Glomerular Filtration Rate as a Prognostic Factor for Long-Term Mortality after Acute Pulmonary Embolism

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Significance of the Study

• This original prospective cohort study explores the importance of renal function not only as a short-term but also as a long-term prognostic marker for patients with acute PE. The results of this study suggest the usefulness of estimated glomerular filtration rate and creatinine clearance as an additional tool for risk stratification of these patients in clinical practice.

Keywords
Glomerular filtration rate · Mortality · Pulmonary embolism · Renal insufficiency · Venous thromboembolism

Abstract

Background: In-hospital mortality for patients presenting with acute pulmonary embolism (PE) has been reported to be up to 7 times higher for patients with decreased estimated glomerular filtration rate (eGFR). However, few studies have assessed its effect on long-term mortality. Objective: To determine the impact of eGFR and creatinine clearance (CrCl) on long-term all-cause mortality following acute PE in association with other routine laboratory analyses and comorbidities. Patients/Methods: The prospective study enrolled 141 consecutive patients presenting with objectively confirmed acute PE. Demographic, clinical data, comorbidities, and laboratory values were recorded. CrCl and GFR were estimated using the Cockcroft-Gault, MDRD, and chronic kidney disease (CKD)-EPI equations. Patients were followed up at 90 days and 1 year after the event. Results: In univariate analyses, age, active cancer, PE severity index (PESI), CrCl and eGFR, D-dimer value, and high-density lipoprotein level were found to be significantly associated with mortality in 90 days and 1 year. Additionally, body mass index was significant in the 1-year follow-up. CrCl by Cockcroft-Gault (90-day: area under the curve [AUC] 0.763; 1-year: AUC 0.718) demonstrated higher discriminatory power for predicting mortality than eGFR by the MDRD (AUC 0.686; AUC 0.609) and CKD-EPI (AUC 0.697; AUC 0.630) equations. In multivariate analyses, active cancer, CrCl by Cockcroft-Gault (90-day: hazard ratio [HR] 0.948, 95% CI 0.919–0.979; 1-year: HR 0.967, 95% CI 0.943–0.991), eGFR by CKD-EPI (90-day: HR 0.948, 95% CI 0.915–0.983; 1-year: HR 0.971, 95% CI 0.945–0.998) were found to be independent predictors of mortality. eGFR by MDRD, D-dimer, and PESI value were significant prognostic factors for 90-day mortality. Conclusion: Decreased renal function is a prognostic factor for increased all-cause mortality 90 days and 1 year after acute PE.

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Published by S. Karger AG, Basel
**Introduction**

Venous thromboembolism (VTE) is the third most common cause of death from cardiovascular disease after acute myocardial infarction and stroke [1,2] with an overall annual incidence of 104–183 per 100,000 person years in European ancestry [3]. Renal dysfunction is an important risk factor for cardiovascular disease and is associated with increased mortality and morbidity [4]. The high incidence of VTE in end-stage renal disease, nephrotic syndrome, or stages 3 and 4 chronic kidney disease (CKD) is well known [5–8]. Furthermore, mild to moderate CKD is associated with a procoagulant profile [9].

The prognostic importance of CKD and decreased estimated glomerular filtration rate (eGFR) for patients with acute pulmonary embolism (PE) has been studied; however, there is no definitive data with regard to the impact of CKD on in-hospital mortality for PE [10]. Although various studies show the impact of renal dysfunction on the short-term prognosis in these patients [10–15], few studies have assessed its effect on long-term function as a prognostic marker is yet to be fully determined. Acute PE itself can contribute to acute kidney injury, which predicts higher all-cause mortality in 30 days [16] in addition to previously observed kidney dysfunction and worse short-term outcomes in case of a PE event [13, 14].

The aim of this study was to determine the impact of eGFR and CrCl on long-term all-cause mortality following acute PE in association with other routine laboratory analyses and comorbidities.

