ORIGINAL ARTICLE

Plasma growth differentiation factor 15 levels for predicting serious adverse events and bleeding in acute pulmonary embolism: a prospective observational study

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KEY WORDS

acute pulmonary embolism, adverse events, bleeding, growth differentiation factor 15, venous thromboembolism

ABSTRACT

INTRODUCTION Growth differentiation factor 15 (GDF-15), a cytokine induced in the myocardium by pressure overload and ischemia, has a well-established prognostic role for diseases of the left ventricle. Plasma GDF-15 concentrations were shown to predict bleeding events in patients with atrial fibrillation on anticoagulation.

OBJECTIVES To investigate the prognostic value of GDF-15 in acute pulmonary embolism (PE).

PATIENTS AND METHODS This was a prospective observational study of 77 patients hospitalized for PE. The median length of hospital stay and follow-up was 9 days. Plasma GDF-15 levels were measured using an automated sandwich electrochemiluminescence immunoassay. The outcome measures were: 1) in-hospital serious adverse events (SAE; death, cardiopulmonary resuscitation, need for urgent reperfusion therapy, catecholamine administration), and 2) major bleeding or nonmajor clinically relevant bleeding.

RESULTS There were 12 SAE and 5 bleeding events. The median (interquartile range) GDF-15 concentration at admission was 2354 ng/l (1151–4750 ng/l). GDF-15 concentrations increased according to risk subgroup. Patients with serious adverse events or bleeding events had higher baseline concentrations of GDF-15 (median [interquartile range], 3460 ng/l [2 531–12 363 ng/l] vs 2034 ng/l [1121–4449 ng/l]; $P = 0.01$). The area under the curve for GDF-15, high-sensitivity cardiac troponin T, and N-terminal pro–brain natriuretic peptide concentrations for predicting SAE was similar, the area under the curve of GDF-15 levels for predicting bleeding was 0.783 (95% CI, 0.62–0.946; $P = 0.001$) and 0.71 (95% CI, 0.567–0.853; $P = 0.004$) for predicting any adverse event. In the multivariable analysis, GDF-15 greater than 1680 ng/l emerged as an independent predictor of adverse outcomes (odds ratio, 8.9; $P = 0.047$).

CONCLUSIONS Plasma GDF-15 concentrations may be a promising biomarker for predicting hemodynamic destabilization and bleeding complications in PE.

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INTRODUCTION Growth differentiation factor 15 (GDF-15) is a distant member of the transforming growth factor superfamily (TGF-β), first identified as a chemokine secreted by activated macrophages in response to oxidative stress.[1] A growing body of evidence confirms its diagnostic and prognostic value in patients with acute myocardial infarction, chronic coronary syndromes, chronic heart failure, and in relation to bleeding complications in patients with atrial fibrillation on anticoagulation.[2-9] Moreover, its role in risk stratification for fetal ventricular arrhythmias in patients with non-ischemic dilated cardiomyopathy was also recently reported.[10] Little is known

WHAT'S NEW?

We demonstrated that growth differentiation factor 15 (GDF-15) levels may be accurately employed in predicting serious adverse outcomes and bleeding events in acute pulmonary embolism. We propose a threshold of GDF-15 concentration above 1680 ng/l for that purpose. This is the first report focusing on the feasibility of measuring GDF-15 concentrations in bleeding risk prediction.

about its feasibility in predicting adverse events in acute pulmonary embolism (PE). In terms of pathophysiology, it is generally accepted that both functional ischemia and myocarditis (inflammation) contribute to failure of the right ventricle (RV) in acute PE potentially leading to life-threatening hemodynamic destabilization.[11-14] Therefore, it seems plausible to measure plasma GDF-15 concentrations in patients with acute PE. There are few reports on the potential value of GDF-15 measurements in venous thromboembolism[15-18] which point to the predictive value of plasma GDF-15 concentrations in acute RV failure and high thrombotic burden in deep vein thrombosis, evaluating the potential relationship between GDF-15 levels and the severity of RV dysfunction assessed with biomarkers and imaging modalities, and as such serve as a gateway for further elucidation of the role of GDF-15 in right heart dysfunction and failure in acute PE. Moreover, they shed light on the potential role of serum GDF-15 concentrations as a parameter in mortality prediction algorithms. The importance of refining these algorithms stems from the widespread use of a risk-adapted management strategy in PE, which ranges from home treatment to urgent primary reperfusion depending on current and anticipated PE severity.[19-23]

