Journal of Thrombosis and Haemostasis, **8**: 651–658 DOI: 10.1111/j.1538-7836.2010.03762.x

ORIGINAL ARTICLE

Assessment of renal dysfunction improves troponin-based short-term prognosis in patients with acute symptomatic pulmonary embolism

M. KOSTRUBIEC,* A. ŁABYK,* J. PEDOWSKA-WŁOSZEK,* S. PACHO,* A. WOJCIECHOWSKI,† K. JANKOWSKI,* M. CIURZYŃSKI* and P. PRUSZCZYK*

**Department of Internal Medicine and Cardiology; and †Department of Radiology, The Medical University of Warsaw, Warsaw, Poland*

To cite this article: Kostrubiec M, Łabyk A, Pedowska-Włoszek J, Pacho S, Wojciechowski A, Jankowski K, Ciurzyński M, Pruszczyk P. Assessment of renal dysfunction improves troponin-based short-term prognosis in patients with acute symptomatic pulmonary embolism. *J Thromb Haemost* 2010; **8**: 651–8.

Summary. *Objective*: Current risk stratification in acute pulmonary embolism (APE) includes assessment of clinical status, right ventricular overload and plasma troponin concentrations. As impaired renal function is one of the important predictors of mortality in cardiovascular diseases, we hypothesized that it is an independent early mortality marker in APE. *Material and methods*: In prospective cohort study, we observed 220 consecutive patients (86M/134F, 64 ± 18 years) with APE proven by spiral computed tomography (CT). On admission, echocardiography was performed and blood samples were collected for troponin and creatinine assays. *Results*: The calculated glomerular filtration rate (GFR) differed significantly between 81 pts with low-, 131 pts with moderate- and 8 pts with high-risk APE [71 (19–181) vs. 55 (9–153) vs. 41 (14–68) mL min^{-1}; respectively $P < 0.0001$]. Twenty-three patients died during the 30-day observation. Importantly, GFR was lower in non-survivors than in survivors [35 (9–92) vs. 63 (14–181) mL min^{-1}, $P < 0.0001$]. The area under the curve (AUC) of the GFR receiver-operating characteristic (ROC) curve for predicting mortality was 0.760 (95% CI: 0.698–0.815). In multivariable analysis, independent mortality predictors were GFR, troponin, heart rate and history of chronic heart failure. In normotensive patients, the GFR and cardiac troponins (cTn) ROC curves for prediction of mortality showed no difference (AUC 0.789 and 0.781, respectively). However, Kaplan–Meier analysis showed an additive prognostic value of renal dysfunction. Thus, troponin-positive patients with a GFR ≤ 35 mL mn^{-1} showed 48% 30-day mortality, whereas troponin-positive patients with a GFR > 35 mL mn^{-1} had 11% mortality, and troponin-negative patients with a GFR > 35 mL mn^{-1} had good prognosis, $P < 0.0001$. *Conclusion*: Impaired kidney function, present in 47% of APE patients, is related to all-cause mortality. In initially normotensive patients, a GFR < 35 mL min^{-1} predicts 30-day mortality. Moreover, GFR assessment can improve troponin-based risk stratification of APE.

Keywords: creatinine, modification of diet in renal disease, mortality, prognosis, pulmonary embolism, renal failure.

Correspondence: Maciej Kostrubiec, Department of Internal Medicine and Cardiology, The Medical University of Warsaw, ul. Lindleya 4, 02-005 Warszawa, Poland.
Tel.: +48 22 502 11 44; fax: +48 22 502 13 63.
e-mail: maciej.kostrubiec@wum.edu.pl

Received 26 October 2009, accepted 11 January 2010

Introduction

Risk stratification of patients with acute pulmonary embolism (APE) according to current European guidelines is based on the assessment of hemodynamic stability, evaluation of right ventricular (RV) function and assay of myocardial injury biomarkers [1,2]. However, hemodynamic compromise in APE affects not only the pulmonary circulation, but also other organs. Decreased cardiac output, hypoxemia and elevated central venous pressure can result in renal dysfunction. Glomerular filtration rate (GFR) is one of the generally accepted indicators of increased mortality in various cardiovascular diseases. In acute coronary syndromes, renal dysfunction on presentation was associated with increased early mortality, independently of other conventional risk factors [3,4], and it has been included into the GRACE risk scale [5]. Moreover, impaired renal function also predicts mortality and hospitalization rate in patients with heart failure [6]. Therefore, we hypothesized that renal dysfunction is an independent marker of early mortality in APE, and that renal function assessment may improve troponin-based risk stratification.