**Materials and Methods**

**Study Population**

Patients were eligible for our study if the diagnosis of acute PE was confirmed by computed tomography pulmonary angiography (CTPA). All radiographic images were analyzed by experienced radiologists. All included patients had a recent or first PE symptoms during the previous 10 days. All patients provided written or oral consent for participation in the registry in accordance with local hospital ethics committee requirements. We made all efforts to enroll consecutive patients admitted to the hospital. Data were recorded in a computer-based registry.

**Study Design**

We conducted a prospective cohort study and retrospectively analyzed data in a single hospital. The following parameters were recorded: baseline characteristics of patients; clinical status, including any coexisting or underlying conditions such as chronic heart or lung disease; risk factors for PE; laboratory findings including hemoglobin, leukocytes, platelet count, D-dimers, creatinine, troponin-I, brain natriuretic peptide (BNP), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein, and triglycerides. For all patients, clinical parameters, hemoglobin, leukocytes, platelet count, D-dimers, creatinine, and troponin-I were taken upon admission at the hospital or were recorded from the first test available after the onset of symptoms in cases where the index event took place in the hospital. Creatinine was measured before CTPA was performed. Initial serum creatinine levels were compared to the last repeated measurement before hospital discharge. Using this information and previous records from patient history, patients were classified as having transient, maintained (chronic), or no renal dysfunction. Renal dysfunction was defined as CrCl by Cockcroft-Gault below 60 mL/min. The definitions of transient, maintained (chronic), and no renal dysfunction were as follows: no renal dysfunction – stable estimated CrCl of no less than 60 mL/min; transient – CrCl below 60 mL/min upon admission with return to a value above 60 mL/min during the hospital stay or subsequent measurements in the following 3 months; maintained (chronic) – CrCl persistently below 60 mL/min during the hospital stay and subsequent measurements and previously known CKD in stages 3–5. Active cancer was categorized as newly diagnosed cancer, metastatic cancer, or cancer that is being treated. PE severity index (PESI) was calculated for all patients. Renal function was estimated using CrCl by Cockcroft-Gault and eGFR by MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. All patients had a follow-up at 90 days and 1 year.

**Statistical Analysis**

Data were expressed as absolute numbers and percentage, mean and SD, or median and interquartile range where appropriate. SPSS, version 23.0, was used for all analyses. Univariate analyses were conducted using independent samples t test, Mann-Whitney U test, χ²-test, and Fisher’s exact test where appropriate. To assess the independent effect on mortality of statistically significant variables in univariate analysis, multivariate Cox regression analysis was performed. Variables were tested for collinearity and proportionality assumption. Receiver-operating characteristic (ROC) was used to determine the prognostic value for mortality of different GFR/CrCl estimation formulas. A p value <0.05 was considered statistically significant.

**Results**

The study population consisted of 141 patients of whom 87 (61.7% [95% CI 53.1–69.8]) were female. Mean age was 66 (SD 16) years (range 23–92). All-cause mortality rate within 90 days and 1 year was 13.5% (95% CI 8.3–20.2; n = 19) and 17.7% (95% CI 11.8–25.1; n = 25), respectively. Causes of death were classified as cardiovascular (n = 8), directly attributable to malignancy (n = 9), multiorgan dysfunction (n = 5), and other (n = 3). Demographic, clinical, and laboratory characteristics of patients according to 90-day and 1-year outcomes are presented in Tables 1 and 2.
Table 1. Patient characteristics according to mortality within 90 days