Furthermore, elevated GDF-15 levels have been repeatedly linked to bleeding events in a wide spectrum of patients with atrial fibrillation on anticoagulative treatment and in patients with acute coronary syndromes, as reported in the ARISTOTLE (Apixaban versus Warfarin in Patients with Atrial Fibrillation) and PLATO (Platelet Inhibition and Patient Outcomes) trials, respectively.[24,25] Recently, it was suggested that a predictive value of GDF-15 in atrial fibrillation could be in part attributed to its association with prothrombotic blood alterations.[26] The clinical benefit of those findings is the development of the ABC bleeding score (age, biomarkers, clinical history) which incorporates GDF-15 levels for predicting bleeding events in the atrial fibrillation population.[27] Hemorrhagic complications are also a burden of anticoagulative treatment in PE. Therefore, the aims of this study were as follows: 1) evaluation of plasma GDF-15 levels in acute RV failure in a wide spectrum of clinical, hemodynamic, and biochemical scenarios; 2) association of plasma GDF-15 levels with established biomarkers of RV overload and dysfunction (both laboratory as well as quantitative parameters of RV dysfunction in imaging studies); 3) association of plasma GDF-15 levels with bleeding events in patients with PE on anticoagulation.

PATIENTS AND METHODS

Study design

This was an analysis of an ongoing prospective observational study registered at ClinicalTrials.gov (unique identifier NCT03672123). The study includes consecutive patients hospitalized from February 2019 to December 2019 due to acute PE at a single center. The inclusion criteria were as follows: age older than 18 years old, symptoms suggestive of PE lasting no longer than 14 days, PE confirmed with multislice computed tomography (MSCT), patient consent. The following exclusion criteria were applied: acute coronary syndrome on admission, sepsis on admission, confirmed mitochondrial disease, pregnancy on admission.

Patients were treated according to the contemporary European Society of Cardiology (ESC) guidelines depending on the estimated risk of early mortality and taking into account drug contraindications.[14]

Imaging studies

Pulmonary embolism was confirmed by contrast-enhanced MSCT when thromboemboli were visualized at least at the level of segmental pulmonary arteries. MSCT angiography was performed using an 80-row Toshiba Aquilion Prime CT scanner (Toshiba Medical Systems, Otawara, Japan). The results of CT studies were adjudicated by 2 radiology specialists. The ultrasonographic lower-limb compression tests were performed by a trained radiologist with the Philips XD11XE system (Philips Medical Systems, Best, the Netherlands) using a linear transducer (L12-3) according to the standard protocol.

Transthoracic echocardiography was performed within 24 hours after admission. The examination was performed according to the guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging.[28] All examinations were performed by a physician certified in echocardiography using the Philips iE33 (Philips Medical Systems, Andover, Massachusetts, United States) and EPIQ 7 system (Philips, Eindhoven, the Netherlands). The following quantitative parameters were assessed: 1) end-diastolic diameter of the RV in comparison to the end-diastolic diameter of the left ventricle in the apical 4-chamber view (a right-to-left ventricular diameter ratio); 2) presence of hypokinesis of the free wall of the RV; 3) tricuspid regurgitation peak pressure gradient; 4) tricuspid annular plane systolic excursion; 5) diameter of the inferior vena cava. Right ventricular overload or dysfunction was defined as the presence of any of the following: tricuspid annular plane systolic excursion of less than 16 mm, tricuspid regurgitation jet pressure gradient of more than 30 mm Hg, a right-to-left ventricular diameter ratio greater than 1, distension of the inferior vena cava of more than 20 mm, presence of hypokinesis of the free wall of the RV or presence of the McConnell sign.

