (aged 64.11±2.15 years) and group IV (aged 61.41±2.36 years). In terms of those patients' kidney function, there were substantial differences between the patients' UA in the four groups. Moreover, ALP was found to be highest in group III, and this was associated with the patient's liver function (see table 1). Regarding those patients' plasma electrolyte levels, the k+ and Cl- levels of AHF patients, respectively, were likewise considerably different (see table 1). There were no discernible changes in the blood lipid levels between the four groups in patients with AHF (see table 2). Additionally, the d-dimer was the highest in-patient group VI (details presented in table 2) in AHF patients.

With regard to the risk factors of AHF patients, the p-value for the parallel line test was found to be 0.479, whilst the p-value of model fitting information was found to be 0.008. Therefore, the ordinary logistic regression analysis was performed. According to the ordinary logistic regression analysis results, it revealed that there are

Table 1: Demographic features of the AHF participants. (Continuous parameters are summarized as mean ± SE.)

	Group I (n=46)	Group II (n=76)	Group III (n=27)	Group IV (n=32)	P
Age(years)	68.52±1.82	68.64±1.45	64.11±2.15	61.41±2.36	0.024
Gender(f/m)	16/30	37/39	10/17	10/22	0.260
Pluse (bpm)	93.16±4.42	92.77±3.06	95.12±3.16	99.16±5.62	0.712
Hemoglobin(g/l)	119.92±7.29	130.06±4.63	111.88±9.87	126.44±7.44	0.279
C-reactive protein (mg/l)	30.43±7.91	23.32±3.41	46.77±12.49	34.17±10.82	0.188
Glucose (mmol/l)	8.48±0.67	8.67±0.53	9.56±0.98	7.00±0.45	0.153
Urea Nitrogen (mmol/l)	10.80±1.06	11.65±0.81	19.45±3.46	14.26±2.00	0.066
Creatinine (umol/l)	119.91±17.41	145.18±16.67	349.24±91.83	206.55±60.73	0.054
Uric Acid (umol/l)	415.12±24.33	449.05±17.38	536.35±40.24	523.33±32.43	0.006
k^+ (mmol/l)	4.00±0.08	4.04±0.77	4.73±0.28	4.35±0.26	0.006
Cl^- (mmol/l)	102.82±0.80	101.58±0.72	96.89±3.75	103.51±1.03	0.029
Na^+ (mmol/l)	135.66±0.65	136.63±0.54	135.26±1.19	135.87±0.88	0.554
Albumin (g/l)	36.67±0.65	36.56±0.45	36.09±1.07	36.68±0.72	0.945
AST (u/l)	51.17±14.90	70.42±25.56	139.26±74.86	98.10±44.15	0.449
ALT (u/l)	56.39±25.72	46.78±13.75	110.70±57.70	103.74±49.43	0.361
TBIL (umol/l)	24.67±3.04	23.76±1.85	32.48±6.60	31.51±4.21	0.171
DBIL (umol/l)	6.12±0.93	7.44±0.79	11.94±3.03	9.27±1.68	0.050
IBIL (umol/l)	18.83±2.24	16.47±1.25	17.52±3.24	21.24±2.87	0.425
ALP (u/l)	92.70±6.04	106.75±5.64	137.70±24.49	105.23±8.04	0.043

(AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; ALP: Alkaline Phosphatase.)

Table 2: The blood lipids and d-dimer levels in patients with acute heart failure.

	Group I (n=46)	Group II (n=76)	Group III (n=27)	Group IV (n= 32)	P
Triglycerides (mmol/l)	1.04±0.60	1.21±0.61	1.35±0.16	1.08±0.07	0.079
High-density Lipoprotein (mmol/l)	1.02±0.49	0.99±0.39	3.58±2.69	0.92±0.48	0.135
Low-density Lipoprotein (mmol/l)	2.08±0.10	2.27±0.84	2.31±0.18	2.20±0.15	0.525
Cholesterol (mmol/l)	3.43±0.15	3.43±0.11	3.17±0.29	3.12±0.16	0.323
D-dimer (ug/ml)	1.59±0.31	2.43±0.40	5.06±1.56	6.02±1.38	0.011

significant relationship between the elevated d-dimer levels and "cold and dry" in patients suffering from acute heart failure (OR 1.12, 95% CI (0.017;0.212); P=0.022). These details are presented in Table 3.