| Patients, n (%) | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|----------------|--------------|---------------------|------------------|---------|
|                | 141 (100)    | 19 (13.5)           | 122 (86.5)       | –       |
| **Demographic features** |             |                     |                  |         |
| Age, years, mean ± SD    | 66±16        | 73±13               | 65±16            | 0.030*  |
| Gender, female, n (%)    | 87 (61.7)    | 12 (63.2)           | 75 (61.5)        | 0.888   |
| BMI, kg/m², mean ± SD    | 29.5±5.7     | 27.3±5.2            | 29.8±5.7         | 0.058   |
| **Comorbidities, n (%)** |             |                     |                  |         |
| Chronic heart failure    | 62 (44.0)    | 9 (47.4)            | 53 (43.4)        | 0.748   |
| Chronic lung disease     | 17 (12.1)    | 1 (5.3)             | 16 (13.1)        | 0.469   |
| Diabetes                 | 22 (15.6)    | 5 (26.3)            | 17 (13.9)        | 0.179   |
| Atrial fibrillation      | 28 (19.9)    | 5 (26.3)            | 23 (18.9)        | 0.536   |
| Myocardial infarction    | 26 (18.4)    | 5 (26.3)            | 21 (17.2)        | 0.347   |
| Cerebral ischemia        | 14 (9.9)     | 2 (10.5)            | 12 (9.8)         | 1.000   |
| Arterial hypertension    | 92 (65.2)    | 10 (52.6)           | 82 (66.4)        | 0.469   |
| Active cancer            | 18 (12.8)    | 10 (52.6)           | 8 (6.6)          | <0.001* |

**Haemodynamic data, median (IQR)**

|                          | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|--------------------------|--------------|---------------------|------------------|---------|
| Systolic blood pressure, mm Hg | 130 (110–140) | 130 (110–145)    | 130 (110–140)    | 0.889   |
| Respiratory rate, ×/min  | 18 (16–22)   | 18 (15–21)         | 18 (16–22)       | 0.764   |
| Heart rate, bpm          | 90 (78–104)  | 80 (68–90)         | 90 (80–104)      | 0.073   |

**Scales**

| Scale                         | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|-------------------------------|--------------|---------------------|------------------|---------|
| PESI, median (IQR)            | 89 (74–107)  | 119 (91–138)       | 88 (71–102)      | 0.002*  |

**Risk factors, n (%)**

| Risk factor                  | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|------------------------------|--------------|---------------------|------------------|---------|
| Transient risk factor        | 44 (31.2)    | 5 (26.3)            | 39 (32.0)        | 0.621   |
| Prior VTE                    | 25 (17.7)    | 2 (10.5)            | 23 (18.9)        | 0.527   |

**Laboratory data**

| Laboratory data               | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|-------------------------------|--------------|---------------------|------------------|---------|
| eGFR (Cockcroft-Gault), ml/min| 81 (58–113)  | 55 (34–77)          | 84 (61–115)      | <0.001* |
| eGFR (MDRD), ml/min/1.73 m²   | 70 (55–88)   | 49 (41–77)          | 71 (59–91)       | 0.010*  |
| eGFR (CKD-EPI), ml/min/1.73 m²| 70 (54–86)   | 44 (38–76)          | 71 (56–88)       | 0.006*  |
| CrCl <60 (Cockcroft-Gault, ml/min) | 38 (27.7) | 11 (57.9)          | 27 (29.9)        | 0.002*  |
| eGFR <60 (MDRD, ml/min/1.73 m²)| 42 (30.7)   | 11 (57.9)           | 31 (26.3)        | 0.006*  |
| eGFR <60 (CKD-EPI, ml/min/1.73 m²)| 48 (35.0) | 11 (57.9)          | 37 (31.4)        | 0.024*  |

**Renal dysfunction, n (%)**

| Dysfunction                  | All patients | 90-day nonsurvivors | 90-day survivors | p value |
|------------------------------|--------------|---------------------|------------------|---------|
| None                         | 102 (72.3)   | 8 (42.1)            | 94 (77.0)        | 0.002*  |
| Transient                    | 17 (12.1)    | 3 (15.8)            | 14 (11.5)        |         |
| Maintained                   | 22 (15.6)    | 8 (42.1)            | 14 (11.5)        |         |

