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Original Article

Prognostic Value of Renal Dysfunction Indicators in Normotensive Patients With Acute Pulmonary Embolism

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Bülent Altınsoy, MD[1], İbrahim İlker Öz, MD[2], Tacettin Örnek, MD[1], Fatma Erboy, MD[1], Hakan Tanrıverdi, MD[1], Fırat Uygur, MD[1], Nejat Altintas, MD[3], Figen Atalay, MD[1], and Müge Meltem Tor, MD[1]

Abstract

Introduction: Glomerular filtration rate (GFR) and blood urea nitrogen (BUN) are important prognostic indicators for cardiovascular disease. However, data on the relationship between renal dysfunction (RD) and prognosis in patients with acute pulmonary embolism (APE) are limited. The estimated-GFR (eGFR), based on the Modification of Diet in Renal Disease (MDRD) equation, has been suggested as a possible prognostic marker in patients with APE; however, at present, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is thought to be more accurate than the MDRD equation for the estimation of RD. **Objective:** We investigated whether $eGFR_{CKD\text{-}EPI}$ or BUN could predict adverse outcomes (AOs) better than $eGFR_{MDRD}$ in normotensive patients with APE. **Methods:** Ninety-nine normotensive patients with APE (aged 22-96, 56% male) were enrolled in the study retrospectively. Adverse outcomes were defined as the occurrence of any of the following: death, cardiopulmonary resuscitation, use of vasopressors, thrombolysis, or mechanical ventilation. **Results:** In univariate analyses, age, gender (male), heart rate (>110 bpm), serum creatinine, BUN, cardiac troponin (cTn) positivity, right ventricle–left ventricle ratio, $eGFR_{MDRD}$, and $eGFR_{CKD\text{-}EPI}$ were found to be significantly different between those with and without AOs. Comparing area under the curves for AO, we found statistically significant differences between $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ ($P = .01$) but not between BUN and $eGFR_{CKD\text{-}EPI}$ or BUN and $eGFR_{MDRD}$. Furthermore, 30-day mortality was 36% versus 11% in cTn-positive patients with an $eGFR_{CKD\text{-}EPI} < \text{and} \geq 60$ mL/min, respectively. **Conclusion:** There is a close relationship between RD and APE prognosis. We conclude $eGFR_{CKD\text{-}EPI}$ is a potential prognostic marker for risk stratification in normotensive patients with APE.

Keywords
pulmonary embolism, renal failure, uremia

Introduction

In acute pulmonary embolism (APE), hemodynamic instability occurring due to an abrupt increase in pulmonary vascular resistance (PVR) is closely associated with adverse events. Increased PVR results in backward right heart dysfunction, increased central venous pressure (CVP), decreased pulmonary blood flow, and hypotension. Both pulmonary and systemic hemodynamics are maintained at normal levels by increased neurohumoral activation (NHA).[1]

Glomerular filtration rate (GFR) and blood urea nitrogen (BUN) are routinely used as indicators of renal function. Glomerular filtration rate is not only closely associated with preexisting renal pathology but also with hemodynamic alterations. Several formulas have been developed to estimate GFR because reference methods regarding its measurement are expensive, time consuming, and not readily available in many institutions. The most popular method for GFR estimation is the simplified Modification of Diet in Renal Disease (MDRD) equation, which takes into account serum creatinine (sCr) levels, age, race, and gender and is reported in mL/min/1.73 m^2. However, this formula seems to systematically underestimate GFR in patients with normal renal function. Therefore, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been developed, which is reported to be more accurate than the MDRD formula.[2] Blood urea nitrogen is a less specific measure of renal dysfunction (RD) compared to GFR. Blood urea nitrogen concentration is also

[1] Department of Pulmonary Medicine, School of Medicine, Bulent Ecevit University, Esenköy, Kozlu, Zonguldak, Turkey
[2] Department of Radiology, School of Medicine, Bulent Ecevit University, Esenköy, Kozlu, Zonguldak, Turkey
[3] Department of Pulmonary Medicine, School of Medicine, Namık Kemal University, Tekirdağ, Turkey

Corresponding Author:
Bülent Altınsoy, Bülent Ecevit Universitesi Tıp Fakültesi, Göğüs Hastalıkları AD. Esenköy, Kozlu, Zonguldak 67600, Türkiye.
Email: altinsoyb@ymail.com

Table 1. Equations Utilized in Study.[a]