The findings also indicated that there is a relationship between the lower age of patients suffering from acute heart failure and the "cold and dry" (OR 0.95, 95% CI (-0.084;0.011); P=0.011). This is also presented in Table 3.

Table 3: Ordinary logistic regression analysis of parameters associated with acute heart failure.

	Exp(B)	**95%CI**	**P**
Age (years)	0.953	(-0.084，0.011)	0.011
Gender (f)	1.359	(-0.471，1.086)	0.439
Hemoglobin (g/l)	1.002	(-0.006，0.011)	0.6
C-reactive protein (mg/l)	1.002	(-0.006，0.011)	0.583
Glucose (mmol/l)	0.959	(-0.137，0.053)	0.386
Urea Nitrogen (mmol/l)	1.024	(-0.059，0.107)	0.574
Creatinine (umol/l)	1	(-0.003，0.004)	0.791
Uric Acid (umol/l)	0.999	(-0.004，0.002)	0.596
k^+ (mmol/l)	1.292	(-0.254，0.765)	0.325
Cl^- (mmol/l)	1.003	(-0.034，0.040)	0.867
Na^+ (mmol/l)	1.002	(-0.085，0.090)	0.96
Albumin (g/l)	0.955	(-0.161，0.069)	0.432
Alanine Aminotransferase (u/l)	1.003	(-0.002，0.007)	0.273
Total Bilirubin (umol/l)	0.998	(-0.044，0.039)	0.912
Direct Bilirubin (umol/l)	1.019	(-0.070，0.107)	0.678
Alkaline Phosphatase (u/l)	1.003	(-0.004，0.009)	0.403
Triglycerides (mmol/l)	0.433	(-1.827，0.155)	0.098
High-density Lipoprotein (mmol/l)	0.308	(-2.807，0.454)	0.157
Low-density Lipoprotein (mmol/l)	1.887	(-0.365，1.634)	0.213
Cholesterol (mmol/l)	1.083	(-0.686，0.847)	0.837
D-dimmer (ug/ml)	1.121	(0.017，0.212)	0.022
Creatine Kinase (u/l)	0.993	(-0.025，0.010)	0.408

(Abbreviation: OR:odds ratio, CI: confidence intervals.)

DISCUSSION

The key objective of the present cross-sectional clinica study is to assess the risk factors associated with the classification in accordance with the symptoms and signs of AHF patients. Based on the results of the ordinary logistic regression analysis in this clinical study, the following conclusions could be drawn: 1) the elevated d-dimer levels were significant relationship with the key symptoms and indicators of AHF patients. 2) the age of patients had associated with the symptoms and signs in patients with AHF. D-dimer can be defined as a byproduct of cross-linked fibrin's plasmin-mediated breakdown, and it serves as an important marker for thrombogenesis. It can also indicate a hypercoagulable condition that develops following the rupture of plaque Tomura et al. (1991) The production of fibrin in the endogenous fibrinolytic system and the following progression of breakdown determine the plasma concentrations of D-dimer Tomura et al. (1991). Moreover, a number of studies have identified a relationship between heart failure and hemostatic problems [Ng et al. (2014), Lip et al. (1999)]. Furthermore, multiple studies have shown that increased D-dimer levels in HF patients who are hospitalized are linked to poor outcomes Hamatani et al. (2018), Yan et al. (2019), Zorlu et al. (2012).

The vascular system of AHF patients is especially susceptible to thromboembolic events and this is due to coagulation abnormalities in such individuals. Research has shown that there may be a relationship between plasmin-mediated fibrin degradation (another sensitive indicator of ongoing thrombosis), and d-dimer levels (a key marker of a thrombotic burden that indicates the turnover of fibrin secondary to plaque rupture at vascular sites), and an inflammatory vascular state Weitz et al. (2017). In the AHF patients, this may be an indication