| D-dimer, mg/L, median (IQR)  | 8.7 (4.2–16.0) | 15.3 (7.9–33.8)    | 8.3 (4.1–15.6)   | 0.009*  |
| Troponin-1 (abnormal), n (%)| 20 (15.3)     | 5 (26.3)           | 15 (13.4)        | 0.169   |
| BNP, ng/L, median (IQR)     | 319 (91–922)  | 681 (196–1,006)    | 272 (76–901)     | 0.183   |
| Total cholesterol, mmol/L, median (IQR) | 4.2 (3.4–5.1) | 3.7 (3.4–4.8) | 4.3 (3.4–5.1) | 0.301 |
| HDL, mmol/L, median (IQR)   | 0.99 (0.78–1.27) | 0.83 (0.55–0.97) | 1.01 (0.81–1.30) | 0.019* |
| LDL, mmol/L, median (IQR)   | 2.44 (1.87–3.18) | 2.31 (1.73–2.95) | 2.50 (1.89–3.21) | 0.488 |
| TG, mmol/L, median (IQR)    | 1.3 (1.0–1.7)           | 1.4 (1.0–1.7)    | 1.3 (1.0–1.7)   | 0.653   |
| Leukocytes, 10⁹/L, median (IQR) | 10.1 (7.9–12.1) | 11.1 (7.3–13.9) | 10.0 (7.9–12.1) | 0.429 |
| Hemoglobin, g/dL, median (IQR) | 13.0 (11.9–14.6) | 12.4 (11.8–15.1) | 13.1 (11.9–14.5) | 0.623 |
| Platelets, 10⁹/L, median (IQR) | 224 (171–296) | 199 (145–276)    | 227 (174–298)   | 0.149   |

BMI, body-mass index; IQR, interquartile range; PESI, pulmonary embolism severity index; VTE, venous thromboembolism; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. * p < 0.05.
Table 2. Patient characteristics according to mortality within 1 year