Material and methods

Patients and management of pulmonary embolism

Two hundred and twenty patients with symptomatic APE were diagnosed and treated in our department between 2006 and

2009. APE was confirmed by contrast-enhanced spiral computed tomography (CT). APE was diagnosed when symptoms of PE had been present for no longer than 14 days before the diagnosis. On admission clinical data and blood samples for creatinine and troponin concentrations were collected, and echocardiography for right ventricular overload was performed. High-, moderate- and low-risk APE groups were defined according to European Society of Cardiology Guidelines [1], with assignment based on systemic systolic blood pressure measured on admission, echocardiographic assessment of right ventricular function and plasma troponin concentration. Shock or systemic systolic blood pressure < 90 mmHg identified high-risk patients. Moderate-risk patients were characterized by systemic systolic blood pressure > 90mmHg and the presence of right ventricular dysfunction and/or elevated plasma troponin concentrations. The low-risk group included hemodynamically stable patients without right ventricular dysfunction or signs of myocardial injury. The endpoint of the study was defined as all-cause death. The death causes were determined based on clinical symptoms, accessory examinations including echocardiography and other available investigation. If there was any doubt in a situation an autopsy was performed. All events were recorded up to 30 days after the diagnosis of APE.

Biochemical assays

In all cases, venous peripheral blood samples for measurement of creatinine were drawn on admission before treatment. Blood samples were collected in standardized tubes containing dipotassium ethylenedinitro tetraacetic acid (EDTA) and stored at room temperature. All measurements were performed 30 min after blood collection. Creatinine was measured by a rate blanked method that is based on the Jaffé reaction. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula. The abbreviated MDRD equation is: GFR $= 186 \times (\mathrm{Scr}^{-1.154} \times \mathrm{Age}^{-0.203} \times (0.742$ if female$) \times (1.210$ if African-American), where serum creatinine (Scr) is measured in milligram per deciliter and age in years [7].

Blood samples were simultaneously collected for routine assays and assessment of creatinine and plasma troponin. In the years 2006–2007, troponin T (Roche, electrochemiluminescence method – ECLIA, Mannheim, Germany) was assessed in our laboratory, while from May 2007 troponin I (Dimension® RxL, Dade Behring, Frankfurt, Germany) was measured. When the results were below the lower limit of detection for cTnT (< 0.01 μg L^{-1}) or cTnI (< 0.01 μg L^{-1}), they were considered as '0.00' for analysis. Based on reference values of our laboratory, plasma concentrations of cTnT > 0.03 μg L^{-1} and cTnI > 0.10 μg L^{-1} were considered to indicate myocardial injury. When continuous values were necessary for statistical analysis, troponin T and troponin I values were expressed as the ratio of assayed plasma concentration to the laboratory reference value. The protocol of this study was approved by the Local Bioethics Committee. All participating patients expressed their prior informed consent.

Echocardiography

Transthoracic echocardiography for the assessment of RV dysfunction was performed using a Philips iE33 echocardiography system within 24 h after admission. The examinations were digitally recorded on admission by an experienced echocardiographer blinded to the results of biochemical assays. RV overload was diagnosed when echocardiography showed: (i) RV free wall hypokinesis and RV/LV > 0.9 in a four-chamber view, and/or (ii) an elevated tricuspid valve pressure gradient exceeding 30 mmHg with a shortened acceleration time of pulmonary ejection below 80 ms.

Spiral computed tomography

Spiral CT was performed using a GE Bright Speed 'G' 16-slice CT and a Toshiba Aquilion 64-slice CT. Angio-CT scans of pulmonary arteries were obtained 10 s after initiation of intravenous administration of 80 mL of non-ionic iodinated contrast medium (30 mL – flow rate 5 mL s^{-1} and 50 mL – flow rate 3 mL s^{-1}). PE was diagnosed when thromboemboli were visualized in at least segmental arteries.

Statistical analysis

This is a prospective observational cohort study. Data characterized by a normal distribution are expressed as mean followed by standard deviation. Parameters without such a distribution are expressed as median with range. Student's or Mann–Whitney's tests were used for comparisons between two groups, while comparisons between more than two groups were performed by ANOVA or Kruskal–Wallis tests. The χ^2-test was used to compare discrete variables (with Yates' correction when appropriate). ROC curves were analyzed to assess the optimal cut-off values of GFR for mortality. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the chosen cut-off value. Kaplan–Meier analysis was used to investigate cumulative 30-day survival rate. The impact of GFR and other clinical factors on mortality was evaluated using univariable Cox proportional-hazards regression. Forward stepwise selection with a 0.1 level for staying in the model was used to identify significant predictors in multivariable analysis. For better presentation, a hazard ratio of GFR was recalculated from 'per 1 mL min^{-1} increase' to 'per 10 mL min^{-1} decrease' and for heart rate from 'per 1 beat' to 'per 10 beats'. The significance of difference in survival between groups with a GFR below and above the cut-off value was assessed by the log-rank test. Receiver-operating characteristic (ROC) analysis was also performed for cTn in mortality prediction and compared with the ROC curve for GFR. All tests were two-sided. Data were considered significant at $P < 0.05$. STATISTICA (StatSoft 8.0, Inc. 2007, Tulsa, OK, USA) and MEDCALC (Version 11.0.0.0, Mariakerke, Belgium) software were used for statistical calculations.