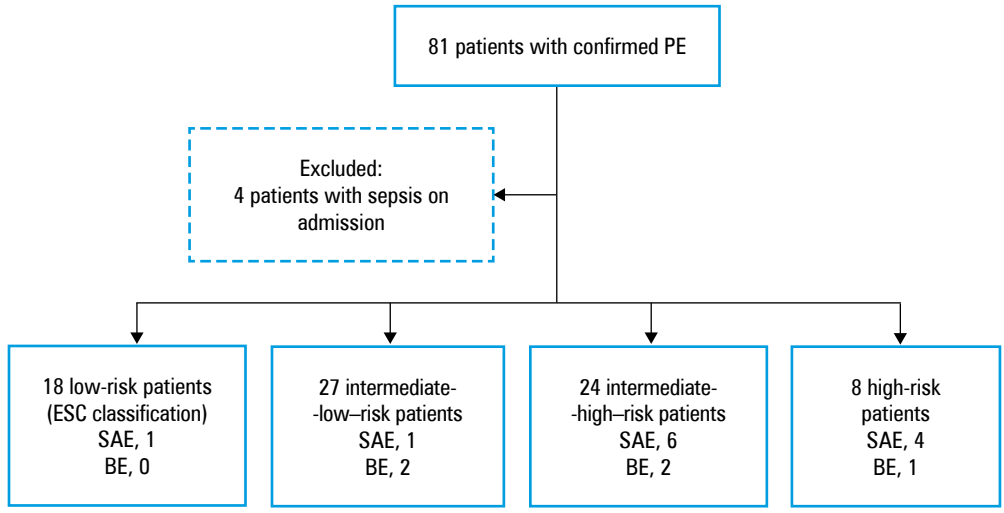

FIGURE 1
Flow of patients
Abbreviations:
BE, bleeding events; ESC, European Society of Cardiology; PE, pulmonary embolism; SAE, serious adverse events

Biochemical analysis All test tubes containing specimens were blinded using a numerical code unique for each patient. All analyses were performed with the Roche Cobas E601 or E411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany, United Kingdom). Blinded patient data were stored in a dedicated database.

Blood samples were collected from patients within the first 24 hours from admission. Samples obtained from each patient were then immediately centrifuged at 4000 rpm for 15 minutes to obtain plasma, which was then frozen in –80 °C until further analysis. Concentrations of GDF-15 were quantitatively measured as a single batch after a single thaw cycle using an automated sandwich electrochemiluminescence immunoassay with a reference range of values from 400 to 20 000 ng/l (Roche Diagnostics GmbH, Mannheim, Germany).

Serum high-sensitivity cardiac troponin T (cTnT-hs) and N-terminal pro–brain natriuretic peptide (NT-proBNP) concentrations were measured quantitatively using an automated sandwich electrochemiluminescence immunoassay from blood collected within the first 24 hours from admission (Roche Diagnostics GmbH, Mannheim, Germany). For cTnT-hs, levels above 0.014 ng/ml were considered elevated, and for NT-proBNP, concentrations above 600 pg/ml were considered above the upper limit of normal. Anemia was defined as hemoglobin level below 12 g/dl for women and 13 g/dl for men. Impaired kidney function was defined as estimated glomerular filtration rate below 60 ml/min/1.73 m^2.

Clinical evaluation and calculation of the simplified pulmonary embolism severity index The clinical evaluation was performed by the attending physician during the first medical contact with the patient. Arterial blood pressure, heart rate per minute, oxygenation of the arterial blood measured percutaneously were noted. The simplified pulmonary embolism severity index (sPESI) score was calculated by the attending physician or assessed retrospectively using baseline parameters.

Classification of bleeding Bleeding events that fulfilled the classification proposed by the International Society on Thrombosis and Haemostasis were included in the study.[29,30] Events were classified as: 1) major bleeding (MB) defined as fatal bleeding and / or symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular), bleeding with a fall in hemoglobin of 2 g/dl or more, and / or bleeding leading to a transfusion of 2 or more units of packed red blood cells or whole blood; or 2) clinically relevant nonmajor bleeding (CRNMB) defined as any sign or symptom of hemorrhage that does not meet the criteria for a major bleed but prompts a clinical response, understood as one of the following: hospital admission for bleeding or increased level of care, a face-to-face evaluation, or requiring medical attention by a healthcare professional.