|                        | All patients | 1-year nonsurvivors | 1-year survivors | p value |
|------------------------|--------------|---------------------|------------------|---------|
| **Patients, n (%)**    | 141 (100.0)  | 25 (17.7)           | 116 (82.3)       |         |
| **Demographic features** |             |                     |                  |         |
| Age, years, mean ± SD  | 66±16        | 73±13               | 64±16            | 0.010*  |
| Gender, female, n (%)  | 87 (61.7)    | 13 (52.0)           | 74 (63.8)        | 0.271   |
| BMI, kg/m², mean ± SD  | 29.5±5.7     | 27.1±5.0            | 30.0±5.7         | 0.030*  |
| **Comorbidities, n (%)** |             |                     |                  |         |
| Chronic heart failure  | 62 (44.0)    | 11 (44.0)           | 51 (44.0)        | 0.997   |
| Chronic lung disease   | 17 (12.1)    | 2 (8.0)             | 15 (12.9)        | 0.737   |
| Diabetes               | 22 (15.6)    | 7 (28.0)            | 15 (12.9)        | 0.072   |
| Atrial fibrillation    | 28 (19.9)    | 6 (24.0)            | 22 (19.0)        | 0.585   |
| Myocardial infarction  | 26 (18.4)    | 5 (20.0)            | 21 (18.1)        | 0.782   |
| Cerebral ischemia      | 14 (9.9)     | 2 (8.0)             | 12 (10.3)        | 1.000   |
| Arterial hypertension  | 92 (65.2)    | 15 (60.0)           | 77 (66.4)        | 0.543   |
| Active cancer          | 18 (12.8)    | 13 (52.0)           | 5 (4.3)          | <0.001* |
| **Haemodynamic data, median (IQR)** |             |                     |                  |         |
| Systolic blood pressure, mm Hg | 130 (110–140) | 130 (116–149) | 130 (110–140) | 0.445   |
| Respiratory rate, ×/min | 18 (16–22)    | 18 (16–22)          | 18 (16–22)       | 0.737   |
| Heart rate, bpm         | 90 (78–104)  | 86 (73–106)         | 90 (78–104)      | 0.332   |
| **Scales**             |             |                     |                  |         |
| PESI, median (IQR)     | 89 (74–107)  | 111 (93–138)        | 87 (70–99)       | <0.001* |
| **Risk factors, n (%)** |             |                     |                  |         |
| Transient risk factors  | 44 (31.2)    | 6 (24.0)            | 38 (32.8)        | 0.391   |
| Prior VTE              | 25 (17.7)    | 4 (16.0)            | 21 (18.1)        | 1.000   |
| **Laboratory data**    |             |                     |                  |         |
| eGFR continuous, median (IQR) |         |                     |                  |         |
| CrCl (Cockcroft-Gault), mL/min | 81 (58–113)  | 60 (36–95)          | 84 (61–117)      | 0.001*  |
| eGFR (MDRD), mL/min/1.73 m² | 70 (55–88)   | 62 (43–85)          | 70 (59–90)       | 0.090   |
| eGFR (CKD-EPI), mL/min/1.73 m² | 70 (54–86)   | 56 (41–79)          | 71 (56–89)       | 0.043*  |
| eGFR categorical, n (%) |             |                     |                  |         |
| CrCl <60 (Cockcroft-Gault, mL/min) | 38 (27.7)  | 13 (52.0)           | 25 (22.3)        | 0.003*  |
| eGFR <60 (MDRD, mL/min/1.73 m²) | 42 (30.7)    | 12 (48.0)           | 30 (26.8)        | 0.038*  |
| eGFR <60 (CKD-EPI, mL/min/1.73 m²) | 48 (35.0)    | 13 (52.0)           | 35 (31.3)        | 0.049*  |
| **Renal dysfunction, n (%)** |             |                     |                  |         |
| None                   | 102 (72.3)   | 12 (48.0)           | 90 (77.6)        | 0.004*  |
| Transient              | 17 (12.1)    | 4 (16.0)            | 13 (11.2)        |         |
| Maintained             | 22 (15.6)    | 9 (36.0)            | 13 (11.2)        |         |
| D-dimer, mg/L, median (IQR) | 8.7 (4.2–16.0) | 13.5 (6.5–25.4) | 8.3 (4.1–15.6) | 0.033*  |
| Troponin-I (abnormal), n (%) | 20 (15.3)    | 5 (20.0)            | 15 (14.2)        | 0.536   |
| BNP, ng/L, median (IQR) | 319 (91–922) | 545 (142–1,016)     | 314 (78–897)     | 0.342   |
| Total cholesterol, mmol/L, median (IQR) | 4.2 (3.4–5.1) | 3.7 (3.4–4.6) | 4.4 (3.5–5.1) | 0.097   |
| HDL, mmol/L, median (IQR) | 0.99 (0.78–1.27) | 0.86 (0.62–1.18) | 1.01 (0.81–1.35) | 0.039*  |
| LDL, mmol/L, median (IQR) | 2.4 (1.9–3.2) | 2.3 (1.5–2.8) | 2.6 (1.9–3.2) | 0.157   |
| TG, mmol/L, median (IQR) | 1.3 (1.0–1.7) | 1.4 (1.0–1.7) | 1.3 (1.0–1.7) | 0.661   |
| Leukocytes, 10^9/L, median (IQR) | 10.1 (7.9–12.1) | 10.0 (7.7–11.8) | 10.2 (7.8–12.3) | 0.893   |
| Hemoglobin, g/dL, median (IQR) | 13.0 (11.9–14.6) | 12.2 (11.0–14.4) | 13.1 (12.0–14.6) | 0.183   |
| Platelets, 10^9/L, median (IQR) | 224 (171–295) | 199 (152–270) | 227 (177–301) | 0.110   |
Overall, 12.1% \((n = 17)\) of patients had transient renal dysfunction, and 15.6% \((n = 22)\) had maintained renal dysfunction. In patients with maintained renal dysfunction, 90-day and 1-year mortality was 36.4% \((n = 8)\) and 40.9% \((n = 9)\), in transient dysfunction 17.6% \((n = 3)\) and 23.5% \((n = 4)\), and in patients with no renal dysfunction 7.8% \((n = 8)\) and 11.8% \((n = 12)\). The difference between mortality rates in patients with transient, maintained, or no renal dysfunction was statistically significant \((p = 0.002\) at 90 days; \(p = 0.004\) at 1 year). Differences in mortality rates between transient versus no renal dysfunction did not demonstrate statistical significance \((90\text{-day}: p = 0.192; 1\text{-year}: p = 0.243)\), but significance was found between maintained versus no renal dysfunction \((90\text{-day}: p = 0.001; 1\text{-year}: p = 0.003)\).