Results

Patients' characteristics and clinical course

The study included 220 consecutive patients with APE, 86 males and 134 females, aged 64 ± 18 years. Clinically high-risk APE was diagnosed in 8 (4%) patients, whereas the remaining 212 patients were normotensive on admission (systemic systolic blood pressure > 90 mmHg). Low-risk APE was found in 81 (37%) patients, and 131 (59%) cases formed a subgroup with moderate-risk APE. The clinical characteristics of the non-high-risk groups are presented in Table 1.

All patients received standard anticoagulant therapy with intravenous unfractionated heparin (UFH) or a subcutaneous body mass-adjusted dose of low-molecular weight heparin. High-risk APE was considered an indication for thrombolysis (infusion of recombinant tissue plasminogen activator – either 100 mg over 1 h, or 0.6 mg kg^{-1} body mass maximum 50 mg over 15 min). Hemodynamic deterioration in initially stable patients was also considered an indication for thrombolysis. However, the decision to start thrombolytic treatment was made by the attending physician. Patients with severe renal insufficiency (GFR < 30 mL min^{-1}) were initially treated with UFH under activated partial thromboplastin time (APTT) control. Renal function did not influence the decision about starting the thrombolytic treatment.

Twenty-three (10%) out of 220 patients died by the 30th day of observation. Four deaths occurred in the high-risk PE group (mortality 50%), whereas 18 fatal cases initially had moderate-risk PE (mortality 14%), and one death was reported in the low-risk APE group (mortality 1%). There were 17 APE-related deaths, which comprised deaths caused by clinically diagnosed irreversible RV insufficiency or recurrent PE (APE mortality 8%). In the remaining non-survivors, in five cases major hemorrhagic events probably contributed to death, whereas one woman died as a result of generalized ovarian cancer. There were four deaths in the group of 26 thrombolyzed patients. One or more of the following coexisting diseases – chronic obstructive pulmonary disease, neoplasm, congestive heart failure, coronary artery disease, hypertension, diabetes mellitus, previously diagnosed renal disease – was present in 146 (66%) of the studied subjects.

Renal function and clinical course

GFR values differed significantly between the patients with low-risk, moderate-risk and high-risk APE (Fig. 1). GFR was significantly higher in the group with low-risk APE than in patients with moderate- or high-risk APE ($P < 0.0001$ and $P = 0.001$, respectively), while the difference between moderate- and high-risk APE failed to reach statistical significance ($P = 0.08$). It is worth noting that 7 (88%) patients with high-, 74 (56%) with moderate-, and 23 (28%) with low-risk APE had a GFR below 60 mL min^{-1}. Importantly, GFR on admission was significantly lower in non-survivors than in survivors (Fig. 2).

Table 1 Characteristics of 212 patients normotensive on admission with acute pulmonary embolism, according to clinical outcome

	All pts $n = 212$	Non-survivors $n = 19$	Survivors $n = 193$	P
Age (years)	64 ± 18	75 ± 13	62 ± 18	0.003
Gender (F/M) *n* (%)	131 (62)/81 (38)	12 (63)/7 (37)	119 (62)/74 (38)	0.90
Heart rate (1 min^{-1})	95 ± 22	108 ± 22	93 ± 21	0.004
SBP (mmHg)	128 ± 20	130 ± 28	128 ± 19	0.74
DBP (mmHg)	79 ± 12	80 ± 16	79 ± 11	0.66
Creatinine (mg dL^{-1})	1.02 (0.41–5.02)	1.50 (0.60–5.02)	1.00 (0.41–4.30)	0.0001
GFR (mL min^{-1})	62 (9–181)	35 (9–93)	64 (14–181)	< 0.0001
GFR < 35 mL min^{-1}	28 (13)	10 (53)	18 (9)	< 0.0001
cTnT (μg L^{-1}) $n = 77$	0.00 (0.00–0.63)	0.11 (0.00–0.56)	0.00 (0.00–0.63)	0.003
cTnI (μg L^{-1}) $n = 143$	0.08 (0.00–7.38)	0.40 (0.05–4.46)	0.05 (0.00–7.38)	0.004
cTn ≥ 0.01 (μg L^{-1}) *n* (%)	118 (56)	19 (100)	99 (51)	0.0001
Significant elevation of cTn *n* (%)	90 (42)	18 (95)	72 (37)	< 0.0001
RV overload in ECHO *n* (%)	123 (58)	16 (84)	107 (55)	0.01
Comorbidity* *n* (%)	140 (66)	17 (89)	123 (64)	0.045
CHF *n* (%)	27 (13)	9 (47)	18 (9)	< 0.0001
CAD *n* (%)	46 (22)	7 (37)	39 (20)	0.09
COPD *n* (%)	19 (9)	2 (11)	17 (8)	0.86
Neoplasm *n* (%)	26 (12)	2 (11)	24 (12)	0.90
Hypertension *n* (%)	71 (33)	11 (58)	60 (31)	0.04
Diabetes mellitus *n* (%)	35 (17)	7 (37)	28 (15)	0.03
Previously reported renal disease *n* (%)	43 (20)	7 (37)	36 (19)	0.11

GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; cTn, cardiac troponin; RV, right ventricle; NS, non-significant.