1. $eGFR_{CKD\text{-}EPI}$	$GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) $\times$ 1.159 (if black)
2. $eGFR_{MDRD}$	$GFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times 1.212$ (if black) $\times$ 0.742 (if female)

Abbreviations: min, the minimum of Scr/κ or 1; max, the maximum of Scr/κ or 1; Scr, serum creatinine (mg/dL), GFR, glomerular filtration rate, BUN, blood urea nitrogen, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.
[a]$\kappa = .7$, $\alpha = -.329$ for females, $\kappa = .9$, $\alpha = -.411$ for males.

affected by hemodynamics, and in particular neurohumoral mediators, and recent evidence suggests that it is a better prognostic marker for heart failure (HF) than is GFR.[3,4]

Renal dysfunction is an important prognostic factor for cardiovascular disease (CVD) and is associated with increased mortality and morbidity,[5] but data on the relationship between RD and APE prognosis are limited to a few studies. The use of GFR to improve APE risk stratification has been suggested; however, previous studies have mostly used the MDRD equation to calculate the estimated GFR (eGFR).[6-8] In this study, we assessed whether $eGFR_{CKD\text{-}EPI}$ or BUN is a better prognostic factor for APE compared to $eGFR_{MDRD}$.

Materials and Methods

Patients and Study Design

This cross-sectional, retrospective observational study was conducted at the Department of Pulmonary Medicine at Bulent Ecevit University Hospital, Zonguldak, Turkey. The study was approved by the Ethics Review Board of Bulent Ecevit University. Patients with APE were identified from January 1, 2013, to December 31, 2013, using an electronic patient database and patient charts. One hundred and nine (n = 109) patients with symptomatic APE were diagnosed and treated during this period (consecutively). Of the 109 patients, 10 were excluded from the study due to high-risk APE (systolic blood pressure < 90 mm Hg on admission, n = 3) and uncertain diagnosis (intermediate probability ventilation/perfusion [V/Q] scan, n = 7). Ultimately, the study population consisted of 99 patients. The APE diagnosis was based on computed tomography pulmonary angiography (CTPA; n = 79), high probability V/Q scan (n = 18), and compression sonography of the leg veins with high clinical probability (n = 2). Chronic obstructive pulmonary disease, asthma, interstitial lung diseases, and pneumoconiosis were regarded as chronic lung diseases (CLDs). Heart failure was determined based on less than 50% ejection fraction of the left ventricle and/or clinically overt HF. Stroke (ischemic or hemorrhagic) or paresis was regarded as cerebrovascular accident. Cardiovascular disease was defined as the presence of at least one of the following conditions: ischemic heart disease, HF, stroke, or chronic kidney disease (CKD). Adverse clinical outcome was defined as the occurrence of any of the following: death, cardiopulmonary resuscitation, use of vasopressors, thrombolysis, or mechanical ventilation. Three senior physicians determined 30-day mortality and adverse outcome after carefully reviewing all available data. PE-related mortality was defined as death after cardiopulmonary resuscitation, use of vasopressors, thrombolysis, or need for mechanical ventilation.

Laboratory Analyses

On admission, venous blood samples were collected for creatinine, BUN, and troponin concentrations. All measurements were performed before the diagnostic procedures. Serum creatinine levels were analyzed using the Jaffe method and an Advia 2400 analyzer (Siemens Diagnostics, Tarrytown, New York). The BUN levels were measured using a biuret reagent and an Advia 2400 analyzer.

Troponin I and T were measured at different times (before and after June 2013, respectively). Therefore, statistical analysis was based on troponin positivity instead of continuous values. Troponin T levels were measured by electrochemiluminescence using the Elecsys e411 analyzer (Roche, Mannheim, Germany). Troponin I levels were measured by chemiluminescence using the Advia Centaur CP (Siemens, Munich, Germany).

Estimation of GFR

The equations used for GFR estimation are summarized in Table 1. The National Kidney Disease Education Program recommends reporting categorical (simply as $\geq$60 mL/min/1.73 m^2) instead of exact numbers for eGFR values $\geq$ 60 mL/min/1.73 m^2, based on known inaccuracies for GFR values > 60 mL/min/1.73 m^2.[9] Therefore, 60 mL/min/1.73 m^2 was used as the cutoff for normal eGFR in the statistical analysis.