In univariate analyses, characteristics that were statistically significantly associated with 90-day mortality were age, presence of active cancer, higher PESI score, absolute CrCl value by Cockcroft-Gault, and eGFR by MDRD and CKD-EPI, as well as CrCl < 60 mL/min and eGFR < 60 mL/min/1.73 m², D-dimer value, and HDL level. Values that were statistically significantly associated with 1-year mortality were age, body mass index, presence of active cancer, PESI score, absolute CrCl value by Cockcroft-Gault and eGFR by CKD-EPI, CrCl < 60 mL/min by Cockcroft-Gault and eGFR < 60 mL/min/1.73 m² by MDRD and CKD-EPI, D-dimer value, and HDL level. None of the assessed hemodynamic values, comorbidities apart from cancer, and transient risk factors were associated with mortality at both 90 days and 1 year.

Variables significantly associated with mortality \((p < 0.05)\) in the univariate analyses were included in multivariate Cox regression model (Table 3). All variables were tested for collinearity using variance inflation factor in

### Table 3. Cox regression analysis of factors associated with mortality

| Variable | 90-day mortality | 1-year mortality |
|----------|------------------|------------------|
|          | HR (95% CI)      | \(p\) value      | HR (95% CI)      | \(p\) value      |
| **Including CrCl by Cockcroft-Gault** | | | | |
| Age (years) | 1.041 (0.957–1.133) | 0.344 | 1.026 (0.959–1.098) | 0.457 |
| BMI (kg/m²) | 1.053 (0.914–1.213) | 0.475 | 0.980 (0.861–1.116) | 0.765 |
| Active cancer (yes) | 85.584 (9.375–781.281) | <0.001* | 45.807 (7.772–270.000) | <0.001* |
| CrCl (Cockcroft-Gault, mL/min) | 0.948 (0.919–0.979) | 0.001* | 0.967 (0.943–0.991) | 0.008* |
| D-dimer (mg/L) | 1.052 (1.014–1.091) | 0.007* | 1.030 (0.998–1.063) | 0.069 |
| HDL (mmol/L) | 0.188 (0.021–1.659) | 0.132 | 0.384 (0.069–2.148) | 0.276 |
| PESI | 0.942 (0.892–0.994) | 0.029* | 0.965 (0.924–1.008) | 0.108 |

| **Including eGFR by MDRD** | | | | |
| Age (years) | 1.097 (1.002–1.201) | 0.046* | 1.056 (0.989–1.128) | 0.104 |
| BMI (kg/m²) | 0.938 (0.824–1.069) | 0.338 | 0.903 (0.801–1.019) | 0.099 |
| Active cancer (yes) | 84.950 (7.838–920.761) | <0.001* | 30.101 (5.160–175.589) | <0.001* |
| eGFR (MDRD, mL/min/m²) | 0.952 (0.920–0.985) | 0.005* | 0.981 (0.958–1.005) | 0.120 |
| D-dimer (mg/L) | 1.044 (1.009–1.081) | 0.014* | 1.023 (0.992–1.055) | 0.145 |
| HDL (mmol/L) | 0.205 (0.023–1.829) | 0.156 | 0.360 (0.063–2.069) | 0.252 |
| PESI | 0.940 (0.887–0.995) | 0.034* | 0.971 (0.929–1.014) | 0.184 |