*Comorbidity – at least one of following: chronic heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), neoplasm, hypertension, diabetes mellitus, previously reported renal disease.

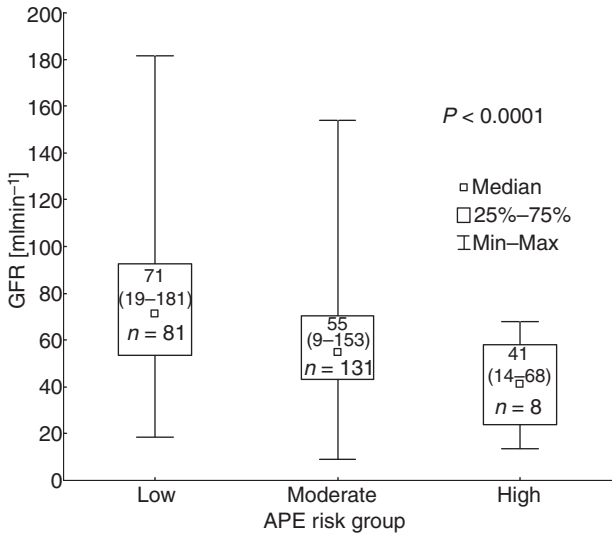

Fig. 1. Glomerular filtration rate (GFR) values in patients with low-, moderate- and high-risk acute pulmonary embolism (APE).

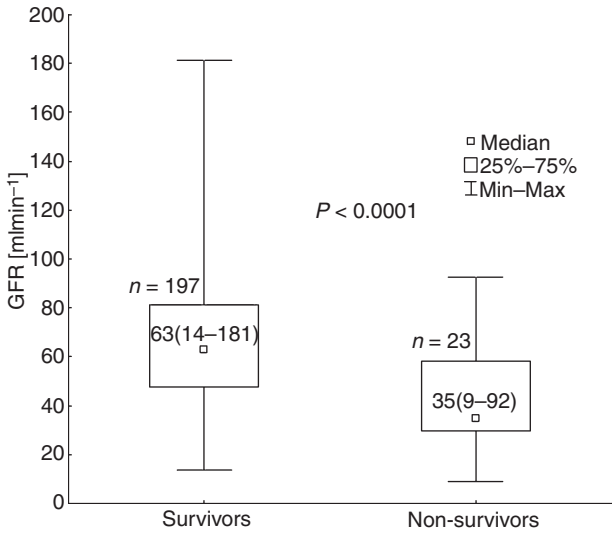

Fig. 2. Glomerular filtration rate (GFR) values in non-survivors and survivors.

There were four deaths in the group of 26 patients who received thrombolysis. Only one death resulted from massive bleeding and occurred in a patient with a GFR of 82 mL min^{-1}. No significant difference was observed between patients who received thrombolysis and those who did not receive thrombolysis with respect to GFR [59 (14–91) vs. 62 (9–181) mL min^{-1} respectively, $P = 0.17$].

Survival analysis

The area under the ROC curve of GFR was 0.760 (95% CI: 0.698–0.815) for predicting 30-day mortality (Fig. 3). GFR ≤ 35 mL min^{-1} on admission, a cut-off point chosen on the base of ROC curve analysis, was present in 32 (15%) patients and showed significant sensitivity, specificity, PPV and NPV for prediction of death within 30 days after admission (52%, 90%, 38% and 94%, respectively). In patients with GFR ≤35 mL min^{-1}, there were 10 APE-related deaths and two deaths related to major bleeding; however, both patients with fatal hemorrhage had elevated cTn and echocardiographic signs of RV dysfunction.

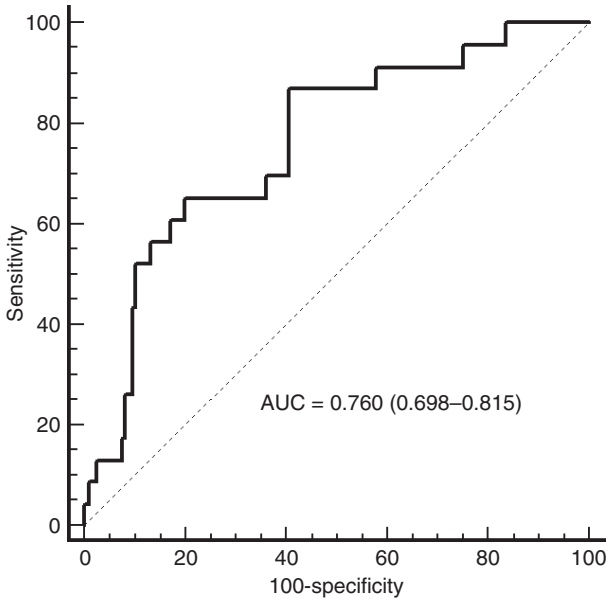

Fig. 3. Receiver-operating characteristic (ROC) curve of glomerular filtration rate (GFR) for predicting 30-day mortality. AUC, area under the curve.

