Chronic kidney disease: Prognostic marker of nonfatal pulmonary thromboembolism

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ABSTRACT

Objective: Renal dysfunction is associated with increased cardiovascular morbidity and mortality. The alteration in renal function as a marker of mortality in pulmonary thromboembolism (PTE) has not been studied extensively.

Methods: Four hundred four consecutive patients diagnosed with non-high-risk PTE (without cardiogenic shock or blood pressure <90 mm Hg) were prospectively enrolled in the study between 2005-2010. Kidney function, based on glomerular filtration rate (GFR), calculated by the simplified modification in diet in renal disease (MDRD) equation (sMDRD); troponin I; B-type natriuretic peptide (BNP); and echocardiographic markers of right ventricular (RV) function were determined in survivors versus non-survivors after a 2-year follow-up.

Results: GFR was significantly lower in non-survivors than in survivors: 51.85±19.08 mL/min/1.73 m² and 71.65±23.21 mL/min/1.73 m², respectively (p=0.000). The highest 2-year mortality rate (20%) was recorded in patients with moderate renal dysfunction associated with RV dysfunction. Using multivariate analysis, we found that GFR is an independent predictor of 2-year mortality (OR 0.973, 95% CI: 0.959-0.987, p=0.000), besides troponin I, dyslipidemia, acceleration time of pulmonary ejection, pericardial effusion, and BNP.

Conclusion: The association of renal dysfunction with right ventricular dysfunction in patients with non-fatal pulmonary thromboembolism resulted in high mortality. Renal dysfunction, assessed by glomerular filtration rate, may be used in the risk stratification of patients with non-high-risk pulmonary thromboembolism, besides troponin I, BNP, and right ventricle echocardiographic dysfunction markers.

Keywords: creatinine clearance, filtration rate, pulmonary thromboembolism, mortality, MDRD

Introduction

Pulmonary thromboembolism (PTE) is the third most common cause of hospital admission after acute myocardial infarction and stroke (1, 2). Chronic kidney disease (CKD) is associated with increased cardiovascular morbidity and mortality. The high incidence of venous thromboembolism in acute end-stage renal disease, nephrotic syndrome, or stages 3 and 4 CKD is well known (3-7). The relationship between venous thromboembolism-related mortality and renal dysfunction, assessed by glomerular filtration rate (GFR), has not been fully elucidated.

Methods

Four hundred four patients diagnosed with PTE between 2005 and 2010 were prospectively enrolled in this study. The diagnosis of pulmonary thromboembolism was made by: angio-CT scan, pulmonary ventilation-perfusion scintigraphy (high or intermediate probability of PTE, and compression ultrasonography (presence of deep vein thrombosis of the lower limbs). The main goal of this study was to determine mortality of all causes in our study group. The inclusion criteria were: patients aged >18 with low and intermediate risk (non-high-risk) PTE, without previous oral anticoagulant therapy. The exclusion criteria were: patients with high-risk PTE [associated with cardiogenic shock or blood pressure <90 mm Hg (8)], patients with end-stage diseases and life expectancy below 1 year, patients at high risk of bleeding during anticoagulant therapy [previous gastrointestinal bleeding of irreversible cause, advanced chronic kidney (stage 5 CKD) or liver hepatic disease, previous hemorrhagic stroke, poor anticoagulant control, and suboptimal monitoring of anticoagulant therapy], and patients enrolled in other studies. Low-risk
PTE was defined by the absence of RV dysfunction or signs of myocardial injury. Intermediate-risk PTE was defined by increased serum levels of troponin and/or pro-BNP and/or RV dysfunction with blood pressure >90 mm Hg. All patients received standard anticoagulant therapy with intravenous unfractionated heparin or a subcutaneous weight-adjusted dose of low-molecular-weight heparin, followed by oral anticoagulants (acenocoumarol).