of a systemic prothrombotic condition that is characterised by localized vessel wall-related fibrin production and breakdown. Moreover, this is associated with unstable atherosclerotic plaque activity. Davies et al. (1990) The predictive impact of d-dimer impacts the mortality of AHF patients. The mechanism underlying this may be influenced by the different pathogenic pathways of thrombotic events that are involved in processes of atherosclerosis, inflammatory conditions and infectious disease Simes et al. (2018). Moreover, a number of studies have shown a strong correlation between d-dimer levels and increased mortality in patients with heart disease Simes et al. (2018), Oldgren et al. (2001), Moss et al. (1999), Mjelva Øistein et al. (2016). Research thus indicates that higher D-dimer levels could independently predict all-cause mortality in heart failure patients during a 1-year follow-up Huang et al. (2022) In terms of AHF, it has already been established that AHF and outpatients have higher levels of d-dimer in their bodies Davis et al. (2000), Jafri et al. (1993). Nonetheless, very few studies have examined this risk factors in AHF patients based on their symptoms and signs in the clinical literature. D-dimer has always been considered a key indicator of a temporary hypercoagulable state, although recent research has indicated that this condition can be persistent, particularly in those who have been hospitalised due to acute heart failure patients. Amin et al. (2012) Moreover, AHF patients often experience immobility and hemodynamic changes that have pro-thrombotic causes, although such changes are reversible and treatable. Additionally, endothelial damage, persistent hemodynamic irregularities, and chronic systemic inflammatory condition in AHF patients may be able to control the long-term risk factors of thrombosis. There also appears to be a relationship between elevated d-dimer levels and AHF prognosis, and this reflects cardiac functional status and the severity of the disease severity. Ultimately, this is caused by haemodynamic changes and impaired blood flow in AHF patients. Moreover, the inflammatory reactions that occur in AHF patients could be due to increased d-dimer levels, which induce the synthesis and release of inflammatory cytokines Robson et al. (1994). Thus, in turn, this increases the disease burden in such individuals.

Despite the fact that the ordinary logistic regression also highlighted a significant relationship between the "cold and dry" and lower patient age (OR 0.95, 95% CI (-0.084;0.011); P=0.011). Patients with AHF, particularly those who are elderly, are more likely to experience complications, readmission, and mortality Chiarantini et al. (2010). In addition, there could be potential confounders that were not able to be controlled in this clinical study.

LIMITATIONS

It is important to note that there are several limitations associated with this research, the first of which is that the sample size of this clinical study is quite limited. Additionally, it is possible that the observed differences in clinical outcomes are influenced by confounders that could not be controlled. Moreover, the d-dimer levels of patients in this population may be impacted by multiple comorbidities, i.e., malignancies and deep vein thromboembolism Alehagen et al. (2004). This clinical observational trial was also carried out with Chinese participants, and this largely impacts the generalisability of the clinical findings. What's more, the research participants were assessed for AHF through a clinical examination performed in the acute setting, and thus their symptoms could be non-specific. Therefore, future researchers should consider examining the topic using more accurate assessment methods and larger sample sizes in order to fully understand the risk factors impacting the symptoms and signs in AHF patients.

ABBREVIATIONS

acute heart failure (AHF), odds ratio (OR), confidence intervals (CI), acute decompensated heart failure (ADHF), low-density lipoprotein (LDL), high-density lipoprotein (HDL), urinary albumin-to-creatinine ratio (UACR), aspartate aminotransferase (AST); alanine aminotransferase (ALT); total bilirubin (TBIL); direct bilirubin (DBIL); indirect bilirubin (IBIL); alkaline phosphatase (ALP).

DECLARATIONS

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. The ethics committees of the Lanzhou University Second Hospital (the reference number of the ethics vote: 2022A-514) provided approval for this study. All patients who agreed to participate were asked to sign informed consent forms.

Consent for publication

"Not applicable".

Availability of data and materials

The datasets generated or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

All authors declare that there are no conflict of interests or special relationships with industry in this clinical study.

Funding

This work was supported by Gansu Youth Science and Technology Project [21JR1RA156].

Authors' contributions

Li Song is the corresponding author in the clinical study, including designed this study, collected and analyzed data, and wrote the manuscript, and made the decision to submit and publish the manuscript. Juanjuan Liu is the first author in this study, and she collected and analyzed data, and wrote the manuscript. Peiwu Li were responsible for collected data.

Acknowledgements

"Not applicable".

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, et al. 2016. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 37(27):2129-200.