Computed Tomography Pulmonary Angiography

A multidetector CT system (Activision 16-row CT scanner; Toshiba Medical Systems, Otawara, Japan) was used for CT imaging. A total of 100 mL nonionic contrast agent (Ultravist 370; Bayer Schering Pharma, Berlin, Germany) were given at a rate of 3.0 mL/s via a peripheral venous line. Routine CTPA protocols were used for all patients, and the parameters were 120 kV, 144 effective mAs, a pitch factor of 0.938, a helical factor of 15.0, a rotation time of 0.75 s, and a reconstruction interval of 1 mm. Automatic bolus tracking was performed in the pulmonary trunk with a trigger of 120 Hounsfield units.

For each patient, CT imaging analysis was performed by the radiologist (I.O.) using a multimodality workstation (Infinitt PACS version 3.0.9.1; Infinitt Co, Ltd, Seoul, Korea). A 4-chamber heart (4-CH) view was constructed as described previously.[10] The maximum diameter of the right ventricle (RV)

and left ventricle (LV) was measured on a reconstructed 4-CH view between the inner aspect of the interventricular septum and the ventricular endocardium, perpendicular to the long axis of the heart. In 2 patients, the pulmonary arteries were not visualized adequately, but the RV–LV ratio and superior vena cava (SVC) diameter could be measured. In those patients, diagnosis was confirmed by V/Q scintigraphy.

The pulmonary vascular obstruction index (PAOI) was calculated as described previously by Qanadli et al.[11] With the Qanadli index, each lung has 10 segmental artery branches (3 to the upper lobes, 2 to both the middle and lingual lobes, and 5 to the lower lobes). The number of obstructed segmental arteries is corrected by a factor of 1 for partial obstruction and by a factor of 2 for complete obstruction. The maximal obstruction index is 40 per patient, which is equivalent to 100% obstruction.

Statistical Analysis

Descriptive statistics of the categorical variables are given as numbers or percentages; continuous variables are given as means (standard deviations) or medians (min-max). A chi-square test was used to evaluate categorical variables. The Student *t* test or Mann-Whitney *U* test was used to compare the means/medians of variables where appropriate. Receiver–operating characteristic (ROC) curves were used to evaluate the predictive power of each eGFR calculation method on adverse clinical events. Statistical comparisons of ROC curves are based on the methods of DeLong et al.[12] Predictors of adverse clinical events among patients with APE were identified using univariate and multivariate logistic regression analyses. Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS, IBM Inc, Chicago, Illinois) and MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Ostend, Belgium). *P* values were 2-sided, and values less than .05 were considered statistically significant. The post hoc power of the study was found to be 0.86 with an effect size of (n1 = 22, p1 = 0.72; n2 = 77, p2 = 0.36) and α 0.05 by Power and Precision Trial 4.1.0.

Results

Baseline Characteristics and Clinical Course

The study population consisted of 44 females and 55 males with a median age of 68 (range: 22-96) years. Overall, 22 (22%) patients had an adverse outcome. In patients with intermediate-risk APE (n = 83), the mortality rate was 18%.[1] No deaths were observed in patients with low-risk APE (n = 16). The all-cause 30-day mortality rate was 15% (n = 14), and median survival time was 17 (range 2-30) days. APE-related mortality was 10% (n = 10); the remaining 4 patients died due to pneumonia (n = 1), COPD (n = 1), brain and hepatic abscesses (n = 1), and septic shock (n = 1). All patients were given standard anticoagulant therapy with intravenous unfractionated heparin (UFH) or a subcutaneous low-molecular-weight heparin (body mass adjusted). Massive hemorrhage (gross hematuria) caused by UFH was observed in 1 patient who died because of APE-related respiratory failure. No hemorrhage-associated deaths were observed. Eight patients received thrombolytic treatment. Hemodynamic deterioration in patients who presented as hemodynamically stable was considered an indication for thrombolytic treatment. The mortality rate was 38% (n = 3) in the group receiving thrombolytic treatment. The values of $eGFR_{MDRD}$ (<60 mL/min) and $eGFR_{CKD\text{-}EPI}$ (<60 mL/min) were noted in 42% and 49% of patients with intermediate risk and in 19% and 19% of patients with low-risk APE, respectively. Significant differences between patients with $eGFR_{CKD\text{-}EPI}$ < and ≥ 60 mL/min/1.73 m^2 with respect to APE-related death (21% vs 4%, $P = .008$) and thrombolytic therapy (17% vs 2%, $P = .008$) were observed, but no differences were found with respect to all-cause 30-day mortality (21% vs 9%, $P = .107$). No significant differences were observed between patients with $eGFR_{MDRD}$ < and > 60 mL/min/1.73 m^2 with respect to APE-related death (16% vs 8%, $P = .242$) and all-cause 30-day mortality (19% vs 12%, $P = .335$), but thrombolytic therapy was significantly different between the groups (19% vs 2%, $P = .002$). Clinical characteristics are presented in Table 2.