Table 1. Demographic, clinical, and laboratory characteristics of patients according to clinical course

| Parameters       | All patients (n=404) | Non-survivors (n=33) | Survivors (n=371) | P  |
|------------------|----------------------|----------------------|-------------------|----|
| Clinical         |                      |                      |                   |    |
| Age, years       | 62.32±14.26          | 69.03±11.17          | 61.73±14.37       | 0.005* |
| Men n (%)        | 205 (50.7)           | 14 (42.4)            | 191 (51.5)        | 0.319 |
| SBP, mm Hg       | 132.21±21.60         | 131.21±28.14         | 132.30±20.96      | 0.305 |
| DBP, mm Hg       | 80.63±12.38          | 81.21±11.39          | 80.58±12.47       | 0.791 |
| Heart rate >90/bpm | 174 (43.1)          | 16 (48.5)            | 158 (42.6)        | 0.512 |
| AF, n (%)        | 153 (37.9)           | 15 (45.5)            | 138 (37.2)        | 0.349 |
| SaO2             | 89.71±8.121          | 87.28±7.92           | 90.03±8.11        | 0.102 |
| COPD, n (%)      | 99 (24.5)            | 10 (30.3)            | 89 (24.0)         | 0.419 |
| Hypertension, n (%) | 171 (42.3)          | 13 (39.4)            | 158 (42.6)        | 0.722 |
| DM, n (%)        | 75 (18.6)            | 8 (24.2)             | 67 (18.1)         | 0.381 |
| CHD, n (%)       | 217 (53.7)           | 21 (63.6)            | 196 (52.8)        | 0.233 |
| Cancer, n (%)    | 16 (4.0)             | 0 (0.0)              | 16 (4.3)          | 0.223 |
| Dyslipidemia, n (%) | 99 (24.5)           | 1 (3.0)              | 98 (26.4)         | 0.003* |
| Biological       |                      |                      |                   |    |
| BNP, pg/mL       | 336.70±535.116       | 913.82±907.65        | 285.23±456.14     | 0.000* |
| Troponin I, ng/mL | 0.03±0.20            | 0.15±0.69            | 0.01±0.04         | 0.000* |
| GFR, mL/min/1.73 m² | 70.04±23.52         | 51.85±19.08          | 71.65±23.21       | 0.000* |
| Echocardiographic|                      |                      |                   |    |
| PE, n (%)        | 92 (22.8)            | 13 (39.4)            | 79 (21.3)         | 0.018* |
| Severe TR, n (%) | 177 (43.8)           | 11 (33.3)            | 166 (44.7)        | 0.206 |
| TAPSE, mm        | 17.91±4.58           | 17.45±3.84           | 17.95±4.64        | 0.577 |
| AT, ms           | 99.99±18.62          | 94.00±18.86          | 100.52±18.54      | 0.054* |
| sPAP, mm Hg      | 70.19±22.82          | 73.03±19.18          | 69.94±23.12       | 0.708 |
| RVTD, mm         | 37.08±9.15           | 37.94±7.49           | 37.01±9.28        | 0.575 |

AF - atrial fibrillation; AT - acceleration time; CHD - coronary heart disease; COPD - chronic obstructive bronchopneumopathy; DBP - diastolic blood pressure; DM - diabetes mellitus; GFR - glomerular filtration rate; IVS - interventricular septum; PE - pericardial effusion; RV - right ventricle; RVTD - right ventricular telediastolic diameter; SaO2 - oxygen saturation in room air; SBP - systolic blood pressure; sPAP - systolic pulmonary arterial pressure; TR - tricuspid regurgitation; *means p<0.05

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) for Windows. The quantitative data were expressed as mean and standard deviation, while the qualitative data were expressed as median and range. The normal distribution of quantitative data was assessed by Kolmogorov-Smirnov fit test; to compare two groups, we used chi-square test for qualitative data, student t-test for normally distributed quantitative data, and Mann-Whitney U test for abnormally distributed quantitative data. The comparisons between more than two groups were made using ANOVA (for normally distributed quantitative data) and Kruskal-Wallis (for non-normally distributed quantitative data) tests. The parameters that were significant in the univariate analysis were brought into a forward stepwise bivariate logistic regression model in order to better investigate their influence. The Hosmer-Lemeshow goodness-of-fit test was used to check if the model fit the real data well. The parameters included into the model were also checked against multi-collinearity. A p value >0.05 was considered statistically significant.

Results

Enrolled in this study were 438 patients; 34 (7.76%) patients were lost to follow-up (up to 2 years), and therefore, the study group included 404 patients. Mean age was 62.32±14.26 years; 205 (50.7%) patients were men. Only 14 (3.8%) patients were low-risk; 357 (96.2%) patients were assigned to the intermediate-risk group. Thirty-three deaths were recorded, all in the intermediate-risk group. The clinical characteristics of the patients are shown in Table 1. GFR was significantly lower in
non-survivors than in survivors: 51.85±19.08 mL/min/1.73 m² versus 71.65±23.21 mL/min/1.73 m² (p=0.000).