| **Including eGFR by CKD-EPI** | | | | |
| Age (years) | 1.088 (0.994–1.192) | 0.068 | 1.052 (0.984–1.125) | 0.139 |
| BMI (kg/m²) | 0.943 (0.827–1.075) | 0.380 | 0.909 (0.805–1.025) | 0.119 |
| Active cancer (yes) | 92.361 (8.111–1,051.775) | <0.001* | 38.757 (6.158–243.948) | <0.001* |
| eGFR (CKD-EPI, mL/min/m²) | 0.948 (0.915–0.983) | 0.003* | 0.971 (0.945–0.998) | 0.038* |
| D-dimer (mg/L) | 1.046 (1.010–1.084) | 0.012* | 1.025 (0.994–1.057) | 0.113 |
| HDL (mmol/L) | 0.213 (0.023–1.937) | 0.170 | 0.399 (0.069–2.297) | 0.304 |
| PESI | 0.937 (0.884–0.994) | 0.031* | 0.965 (0.923–1.010) | 0.128 |

BMI, body mass index; HR, hazard ratio; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.* \(p < 0.05\).
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Using the Cox regression model, we found active cancer, CrCl by Cockcroft-Gault, D-dimer value, and PESI value to be independent predictors of mortality within 90 days. Active cancer and CrCl were also found to be significant predictors in 1-year analysis. Using CrCl as a categorical variable (<60 mL/min) in the Cox regression model, hazard ratio (HR) was 21.766 (95% CI 2.961–159.989, p = 0.002) for 90-day mortality, and HR 8.193 (95% CI 1.928–34.816, p = 0.004) for 1-year mortality.

Although the MDRD and CKD-EPI equations demonstrated lower discriminatory power in ROC curves in comparison with Cockcroft-Gault formula, Cox regression analysis was also separately performed with eGFR calculated using MDRD and CKD-EPI equations, respectively. eGFR by MDRD as a continuous variable remained significant at 90 days but failed to demonstrate significance at 1 year. eGFR by CKD-EPI was statistically significant both at 90 days and 1 year.

Discussion

The results of our study demonstrate decreased renal function, determined by estimated CrCl and eGFR, as an independent statistically significant prognostic factor for increased mortality after acute PE within 90 days and 1 year. Not surprisingly, active cancer was the major predictor of death after acute PE during the follow-up period, which is consistent with earlier studies [17, 18]; however, CrCl and eGFR retained significance when cancer was considered in multivariate analysis. Patients with CrCl <60 mL/min had up to 21-fold and 8-fold elevated risk of death during the 90-day and 1-year follow-up period, respectively. Importantly, numerous previous studies have shown association of decreased eGFR with the occurrence or recurrence of VTE [9, 19]. Also, previous studies have demonstrated that advanced CKD may worsen outcomes of patients presenting with acute PE, and in combination with other comorbidities may expose these patients to increased risk of mortality [10].

Fig. 1. ROCs for eGFR/CrCl. a 90-day follow-up. b 1-year follow-up. AUC, area under the curve; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
real et al. [11] show that the ORs for fatal PE in patients with CrCl between 30 and 60 mL/min and in those with CrCl < 30 mL/min are 2.7 and 7.2, respectively, compared to subjects in whom CrCl was > 60 mL/min. Kidney dysfunction has been previously observed in patients with acute PE and was found to be associated with worse short-term outcomes [12–14]. GFR was lower in nonsurvivors than in survivors (35 vs. 63 mL/min, \( p < 0.0001 \)) in a prospective cohort study performed in Poland with AUC values similar to our study [13]. These studies, however, have only assessed short-term outcomes of acute PE.