Renal Function Markers and Adverse Outcome

On admission, 3 patients were classified as having severe RD (<30 mL/min), 1 using $eGFR_{MDRD}$ and 2 using $eGFR_{CKD\text{-}EPI}$. $eGFR_{CKD\text{-}EPI}$ < 60 mL/min was noted in 44 (44%) patients, while $eGFR_{MDRD}$ < 60 mL/min was noted in 38 (38%) patients. BUN > 20 mg/dL was noted in 47 (46%) patients. Areas under the adverse outcome ROC curves were compared for BUN, $eGFR_{MDRD}$, and $eGFR_{CKD\text{-}EPI}$ (Figure 1). Statistically significant differences was present between $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ ($P = .008$, 95% confidence interval [CI]: 0.010-0.067) in prediction of adverse outcome but not between BUN and $eGFR_{CKD\text{-}EPI}$ ($P = .306$, 95% CI: −0.055-0.174) or between BUN and $eGFR_{MDRD}$ ($P = .116$, 95% CI: −0.024-0.220).

Multivariate Analysis

Variables significantly associated with adverse outcome in the univariate analyses were included in a multivariate logistic regression model (Table 3). Using multivariate analysis, we found that $eGFR_{CKD\text{-}EPI}$ (odds ratio [OR] 7.18, 95% CI 1.12-45.92, $P = .037$), cTn positivity (OR 9.84, 95% CI 1.24-77.93, $P = .03$), and heart rate (>110 beat/min; OR 8.47, 95% CI 1.44-49.77, $P = .018$) were independent predictors of adverse outcome. In the next analysis, $eGFR_{MDRD}$ was used instead of $eGFR_{CKD\text{-}EPI}$, and $eGFR_{MDRD}$ (< 60 mL/min/1.73 m^2) (OR 6.42, 95% CI 1.08-38.26, $P = .041$), cTn positivity (OR 9.24, 95% CI 1.18-72.18, $P = .034$), and heart rate (>110 beats/min; OR 7.20, 95% CI: 1.29-40.21, $P = .025$) remained significant.

Table 2. Baseline Characteristics.

	All, n = 99	Nonadverse, n = 77	Adverse, n = 22	*P* Value
Age, years	68 (22-96)	66 (22-96)	78 (47-85)	.001[a]
Gender (male), n (%)	55 (56)	39 (51)	16 (73)	.066
Heart rate (>110), n (%)	24 (25)	13 (17)	11 (50)	.002[a]
SBP, mm Hg	120 (100-240)	120 (100-240)	125 (100-160)	.895
Creatinine, mg/dL	1.1 (0.5-2.4)	1.1 (0.5-2.4)	1.26 (0.6-2.2)	.023[a]
BUN, mg/dL	20 (8-75)	18 (8-72)	31 (14-75)	.001[a]
Chronic lung disease, n (%)	42 (42)	31 (40)	11 (50)	.415
Heart failure, n (%)	26 (26)	19 (25)	7 (32)	.502
Reported renal disease, n (%)	11 (11)	7 (9)	4 (18)	.260
Hypertension, n (%)	57 (58)	42 (55)	15 (68)	.254
Diabetes mellitus, n (%)	33 (33)	23 (30)	10 (46)	.171
Cancer, n (%)	14 (14)	11 (14)	3 (14)	1
CVD, n (%)	59 (60)	44 (58)	15 (68)	.352
CVA, n (%)	10 (10)	4 (5)	6 (27)	.008[a]
eGFR continuous, mL/min/1.73 m^2				
MDRD	64 (28-143)	66 (28-126)	55 (31-143)	.040[a]
CKD-EPI	64 (26-118)	66 (26-118)	49 (29-104)	.009[a]
eGFR categorical (< 60 mL/min/1.73 m^2)				
MDRD, n (%)	38 (38)	25 (33)	13 (59)	.024[a]
CKD-EPI, n (%)	44 (44)	28 (36)	16 (72)	.002[a]
cTn positivity[b], n (%)	42 (48)	28 (41)	14 (74)	.011[a]
Radiological[c]				
RV–LV ratio	1.14 (0.7-2.3)	1.12 (0.7-2.13)	1.23 (0.82-2.31)	.046[a]
PAOI (%)	33 (8-83)	33 (8-78)	35 (8-83)	.495
SVC diameter, mm	2.43 (1.57-3.34)	2.38 (1.59-3.12)	2.58 (1.57-3.34)	.285