2. Gheorghiade M, Zannad F, Sopko G, et al. 2005. Acute heart failure syndromes: current state and framework for future research. Circulation. 112(25):3958-68.

3. Storrow AB, Jenkins CA, Self WH, et al. 2014. The burden of acute heart failure on.S. Emergency departments. JACC Heart Fail. 2(3):269-77.

4. Meade TW, Mellows S, Brozovic M, et al. 1986. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park heart study. Lancet. 2(8506):533-7.

5. Nohria A, Tsang SW, Fang JC, et al. 2003. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 41(10):1797-804.

6. Tomura S, Nakamura Y, Deguchi F, et al. 1991. Coagulation and fibrinolysis in patients with chronic renal failure undergoing conservative treatment. Thromb Res. 64(1):81-90.

7. Ng LL, Sandhu JK, Narayan H, et al. 2014. Pro-substance p for evaluation of risk in acute myocardial infarction. J Am Coll Cardiol. 64(16):1698-707.

8. Lip GY, Gibbs CR. 1999. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. J Am Coll Cardiol. 33(5):1424-26.

9. Hamatani Y, Nagai T, Nakai M, et al. 2018. Elevated Plasma D-Dimer Level Is Associated with Short-Term Risk of Ischemic Stroke in Patients with Acute Heart Failure. Stroke. 49(7):1737-40.

10. Yan W, Liu J, Liu H, et al. 2019. Elevated D-dimer levels predict adverse outcomes in hospitalised elderly patients with chronic heart failure. Intern Med J. 49(10):1299-306.

11. Zorlu A, Yilmaz MB, Yucel H, et al. 2012. Increased d-dimer levels predict cardiovascular mortality in patients with systolic heart failure. J Thromb Thrombolysis. 33(4):322-28.

12. Weitz JI, Fredenburgh JC, Eikelboom JW. 2017. A test in context: D-dimer. J Am Coll Cardiol. 70(19):2411-20.

13. Davies MJ. 1990. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 82(3 Suppl):II38-46.

14. Simes J, Robledo KP, White HD, et al. 2018. D-Dimer predicts long-term cause-specific mortality, cardiovascular events, and cancer in patients with stable coronary heart disease. Circulation. 138(7):712-23.

15. Oldgren J, Linder R, Grip L, et al. 2001. Coagulation activity and clinical outcome in unstable coronary artery disease. Arterioscler Thromb Vasc Biol. 21(6):1059-64.

16. Moss AJ, Goldstein RE, Marder VJ, et al. 1999. Thrombogenic factors and recurrent coronary events. Circulation 99(19):2517-22.

17. Mjelva Øistein R, Pönitz V, Brügger-Andersen T, et al. 2016. Long-Term prognostic utility of pentraxin 3 and D-dimer as compared to high-sensitivity C-reactive protein and B-type natriuretic peptide in suspected acute coronary syndrome. Eur J Prev Cardiol. 23(11):1130-40.

18. Huang L, Liang L, Tian P, et al. 2022. D-dimer and outcomes in hospitalized heart failure patients across the ejection fraction phenotypes. ESC Heart Fail. 9(5):3060-70.

19. Davis CJ, Gurbel PA, Gattis WA, et al. 2000. Hemostatic abnormalities in patients with congestive heart failure: Diagnostic signifificance and clinical challenge. Int J Cardiol. 75(1):15-21.

20. Jafri SM, Ozawa T, Mammen E, et al. 1993. Platelet function, thrombin and fibrinolytic activity in patients with heart failure. Eur Heart J. 14(2):205-12.

21. Amin AN, Varker H, Princic N, et al. 2012. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. J Hosp Med. 7(3):231-38.

22. Robson SC, Shephard EG, Kirsch RE. 1994. Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1 beta, IL-6 and plasminogen activator inhibitors from monocytes in vitro. Br J Haematol. 86(2):322-26.

23. Chiarantini D, Volpato S, Sioulis F, et al. 2010. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. J Card Fail. 16(5):390-95.

24. Alehagen U, Dahlström U, Lindahl TL. 2004. Elevated D-dimer level is an independent risk factor for cardiovascular death in out-patients with symptoms compatible with heart failure. Thromb Haemost. 92(6):1250-58.