Renal dysfunction and clinical parameters

Compared to patients without renal dysfunction, patients with PTE and low GFR (<90 mL/min/1.73 m²) are more likely to be older and female and have a higher body mass index (Table 2). In addition, they had more comorbidities, such as diabetes mellitus, coronary heart disease, previous deep thrombophlebitis or varicose veins, COPD, and/or heart failure.

Table 2. Characteristics of patients with pulmonary embolism according to glomerular filtration rate

| Parameters | GFR <30 mL/min/1.73 m² (n=15) | GFR 30-59 mL/min/1.73 m² (n=133) | GFR >60 mL/min/1.73 m² (n=256) | P |
|------------|-------------------------------|-------------------------------|-------------------------------|----|
| Clinical   |                               |                               |                               |    |
| Age, years | 71.60±11.38                   | 68.56±11.53                   | 58.54±14.35                   | 0.000*|
| Men, n (%) | 4 (26.7)                      | 51 (38.3)                     | 150 (58.6)                    | 0.000*|
| SBP, mm Hg | 143.67±28.93                  | 129.39±19.77                  | 133.01±21.83                  | 0.167 |
| DBP, mm Hg | 81.33±19.22                   | 79.06±11.84                   | 81.41±12.14                   | 0.224 |
| Heart rate >90/bpm | 5 (33.3) | 64 (48.1) | 105 (41.0) | 0.301 |
| AF, n (%) | 7 (46.7)                      | 56 (43.6)                     | 88 (34.4)                     | 0.158 |
| SaO₂ | 84.40±6.73                    | 88.86±8.58                    | 90.43±7.80                    | 0.156 |
| COPD, n (%) | 4 (26.7) | 39 (29.3) | 56 (21.9) | 0.264 |
| Hypertension, n (%) | 9 (60.0) | 57 (42.9) | 105 (41.0) | 0.347 |
| DM, n (%) | 5 (33.3)                      | 32 (24.1)                     | 38 (14.8)                     | 0.028* |
| CHD, n (%) | 9 (60.0)                      | 78 (58.6)                     | 130 (50.8)                    | 0.297 |
| Cancer, n (%) | 0 (0.0) | 9 (6.8) | 7 (2.7) | 0.112 |
| Dyslipidemia, n (%) | 3 (20.0) | 27 (20.3) | 69 (27.0) | 0.322 |
| Biological |                               |                               |                               |    |
| BNP (pg/mL) | 351.87±400.43                 | 404.61±477.01                 | 300.40±567.76                 | 0.001* |
| Troponin I (ng/mL) | 0.02±0.03 | 0.06±0.34 | 0.01±0.02 | 0.001* |
| Echocardiographic |                  |                               |                               |    |
| PE, n (%) | 2 (13.3)                      | 33 (24.8)                     | 57 (22.3)                     | 0.574 |
| Severe TR, n (%) | 8 (53.3) | 67 (50.4) | 102 (9.8) | 0.104 |
| TAPSE, mm | 16.87±4.06                    | 17.36±4.34                    | 18.25±4.70                    | 0.132 |
| AT, ms | 89.93±16.84                   | 97.82±18.64                   | 101.71±18.48                  | 0.015* |
| sPAP, mm Hg | 79.20±26.63 | 70.41±20.85 | 69.55±23.54 | 0.688 |
| RVTDD, mm | 40.47±10.81                   | 37.08±8.91                    | 36.88±9.16                    | 0.338 |
| AF - atrial fibrillation; AT - acceleration time; COPD - chronic obstructive bronchopneumopathy; DBP - diastolic blood pressure; DM - diabetes mellitus; GFR - glomerular filtration rate; CHD - coronary heart disease; IVS - interventricular septum; PE - pericardial effusion; RV - right ventricle; RVTDD - right ventricular telediastolic diameter; SaO₂ - oxygen saturation in room air; SBP - systolic blood pressure; sPAP - systolic pulmonary arterial pressure; TR - tricuspid regurgitation; *means p<0.005 |