Abbreviations: SBP, systolic blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CVA, cerebrovascular accident; MDRD, Modification of Diet in Renal Disease; cTn, cardiac troponin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RV/LV ratio, right ventricular to left ventricular diameter ratio; PAOI, pulmonary vascular obstruction index; SVC, superior vena cava.
[a]$P < .05$.
[b]cTn (n = 88).
[c]RV–LV ratio and PAOI (n = 81), SVC diameter (n = 79).

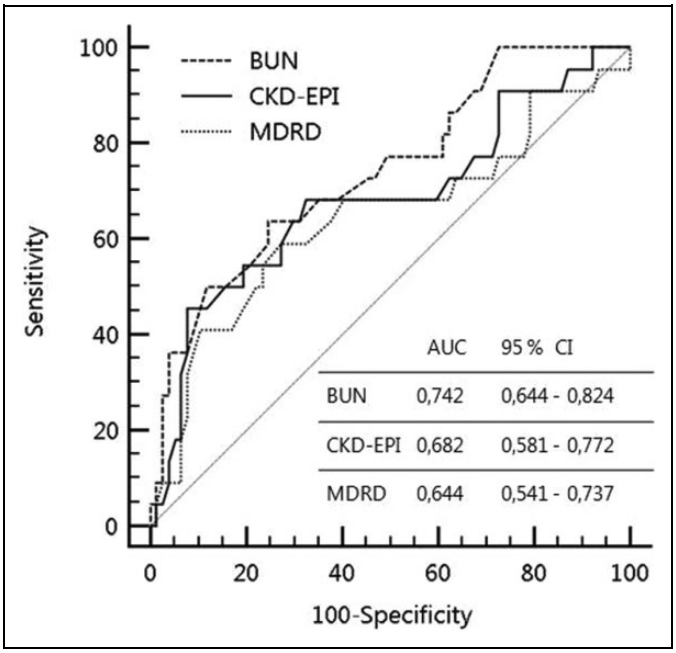

Figure 1. Receiver–operating characteristic curves of indicators of renal dysfunction.

Relationship Among CT Findings, Systolic Blood Pressure, and Renal Function Markers

$eGFR_{CKD\text{-}EPI}$ correlated significantly with RV/LV ratio, PAOI, and SVC diameter ($r = -.31$, $P < .01$; $r = -.23$, $P < .05$; and $r = -.25$, $P < .05$, respectively). $eGFR_{MDRD}$ was also correlated significantly with the above-mentioned variables ($r = -.32$, $P < .01$; $r = -.24$, $P < .05$; and $r = -.31$, $P < .01$, respectively). Blood urea nitrogen correlated significantly with SVC diameter only ($r = .23$, $P < .05$). $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$, nor BUN was significantly correlated with SBP ($P = .72$, $P = .91$, and $P = .12$, respectively). In addition, SBP and RV–LV ratio were significantly correlated ($r = -.22$, $P < .05$).

Stratified Evaluation and Combined Approach

When 45 mL/min was used as the cutoff value for $eGFR_{CKD\text{-}EPI}$, significant differences between patients above and below the cutoff were found for APE-related death (33% vs 6%, $P = .001$), all-cause mortality (40% vs 10%, $P = .002$), and thrombolytic therapy (27% vs 5%, $P = .004$). Similarly, BUN > 32 mg/dL was closely associated with APE-related death (30% vs 5%, $P = .001$), all-cause mortality (40% vs 8%,

Table 3. Univariate and Multivariate Analyses of Factors Associated With Adverse Outcome.