Regarding long-term data, lower eGFR has been demonstrated as an independent predictor of 2-year mortality (OR 0.973, \( p < 0.001 \)) with mortality rate of 20% in patients with moderate renal dysfunction associated with right ventricular dysfunction [20]. The HRs for 90-day and 1-year mortality in our study are comparable to these results. A population-based cohort study in Canada also demonstrated that the adjusted HR for death increased with higher albumin-creatinine ratio and lower eGFR category [21]. In several studies of PE outcomes, eGFR has been assessed using a single creatinine measurement [13, 19–21]; however, patients with acute PE may experience a transient decline of renal function, which improves during treatment. We attempted to group patients according to either transient or maintained nature of the decline of their renal function. Patients with maintained, that is, chronic dysfunction had statistically significantly higher mortality rates at both 90 days and 1 year than patients with normal renal function, whereas transient dysfunction did not significantly demonstrate such an association.

Median D-dimer value was an independently significant prognostic factor in 90-day follow-up in Cox regression; however, it failed to retain significance in 1-year analysis. Several studies have shown an association between elevated D-dimer and increased mortality in 30 days and 3 months after PE. Similarly, it has been associated with higher mortality in cancer patients [22]. PESI was determined to be an independent prognostic factor in the 90-day follow-up period but not at 1-year follow-up. Although PESI was designed as a tool for predicting the 30-day mortality rate, it has been shown to perform accurately also in 3, 6, and 12 months [23]. Unlike what has been reported by numerous authors [20, 24–26], no other routine laboratory tests, including abnormal troponin-I and BNP, or other comorbidities were independent predictors of death in our study. These inconsistencies may be caused by technical limitations of our study due to its observational, noninterventional nature. For instance, BNP levels were tested only in about one-half of patients at nonstandardized points in time. Troponin-I was registered only as normal or abnormal with specific values available only for abnormal values; hence, the abilities of statistical analysis were limited.

**Limitations**

A limitation of our study is the relatively low patient sample size. Due to the modest sample size and lack of uniformly precise documentation of the etiology of death, the causes were not further separated, and only all-cause mortality was assessed. Another potential source of bias was the fact that only patients with PE objectively confirmed by CTPA were included in this study; we left out a considerable number of patients with clinically high suspicion PE whose renal function precluded the use of contrast medium to objectively confirm the diagnosis. Ventilation/perfusion scintigraphy is not performed routinely in our hospital. Many patients with impaired renal function upon admission did not have any previous records of CKD even if their creatinine levels remained elevated during their hospital stay. Six patients (35%) who were included in the transient renal dysfunction category did not have repeated measurements; however, none of

| Variable               | 90-day follow-up   | 1-year follow-up   |
|------------------------|--------------------|--------------------|
|                        | AUC (95% CI)       | p value            | AUC (95% CI)       | p value            |
| CrCl by Cockcroft-Gault| 0.763 (0.634–0.891)| <0.001             | 0.718 (0.601–0.835)| 0.001              |
| eGFR by MDRD           | 0.686 (0.541–0.830)| 0.010              | 0.609 (0.472–0.746)| 0.090              |
| eGFR by CKD-EPI        | 0.697 (0.554–0.839)| 0.006              | 0.630 (0.497–0.763)| 0.043              |

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; AUC, area under the curve; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
Glomerular Filtration Rate in Pulmonary Embolism

In our patient cohort, decreased CrCl or eGFR was shown to be an independent prognostic factor for increased all-cause mortality in 90 days and 1 year after acute PE. Maintained reduction of renal function was significantly associated with higher mortality. D-dimer had prognostic value only in 90-day follow-up period. There was no significant value of comorbidities apart from cancer to predict long-term mortality after PE. We should be aware of the fact that not only are reduced CrCl and eGFR associated with higher risk for PE but CrCl and eGFR also predict short- and long-term mortality after the episode of PE. Future studies are required for the development of strategies to prevent after-VTE events in case of decreased CrCl and eGFR.

Disclosure Statement

The authors state that they have no conflicts of interest.
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