Study endpoints Study endpoints were defined as: 1) in-hospital serious adverse event (SAE; death, need for cardiopulmonary resuscitation, need for urgent reperfusion therapy, need for catecholamine administration); 2) in-hospital MB or CRNMB defined according to the International Society on Thrombosis and Haemostasis.[29,30]

Statistical analysis Data are expressed as parameter or median with interquartile range (IQR) or odds ratio (95% CI). The Kolmogorov–Smirnov test was used to check for normality of data. Continuous variables with a skewed distribution which were then compared using the Mann–Whitney test. Comparisons of more than 2 variables were performed using the Kruskal–Wallis test. For all performed tests, a P value of less than 0.05 was considered significant. The receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC) for GDF-15, cTnT-hs, and NT-proBNP levels for predicting serious adverse events and bleeding events. Analyses were performed using the STATISTICA 13 software (TIBCO Software Inc., Palo Alto, California, United

TABLE 1 Baseline characteristics of 77 patients

Characteristic		Value
Age, y, mean (SD)		63 (19)
BMI, kg/m^2, median (IQR)		28 (23–31)
Female sex		48 (62)
Length of hospital stay, d, median (IQR)		9 (6–15)
COPD		9 (12)
Diabetes mellitus		9 (12)
Neoplasm		14 (18)
CHF		12 (16)
VTE reoccurrence		17 (22)
Atrial fibrillation		13 (17)
Diagnosed thrombophilia (antithrombin deficiency)		1 (1.3)
Low risk at admission		18 (24)
Intermediate-low risk		27 (35)
Intermediate-high risk		24 (31)
High risk		8 (10)
SAE		12 (16)
Bleeding events	Any	5 (6)
	MB	2 (2)
	CRNMB	3 (4)
NT-proBNP, pg/ml, median (IQR)		838 (204.5–2910)
cTnT-hs, ng/ml, median (IQR)		0.031 (0–0.065)
GDF-15, ng/l, median (IQR)		2354 (1143–4779)
Platelet count, g/l, median (IQR)		241 (163–295)
Hemoglobin, g/dl		12.4 (10.7–14.3)
D-dimer, ng/ml		6205 (2046–15948)
Any TTE sign of RV dysfunction or overload		36 (47)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: BMI, body mass index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRNMB, clinically relevant nonmajor bleeding; cTnT-hs, high sensitive troponin T; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; IVC, inferior vena cava; IQR, interquartile range; MB, major bleeding; NT-proBNP, N-terminal natriuretic peptide type B; RV, right ventricle; TTE, transthoracic echocardiography; VTE, venous thromboembolism; others, see **FIGURE 1**

TABLE 2 Bleeding risk factors of the study population

Risk factor	Patients, n (%)
Rivaroxaban	25 (32)
Apixaban	4 (5)
Dabigatran	13 (17)
LMWH	27 (35)
Warfarin	6 (8)
Acenocoumarol	2 (3)
DAPT	2 (3)
SAPT	3 (4)
Impaired kidney function[a]	24 (31)
Impaired liver function	24/71 (34)
Anemia at admission[b]	34/77 (44)
Thrombocytopenia at admission	12/77 (15)

a Impaired kidney function was defined as estimated glomerular filtration rate below 60 ml/min/1.73 m^2

b Anemia was defined as hemoglobin level below 12 g/dl for women and 13 g/dl for men

Abbreviations: DAPT, dual antiplatelet therapy; LMWH, low molecular weight heparin; SAPT, single antiplatelet therapy; others, see **TABLE 1**

States). This study was approved by the local institutional ethics committee and patients provided written informed consent to participate in the study.

RESULTS The final study group included 77 patients: 18 low-risk patients classified according to the ESC algorithm, 27 intermediate-low–risk patients, 24 intermediate-high–risk patients, and 8 high-risk patients were included. The median (IQR) length of hospital stay was 9 (6–15) days. The flow of patients is presented in **FIGURE 1**. Baseline characteristics are presented in **TABLE 1**. Bleeding risk factors are presented in **TABLE 2**.

There were 12 SAE (including 2 cardiopulmonary resuscitations, 2 deaths, 7 percutaneous embolectomies, 1 surgical pulmonary embolectomy) and 5 bleeding events (2 MB and 3 CRNMB). The median (IQR) GDF-15 concentration at admission was 2354 (1151–4750) ng/l. Concentrations of GDF-15 increased according to risk subgroup assessed using the ESC algorithm: for low-risk patients, the median (IQR) GDF-15 concentration was 1281 ng/l (998–1999 ng/l), for intermediate-low–risk, 2354 ng/l (1115–4824 ng/l), for intermediate-high–risk, 2926 ng/l (1395–4692 ng/l), for high-risk patients, 8998 ng/l (5007–16 039 ng/l). Differences in concentrations between the 4 subgroups were significant (P = 0.009).