Renal dysfunction and myocardial injury markers

The mean value of troponin was significantly higher in non-survivors than in survivors (0.15±0.69 ng/mL versus 0.01±0.04 ng/mL; p=0.000). GFR and troponin were statistically significant negatively correlated in both non-survivors (r=-0.291; p=0.045) and survivors (r=-0.275; p=0.049). The mean BNP value was significantly higher in non-survivors compared to survivors (913.82±507.65 µg/mL and 285.23±456.14 µg/mL, respectively; p=0.000). BNP was significantly associated with GFR only in non-survivors (r=-0.552; p=0.003); in survivors, the correlation was statistically insignificant (r=-0.039; p=0.386).
Renal dysfunction and right ventricular dysfunction

GFR and TAPSE were significantly correlated in survivors \((r=+0.064; p=0.012)\) and not significantly correlated in non-survivors \((r=+0.124; p=0.210)\). The same was true for GFR and sPAP \((r=-0.161; p=0.372)\) and survivors \((r=-0.188; p=0.001)\). Acceleration time was statistically significant in both non-survivors \((r=+0.356; p=0.001)\) and survivors \((r=+0.131; p=0.001)\).

The 2-year survival probability in patients with stage 4CKD and RV dysfunction was about 60%; in the absence of severe renal impairment but with RV dysfunction, this probability was approximately 80%, showing the additive prognostic value of GFR (Fig. 3).

Using multivariate analysis, we found GFR to be an independent predictor of 2-year mortality \((OR 0.973, 95\% CI: 0.959-0.987, p=0.000)\), besides troponin I, dyslipidemia, acceleration time of pulmonary ejection, pericardial effusion, and BNP (Table 3).

Discussion

The main finding in this study was that renal dysfunction increases 2-year mortality in patients with non-high-risk PTE. The association between renal dysfunction and PTE was initially sus-
Low GFR is associated with telediastolic RV diameter, maximum tricuspid regurgitation gradient, acceleration time of pulmonary ejection, and the presence of paradoxical movements of the interventricular septum (30). In our study, except for the telediastolic RV diameter, all echocardiographic parameters of RV dysfunction were highly significantly correlated with GFR, even though the correlation was weak; acceleration time of pulmonary ejection showed the best statistical correlation in patients with nonfatal risk. In non-survivors, acceleration time was the only statistically significant parameter. In addition, of the echocardiographic parameters, it was the only one that was found to be an independent predictor of mortality. Acceleration time of pulmonary ejection proved to be a predictive marker of mortality in patients suspected of PTE and an independent marker of survival in patients with nonfatal PTE confirmed by scintigraphy (31). In addition, this parameter is inversely correlated with RV dysfunction and has diagnostic importance in PTE, especially in the presence of proximal thrombi (32-34).

In our study, metabolic syndrome seems to increase mortality risk in patients with renal dysfunction. Dyslipidemia was found to be an independent predictor of mortality. This may occur through the effects of circulating lipid molecules on the vascular endothelium, platelet function, and coagulation factors (35). Diabetes mellitus and obesity are statistically significantly more frequently associated with lower GFR. All of these factors increase the cardiovascular risk and subsequently the risk of kidney damage.

**Study limitations**

The small number of non-survivors is due to the fact that hemodynamically unstable patients with PTE were excluded from the study, with the aim of this study being the assessment of patients at risk for nonfatal PTE. Few autopsies have been performed; therefore, possible recurrences of fatal venous thromboembolism were not diagnosed. The sMDRD formula might show several limitations in patients with GFR over 60 mL/min/1.73 m² (32). The initial group also failed to include patients with a GFR below 15 mL/min/1.73 m², with a single patient being included in this group at the end. This could influence the identification of more significant results in the case of severe renal dysfunction. Data on the history of CKD before PTE could not be obtained from all patients. The diverse etiologies of PTE determined different therapeutic approaches in terms of oral anticoagulation treatment duration. This topic will be further investigated.

**Conclusion**

Concurrence of renal dysfunction and right ventricular dysfunction in patients with a risk for nonfatal pulmonary thromboembolism is associated with high mortality. Renal dysfunction, assessed by glomerular filtration rate, may be used in the risk stratification of patients with non-high-risk pulmonary thromboembolism, besides troponin, BNP, and echocardiographic markers of right ventricular dysfunction.

**Conflict of interest:** None declared.

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