Decrease of GFR was a significant predictor of mortality in univariable Cox's proportional hazard regression analysis (HR 1.50, CI 95%: 1.22–1.85 per 10 mL min^{-1} decrease, $P = 0.0001$). In stepwise multivariable Cox's proportional hazard regression analysis, independent mortality predictors for 30-day all-cause mortality were GFR (HR 1.33, CI 95%: 1.06–1.66, per 10 mL min^{-1} decrease, $P = 0.01$), positive troponin (8.9, CI 95%: 1.6–48.0; $P = 0.01$), heart rate (1.28, CI 95%: 1.10–1.50; per 10 beats, $P = 0.002$) and history of CHF (4.5, CI 95%: 1.9–10.7; $P = 0.001$). In the model were also tested age, gender, systolic and diastolic blood pressure, RV overload in echocardiography, thrombolysis and comorbidities (CAD, COPD, hypertension, diabetes mellitus, history of renal disease and neoplasm), but these parameters were found to be non-significant. In univariable Cox's proportional hazard regression as categorized factor GFR≤35 mL min^{-1} increases the risk of death with an HR of 7.6 (CI 95%: 3.4–17.6, $P < 0.00001$). Decrease of GFR allowed also to predict PE-related mortality with HR 1.46 (CI 95%: 1.43–1.50, per 10 mL min^{-1} decrease, $P = 0.002$).

Renal dysfunction and bleeding complications

Clinically important bleeding (fatal, requiring blood transfusion or associated with a decrease in hemoglobin by ≥2 g dL^{-1})

was noted in 11 patients, and in five cases with important comorbidities likely contributed to death (one patient 2 days after neurosurgery and two patients with neoplasm). GFR ≤ 35 mL min^{-1} was more often present in patients with significant hemorrhage [5 (45%) vs. 27 (12%) patients, $P = 0.01$]; however, GFR values did not differ significantly [43 (9–97) vs. 62 (14–180) mL min^{-1}, $P = 0.11$].

Renal function and right ventricular dysfunction in echocardiography

There were weak, but significant, correlations between GRF and RV diameter ($r = -0.22$, $P < 0.03$), tricuspid regurgitation peak gradient ($r = -0.18$, $P < 0.02$), acceleration time of pulmonary ejection ($r = 0.26$, $P < 0.001$), two-peak pattern of pulmonary ejection ($r = -0.29$, $P = 0.0001$), presence of paradoxical movement of the interventricular septum ($r = -0.23$, $P = 0.002$), and the presence of RV dysfunction ($r = -0.28$, $P = 0.0002$).

Renal function in prognostic assessment of patients with non-high risk APE

In the group of 212 initially normotensive patients, GFR values were also significantly higher in the 193 survivors than in the 19 non-survivors (Table 1). A GFR ≤ 35 mL min^{-1} on admission was found in 28 non-high risk patients and showed the following sensitivity, specificity, PPV and NPV for mortality prediction: 53%, 91%, 36% and 95%. Elevation of troponin above the reference values was present in 90 subjects on admission, including 18 (95%) non-survivors. Sensitivity, specificity, PPV and NPV of cTn elevation for mortality prediction were 95%, 63%, 20% and 99%, respectively.

Comparison of ROC curves for GFR and cTn in patients with non-high risk APE showed no significant difference in both test in 30-day death prediction (difference between AUC 0.008 95% CI: −0.126 to 0.142 $P = 0.907$) (Fig. 4).

Subsequently, the following groups were defined according to the presence of myocardial injury and GFR ≤ 35 mL min^{-1}: 118 patients without myocardial injury and with GFR > 35 mL min^{-1}, 21 subjects with elevated troponin and severely diminished renal function (GFR ≤ 35 mL min^{-1}), and the remaining 73 patients with either signs of myocardial injury or GFR ≤ 35 mL min^{-1}. Kaplan–Meier analysis (Fig. 5) showed that patients with myocardial injury and GFR ≤ 35 mL min^{-1} had 48% (10/21) 30-day all-cause mortality, whereas subjects without both elevated troponins and severely diminished renal function or without any of these risk factors had a much more favorable prognosis (11% and 1% mortality rate, respectively). This combined cut-off point demonstrated sensitivity, specificity, PPV and NPV for mortality prediction of 53%, 94%, 48% and 95%, respectively. Interestingly, only three patients had a GFR ≤ 35 mL min^{-1} and non-elevated troponin and none of them had died during 30-day follow-up (Fig. 6).