Patients who experienced serious adverse events or bleeding events, as well as patients with higher concentrations of established biomarkers of myocardial overload and injury and hypotensive patients had higher baseline concentrations of GDF-15. Additionally, the same observation was made in patients with diagnosed AF, impaired kidney function, anemia, or elevated D-dimer levels (**TABLE 3**). The analyzed echocardiographic signs of RV overload or dysfunction alone, or DVT did not significantly influence plasma GDF-15 levels.

The AUC for GDF-15, cTnT-hs, and NT-proBNP concentrations for predicting SAE was similar: for GDF-15, AUC was 0.679 (95% CI, 0.505–0.854; P = 0.04). For cTnT-hs, AUC was 0.762 (95% CI, 0.596–0.928; P = 0.002). For NT-proBNP, AUC was 0.706 (95% CI, 0.567–0.844; P = 0.004). Pairwise comparisons revealed no significant differences in AUC for ROC curves for the biomarkers (GDF-15 vs cTnT-hs, P = 0.53; GDF-15 vs NT-proBNP, P = 0.84) (**FIGURE 2**). The AUC for GDF-15 levels for predicting bleeding was 0.783 (95% CI, 0.62–0.946; P = 0.001) (**FIGURE 3**), and 0.71 (95% CI, 0.567–0.853; P = 0.004) for predicting any adverse event (**FIGURE 4**). The optimal threshold for GDF-15 in predicting any adverse event (SAE or bleeding) was chosen based on the ROC curve analysis. The value of 1680 ng/l had 94% sensitivity, 41% specificity, negative predictive value of 96%, and positive predictive value of 29%. In the multivariable analysis, GDF-15 levels higher than 1680 ng/l emerged as an independent predictor of a complicated clinical outcome (**TABLE 4**).

TABLE 3 Growth differentiation factor 15 levels in relation to clinical, hemodynamic, and biochemical variables (continued on the next page)

Parameter	Patients, n / total n	GDF-15 concentration, ng/l, median (IQR)	*P* value
Low risk[a]	18/77	1281 (988–1999)	0.001
Non–low risk[a]	59/77	2917 (1485–5137)	
sPESI >0	44/77	3612 (2045–6271)	<0.001
sPESI = 0	33/77	1274 (980–2306)	
SBP <100 mm Hg	8/77	8998 (5007–16 039)	0.003
SBP ≥100 mm Hg	69/77	2052 (1136–3636)	
SI >0.9	11/77	9617 (2052–15 673)	0.003
SI ≤0.9	66/77	2172 (1130–3636)	
cTnT-hs >ULN	49/75	3588 (1791–5565)	<0.001
cTnT-hs ≤ULN	26/75	1281 (984–2034)	
NT-proBNP >ULN	40/73	2989 (1694–5503)	0.009
NT-proBNP ≤ULN	33/73	1939 (1007–2831)	
SAE (+)	12/77	3134 (2248–14 260)	0.049
SAE (–)	65/77	2052 (1130–4477)	
Bleeding (+)	5/77	4577 (3588–11 877)	0.03
Bleeding (–)	72/77	2179 (1133–4613)	
SAE (+) and bleeding (+)	16/77	3460 (2531–12 363)	0.01
SAE (–) and bleeding (–)	61/77	2034 (1121–4449)	
RV/LV >1	10/55	1548 (772–2936)	0.23
RV/LV ≤1	45/55	2322 (1136–4477)	
Hypokinesis of RV free wall	21/74	2917 (1485–4449)	0.56
Normal motion of RV free wall	53/74	2306 (1121–4824)	
McConnell sign (+)	6/74	2364 (1305–3333)	0.85
McConnell sign (–)	68/74	2338 (1133–4787)	
TRPG >30 mm Hg	27/69	3041 (1130–5442)	0.35
TRPG ≤30 mm Hg	42/69	2036 (1274–3636)	
TAPSE <16 mm	14/72	3187 (1791–4477)	0.14
TAPSE ≥16 mm	58/72	1157 (1151–3637)	
IVC diameter >20 mm	12/72	2988 (1791–4449)	0.37
IVC diameter ≤20 mm	58/72	2180 (1130–4808)	
DVT (+)	35/61	1667 (980–3588)	0.11
DVT (–)	26/61	2330 (1707–4577)	
Unprovoked PE	52/77	2334 (1231–3624.5)	0.67
Provoked PE	25/77	2354 (1007–5565)	
First episode of VTE	59/77	2357 (1305–4808)	0.32
Reoccurrence of VTE	18/77	1742 (1007–4577)	
Presence of diagnosed thrombophilia (antithrombin deficiency)	1/77	2917 (NA)	NA
No diagnosed thrombophilia	76/77	2338 (1143–4779)	
Impaired liver function	17/71	2306 (1130–2936)	0.48
Normal liver function	54/71	2355 (1157–4824)	
Impaired kidney function	24/73	4799 (2196–6271)	<0.001
Normal kidney function	49/73	1934 (1007–2917)	
Anemia at admission	34/77	4057 (2357–7069)	<0.001
No anemia at admission	43/77	1485 (988–2531)	
Thrombocytopenia at admission	12/77	2513 (1862–11 356)	0.22
No thrombocytopenia at admission	65/77	2354 (1130–4577)	
D-dimer level ≥500 ng/ml	56/58	2314 (1215–4663)	0.048
D-dimer level <500 ng/ml	2/58	812 (635–988)	