An initially normotensive group decrease of GFR was also a significant predictor of mortality in univariable Cox's proportional hazard regression analysis (HR 1.60, CI 95%: 1.26–2.04, per 10 mL min^{-1} decrease, $P = 0.0001$). In stepwise multivariable Cox's proportional hazard regression analysis for normotensive patients, independent mortality predictors for 30-day all-cause mortality were GFR (HR 1.46, CI 95%: 1.11–1.92, per 10 mL min^{-1} decrease, $P < 0.01$), positive troponin (14.1, CI 95%: 1.4–137.6; $P = 0.02$), increased heart rate (1.31, CI 95%: 1.07–1.61; per 10 beats, $P < 0.01$) and a history of CHF (4.9, CI 95%: 1.9–12.4; $P = 0.001$). In the model were also tested age, gender, systolic and diastolic blood pressure,

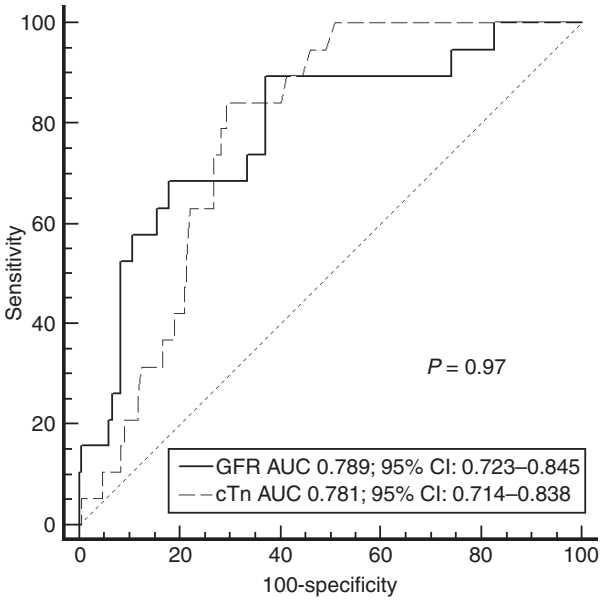

Fig. 4. Comparison of receiver-operating characteristic (ROC) curves for glomerular filtration (GFR) rate calculated by MDRD (GFR) and troponin (cTn) in patients with non-high-risk acute pulmonary embolism (difference between AUC 0.008 95% CI: −0.126 to 0.142 $P = 0.907$).

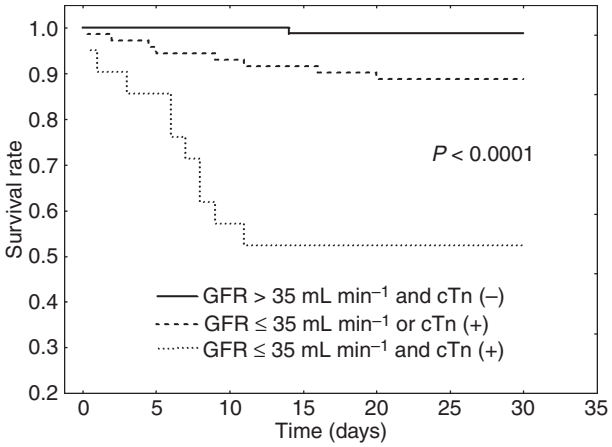

Fig. 5. Cumulative 30-day survival (Kaplan–Meier) of 212 patients with non-high-risk APE, according to glomerular filtration rate and troponin: GFR > 35 mL min^{-1} and non-elevated troponin (solid curve), GFR ≤ 35 mL min^{-1} or troponin elevation (dashed curve), GFR ≤ 35 mL min^{-1} and troponin elevation (dotted curve).

RV overload in echocardiography, thrombolysis and comorbidities (CAD, COPD, hypertension, diabetes mellitus, history of renal disease and neoplasm), but these parameters were found to be non-significant. An univariable Cox's proportional hazard regression categorized as a factor GFR ≤ 35 mL min^{-1} increases the risk of death in normotensive patients with an HR of 8.9 (CI 95%: 3.6–21.9, $P < 0.00001$). However, the decrease in GFR allowed us to also predict PE-related mortality in the non-high risk PE group with HR 1.57 (CI 95%: 1.18–2.10, per 10 mL min^{-1} decrease, $P = 0.002$).

Discussion

Risk stratification is essential in APE because it predominantly determines the therapeutic strategy [1,2]. There is a general agreement that shock and hypotension are principal markers of high risk of early death in APE, and this group should be treated with thrombolysis or embolectomy. It was reported that APE can lead to myocardial injury assessed by cardiac troponin increase [8]. Moreover, in normotensive patients the elevation of any plasma troponins, cTnI or cTnT, indicates a group with an increased mortality rate [9,10]. There is growing evidence that kidney function independently predicts mortality and morbidity after myocardial infarction [3,11] and in heart failure [12]. Even mild kidney dysfunction is associated with increased mortality [11,13]. However, there are limited data on the potential adverse influence of renal function impairment on clinical outcome in patients with venous thromboembolism.