TABLE 3 Growth differentiation factor 15 levels in relation to clinical, hemodynamic, and biochemical variables (continued from the previous page)

Parameter	Patients, n / total n	GDF-15 concentration, ng/l, median (IQR)	*P* value
AF	13/77	3637 (3041–8380)	0.002
No AF	64/77	1969 (1118–4513)	

a According to the European Society of Cardiology classification

Abbreviations: –, absent; AF, atrial firbillation; DVT, deep vein thrombosis; LV, left ventricle; +, present; SBP, systolic blood pressure; SI, shock index; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient; ULN, upper limit of normal; others, see **FIGURE 1** and **TABLE 1**

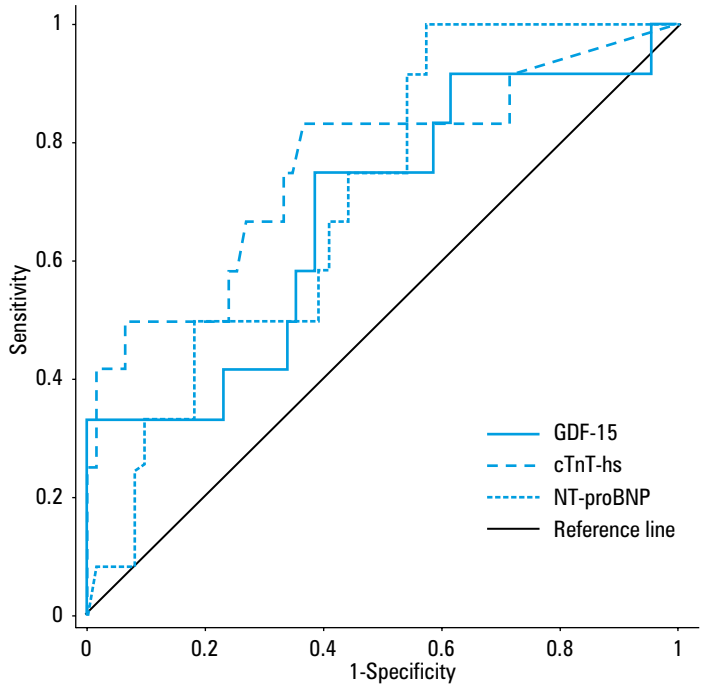

FIGURE 2 Comparison of the area under the curve for the concentrations of growth differentiation factor 15 (GDF-15), high-sensitivity cardiac troponin T (cTnT-hs), and N-terminal pro–brain natriuretic peptide (NT-proBNP) in predicting serious adverse events

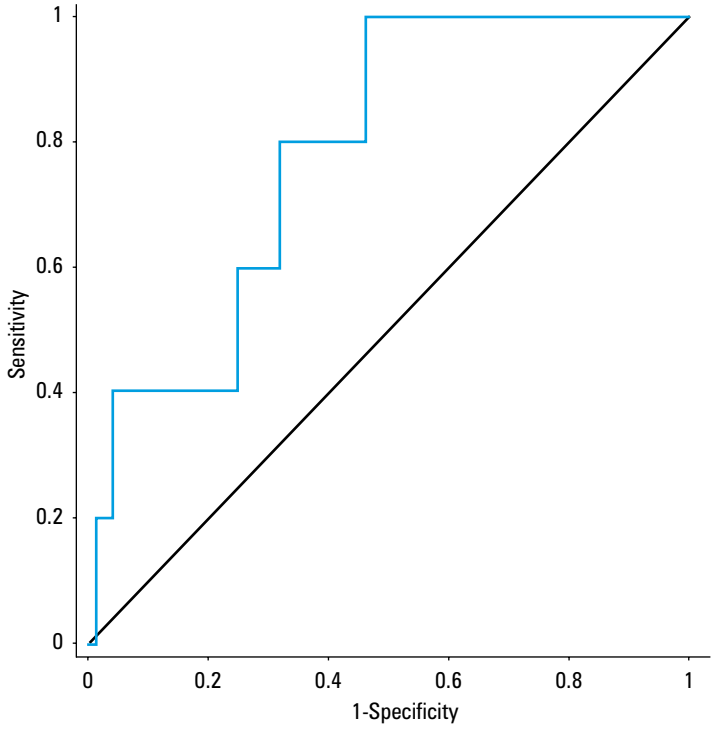

FIGURE 3 The area under the curve (AUC) for concentrations of growth differentiation factor 15 (GDF-15) in predicting bleeding events (major bleeding and clinically relevant nonmajor bleeding). AUC = 0.783 (95% CI, 0.62–0.946; $P = 0.001$).

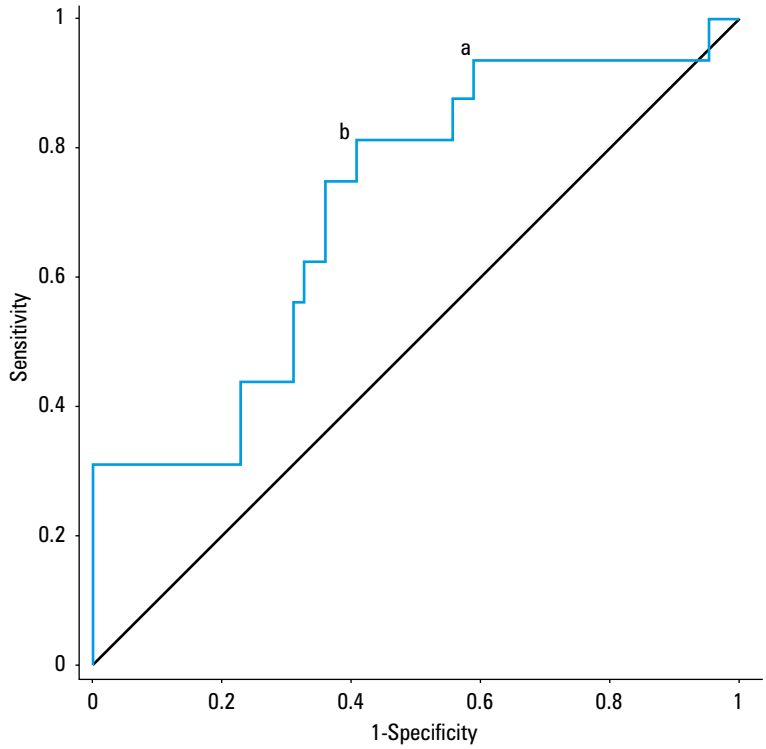

FIGURE 4 The area under the curve (AUC) for concentrations of growth differentiation factor 15 (GDF-15) in predicting all adverse events (serious adverse events and hemorrhagic events). AUC = 0.71 (95% CI, 0.567–0.853; $P = 0.004$).
a The proposed GDF-15 threshold (1680 ng/l)
b The Youden index

TABLE 4 Multivariable logistic regression analysis for the occurrence of any adverse event

Variable	OR (95% CI)	*P* value
GDF-15 >1680 ng/l	8.9 (1.03–77.76)	0.047
cTnT-hs >0.014 ng/ml	0.85 (0.13–13.3)	0.9
SBP <100 mm Hg	1.71 (0.3–9.94)	0.55
NT-proBNP >600 pg/ml	2.41 (0.44–13.3)	0.31

Abbreviations: OR, odds ratio; others, see TABLE 1

DISCUSSION The key finding of this study is that plasma GDF-15 levels are useful in identifying patients at risk of serious adverse and hemorrhagic events in the course of acute PE. In terms of predicting bleeding risk in patients with acute PE, to the best of our knowledge, this is the first report focusing on the role of measuring GDF-15 concentrations in this setting.