Our study of 220 consecutive APE patients revealed that 47% of them have a GFR below 60 mL min^{-1} on admission, indicating at least intermediate renal impairment. In patients with high-risk APE presenting with shock or systemic hypotension, kidney function was more severely compromised when compared with hemodynamically stable patients. Interestingly, the highest GFR values were present in patients with low-risk APE. Importantly, on admission, GFR was significantly lower in non-survivors than in survivors. The cut-off point of GFR (35 mL min^{-1}) found in our study in the ROC curve analysis indicated groups with significant survival differences (38% vs. 6%) and was very close to the value considered as indicative of severe renal failure (30 mL min^{-1}). GFR was a significant predictor of mortality in univariable and multivariable regression analysis together with troponin elevation, heart rate and the presence of CHF. Interestingly, GFR was an even stronger mortality predictor than a history of previous kidney disease, which suggests that acute renal injury may contribute to the pathogenesis of APE. Non-survivors were older and had more comorbidities, especially chronic heart failure, hypertension and diabetes mellitus. All of these factors increase the cardiovascular risk and all can be involved in kidney injury, which itself is also associated with cardiovascular disease and reduced survival [6,14–16].

The creatinine concentration > 177 μmol L^{-1} was found to predict 3-month mortality in the ICOPER registry [17]. In other study, renal insufficiency defined by a plasma creatinine level above 2 mg dL^{-1} significantly predicted death within 7 days with an odds ratio (OR) of 2.66 in univariate analysis; however, in the multivariate model it was a borderline predictor with a *P*-value 0.07 [18]. Our previous study on short-term risk assessment in APE has also suggested that elevated creatinine levels can worsen the prognosis [10]. In all the above studies, elevated creatinine levels were found to be predictive of bad evolution in the univariate analysis, but failed to reach the significance in the multivariate model. Although plasma creatinie level reflects renal function, GFR more precisely estimates kidney function. This is a potential explanation why in our study GFR significantly predicted mortality also in multivariate model. The RIETE investigators recently analyzed 3-month outcomes in patients with a creatinine clearance < 30 mL min^{-1}, and found that 1037 of the 18 251 (5.7%) patients with venous thromboembolism, predominantly deep vein thrombosis, had a creatinine clearance < 30 mL min^{-1} [19]. During the 3-month study period, these patients had an increased incidence of fatal bleeding, fatal PE and all-cause death compared with those with a creatinine clearance > 30 mL min^{-1}. However, the authors underlined that in APE patients with a calculated creatinine clearance < 30 mL min^{-1}, APE recurrence is potentially more dangerous than bleeding complications.

Precise risk stratification of patients with non-high-risk APE is still a subject of interest. Recent European guidelines indicated a high predictive value of troponin concentrations in this group of subjects. We compared plasma troponin and calculated GFR values in mortality prediction. Assessment of kidney function in patients with non-high-risk APE showed similar values for 30-day death prediction to troponin measurements. However, Kaplan–Meier analysis also showed that patients with elevated troponin and simultaneously severely impaired renal function had a significantly worse prognosis (mortality rate 48% for 30-day all-cause death) when compared with patients with elevated plasma troponins only. This composite cut-off point revealed a sensitivity, specificity, PPV and NPV for mortality prediction of 53%, 94%, 48% and 95%, respectively. The results of our study suggest that joint analysis of GFR and cTn can improve the positive predictive value.

A broad spectrum of hemodynamic disturbances can be found in APE, forming a complete hemodynamic stability to a severe shock. The pathophysiology of PE is best known for patients with hypotension or in shock [20]. However, the most of phenomena described for high-risk PE probably can also occur to a lesser extend in normotensive patients especially with RV dysfunction. Cardiac failure in PE patients results from a combination of the increased wall stress and cardiac ischemia that comprise RV function [20]. The thin-walled RV is poorly suited to compensate for acute increases in the afterload, such as in PE. The sudden increase in the RV afterload increases wall tension and leads to acute chamber dilatation and impaired diastolic and systolic function. RV dysfunction along with tricuspid regurgitation increases a central venous pressure and leads to a stagnation of blood in central veins and subsequent passive hyperemia of liver and kidneys [21].

Moreover, especially in PE with hypotension left ventricular (LV) output can be impaired. The interventricular septum paradoxically shifts towards the LV and leads to impaired filling of this chamber under the constraint of a non-compliant pericardium. Acute tricuspid regurgitation resulting from RV dilatation and systolic dysfunction also leads to a diminished right-sided cardiac output and a reduction in the LV preload. The explanation of pathophysiology of APE can often be complicated by pre-existent cardiopulmonary diseases.

Impaired renal function in APE can potentially reflect not only previous chronic renal disease but also deterioration of renal function secondary to hemodynamic disturbances resulting from APE itself. Elevated central venous pressure, hypoxemia and possibly decreased cardiac output can probably contribute to renal dysfunction [22].