It has been shown that ischemic injury, mechanical stretch, neurohormones, and proinflammatory cytokines stimulate the expression of GDF-15 in cardiac myocytes.[31,32] The proposed biological activities of GDF-15 are as follows: 1) the role of GDF-15 in vivo was first described in 2006 using a murine model, in which it was demonstrated that GDF-15 is induced in cardiomyocytes in response to cardiac ischemia, serving a protective function by inhibiting PI3K/Akt kinase-dependent apoptosis[31]; 2) the cardioprotective effect of GDF-15 may be attributed to its capacity to inhibit apoptosis and cardiac hypertrophy through the SMAD protein–related pathways, similar to other members of the TGF superfamily[33]; 3) during cardiac ischemia, GDF-15 is induced locally in the heart and exhibits anti-inflammatory properties by inhibiting leukocyte β_2 integrin activation required for leukocyte recruitment.[34] Inflammation and ischemia are the cornerstones of RV dysfunction leading to failure in acute PE.[35]

Our conclusions are in line with others, who have reported the feasibility of employing GDF-15 levels in predicting adverse events in other cardiovascular diseases, such as myocardial infarction, chronic coronary syndromes, chronic heart failure, acute PE, and atrial fibrillation.[2-9,15-18,24,25]

In our study, GDF-15 showed a satisfactory discriminatory capacity in predicting SAE and any hemorrhagic event (MB and CRNMB) in acute PE, as demonstrated by the AUC of 0.783 (95% CI, 0.62–0.946; $P = 0.001$) for bleeding complications and of 0.710 (95% CI, 0.567–0.853; $P = 0.004$) for predicting any adverse event. Its diagnostic performance in predicting SAE was similar to cTnT-hs. Based on the ROC curve analysis, we propose a threshold of 1680 ng/l for predicting SAE or hemorrhagic complications. Using multivariable analysis, we demonstrated that a GDF-15 level above 1680 ng/l is an independent predictor of a complicated outcome.

The proposed value of 1680 ng/l for acute PE is similar to that suggested by the results of landmark randomized clinical trials in AF. In the RE-LY trial of 8474 patients, GDF-15 concentrations above 1800 ng/l were associated with the highest risk of the occurrence of adverse events.[36] A similar observation in regard to the cutoff value was made in a subanalysis of the ENGAGE AF TIMI-48 trial, which included 8705 patients and demonstrated that baseline GDF-15 levels above 1800 ng/l predicted the 12-month occurrence of bleeding events better than concentrations within the lower tercile of below 1200 ng/l.[37] Lastly,

in the ARISTOTLE trial, out of the tested variables GDF-15 was the most strongly associated with bleeding-related death, with median baseline levels of 2215 ng/l in the described limited subgroup of 31 patients.[38]

Several study limitations should be acknowledged. First, there was a limited number of enrolled patients making this a preliminary report. Second, GDF-15 levels are influenced by circadian rhythm and fasting. Thus, all patients should be tested within the same time frame of several hours. In this study, all blood samples were collected between 7:30 AM and 12:00 PM; however, this slight discrepancy could influence the observed GDF-15 levels. Finally, this study also enrolled patients with AF, which may influence GDF-15 levels. However, AF and PE frequently co-exist and the inclusion of such patients reflect the real-world nature of this study.[39]

Conclusions Based on our research, an appealing hypothesis is that plasma GDF-15 concentration may be a promising biomarker for predicting hemodynamic destabilization and bleeding complications in patients with acute PE, thus providing information on top of other established cardiac biomarkers in acute PE regarding predicting survival. Whether GDF-15 levels can be employed in risk stratification algorithms should be confirmed in a larger trial.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT M. Skowrońska and PP conceived the idea for the study, analyzed the data, and coordinated funding. M. Skrzyńska contributed to the design of the research. Additionally, ZB performed the laboratory analyses and MW and PP analyzed imaging studies. All authors were responsible for data collection. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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