Study limitations

The present cohort included unselected patients hospitalized in a single center with acute PE. We included patients with clinically significant comorbidities, such as diabetes mellitus or congestive heart failure. All patients underwent contrast-enhanced spiral CT, but blood samples were collected no later than 1 h after CT scan. Therefore, it seems that intravenous contrast injection should not affect renal function for the purposes of this study. However, CT with contrast injection was performed in eight patients with a GFR < 20 mL min^{-1} (9–19 mL min^{-1}). In three cases, impaired renal function was not known before urgent CT examination; however, all of them had a favorable clinical course. A strategy of volume supplementation by saline infusion combined with N-acetylcysteine to prevent contrast-induced nephropathy was introduced in five patients with previously reported renal insufficiency; however, three of them died during follow-up (one fatal intracranial hemorrhage and two PE-related deaths). All patients received standard anticoagulant therapy with intravenous unfractionated heparin or a subcutaneous body mass-adjusted dose of low-molecular weight heparin. Patients with severe renal insufficiency or with a high risk of bleeding as a result of other comorbidities were initially treated with UHF under APTT control to avoid possible overdose during LMWH therapy.

Another limitation is that during the study a switch from troponin T to a I assay had occurred in our laboratory. However, it should be underlined the both troponins have been reported to predict similarly mortality in APE [9]. Glomerular filtration rate calculated with the MDRD formula allows only on estimation of the real renal function and has significant limitations especially in patients with severe renal dysfunction; however, it was shown to be a proper and significant factor in many studies [7]. Finally, mortality in our study was too low to analyze the impact of kidney function as a cause of death. There are also some confounding factors, which possibly could

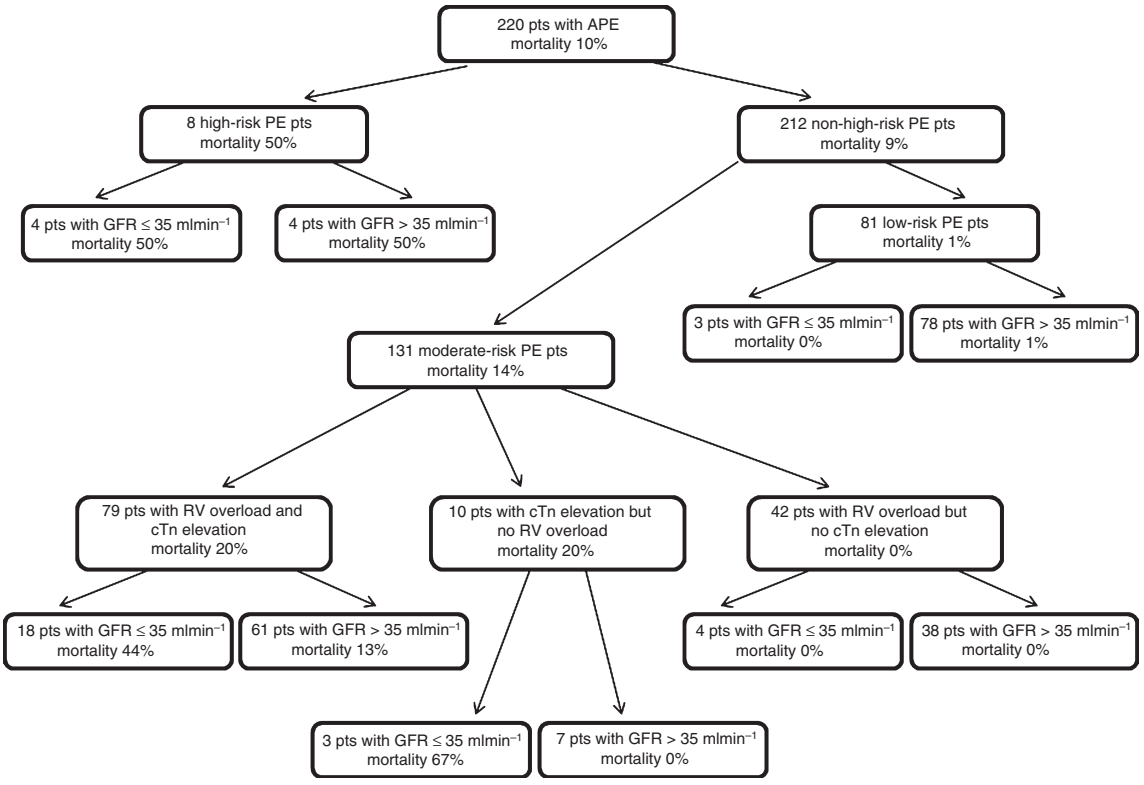

Fig. 6. Diagram of all-cause mortality risk assessment proposed in European Society of Cardiology guidelines [1] and after introducing the glomerular filtration (GFR) estimation (high-risk PE patients – hemodynamicaly unstable with shock or hypotension; moderate-risk PE patients – normotensive but with right ventricular (RV) overload in echocardiography or elevated troponin; low-risk PE without RV overload in echocardiography and signs of myocardial injury).

be worth considering in the analysis for example renal function before the PE episode, the cause of previous renal insufficiency and therapy. Unfortunately, such data are unavailable.

Conclusion

Impaired kidney function, present in 47% of APE patients, is related to all-cause mortality. In initially normotensive patients, a GFR < 35 mL min^{-1} predicts 30-day mortality. Moreover, GFR assessment can improve troponin-based risk stratification of APE.

Acknowledgement

This study was supported by grant MNiSzW: N N402 080934.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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