	Univariate Analysis		Multivariate Analysis (Enter Method)	
Factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years	1.07 (1.02-1.11)	.004[a]	1.06 (0.98-1.14)	.136
Gender (male), n (%)	2.60 (0.92-7.35)	.072	4.62 (0.84-25.34)	.078
Heart rate (>110 beats/min)	4.85 (1.74-13.54)	.003[a]	8.47 (1.44-49.77)	.018[a]
SBP, mm Hg	0.99 (0.97-1.02)	.600	Not selected	
CLD (yes)	1.48 (0.57-3.84)	.416	Not selected	
Heart failure (yes)	1.43 (0.51-4.01)	.503	Not selected	
Kidney (yes)	2.19 (0.58-8.31)	.249	Not selected	
CVD (yes)	1.61 (0.60-4.39)	.354	Not selected	
Hypertension (yes)	1.79 (0.66-4.87)	.257	Not selected	
Diabetes mellitus (yes)	1.96 (0.74-5.17)	.175	Not selected	
Cancer (yes)	0.95 (0.24-3.75)	.939	Not selected	
CVA (yes)	6.75 (1.71-26.73)	.007[a]	3.73 (0.37-37.24)	.262
BUN, mg/dL	1.07 (1.03-1.11)	.001[a]	1.02 (0.96-1.07)	.613
RV–LV ratio	7.21 (1.61-32.38)	.010	1.74 (0.18-16.58)	.633
cTn positivity (yes)	4.10 (1.33-12.67)	.014[a]	9.84 (1.24-77.93)	.030[a]
$eGFR_{CKD\text{-}EPI}$ (yes)[b]	4.67 (1.64-13.29)	.004[a]	7.18 (1.12-45.92)	.037[a]
PAOI	1.02 (0.99-1.04)	.274	Not selected	
$eGFR_{MDRD}$ (yes)[b]	3.00 (1.13-7.96)	.027[a]	Not selected	

Abbreviations: SBP, systolic blood pressure; CVD, cardiovascular disease; CVA, cerebrovascular accident; BUN, blood urea nitrogen; RV/LV ratio, right ventricular to left ventricular diameter ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; cTn, cardiac troponin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PAOI, pulmonary vascular obstruction index.
[a]$P < .05$.
[b]eGFR categorical (<60 mL/min/1.73 m^2).

Table 4. Comparison of cTn Positivity Alone Versus cTn Positivity in Combination With $eGFR_{CKD\text{-}EPI}$ for 30-Day Mortality.

cTn	$eGFR_{CKD\text{-}EPI}$	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Positive	-	73	56	19	94
Positive	<45 mL/min	27	96	50	90
Positive	<60 mL/min	46	88	36	92

Abbreviations: cTn, cardiac troponin (n = 88), death (n = 11); PPV, positive predictive value; NPV, negative predictive value; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

$P = .000$), and the need for thrombolytic therapy (30% vs 5%, $P = .001$).

Also, we compared combined cTn-positivity and $eGFR_{CKD\text{-}EPI}$ (<45 mL/min and <60 mL/min, respectively) and cTn-positivity alone for 30-day mortality in patients with APE. Combined approach improved positive predictive value (PPV) without significant change in negative predictive value (NPV) for 30-day mortality (Table 3). In addition, cTn-positive patients with $eGFR_{CKD\text{-}EPI}$ (<45 mL/min and <60 mL/min, respectively) showed 50%, 36% 30-day mortality, although cTn-positive patients with $eGFR_{CKD\text{-}EPI}$ (≥45 mL/min and ≥60 mL/min, respectively)) 14%, 11% mortality (Table 4).

Discussion

This cross-sectional study demonstrated that both eGFR and BUN are closely associated with APE prognosis in normotensive patients. The same median eGFR values (64 mL/min) were found using both equations. Prevalence of intermediate RD (<60 mL/min/1.73 m^2) was found to be 38% and 44% with $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI}$, respectively. These findings are consistent with previous reports.[6-8,13] Both estimates of eGFR, together with troponin positivity and heart rate (>110 beats/min), were independent predictors for adverse outcome. However, ROC curve analysis showed that $eGFR_{CKD\text{-}EPI}$ was a better predictor of adverse outcome than was $eGFR_{MDRD}$. Blood urea nitrogen was a significant predictor for adverse outcome in the univariate analysis but not in the multivariate analysis.

Renal Dysfunction

Renal arterial blood flow (RABF) is considered to be the most important determinant of GFR. However, increasing evidence suggests that increased CVP is what mainly determines renal function.[14-16] In addition, a number of neurohumoral mediators take part in the regulation of GFR.[17] Decreased GFR in APE can be explained by several mechanisms. First, impaired RABF secondary to decreased cardiac output (CO) can lead to a decrease in GFR. Decreased CO is due to a decrease in preload that results from a number of mechanisms, including increased pulmonary vascular resistance, septal shift, interventricular asynchrony, and/or pericardium-mediated right ventricle–left ventricle interaction.[18] Reduction in RBAF is often considered to be synonymous with hypotension; however, impaired GFR in normotensive patients with HF is a well-known condition

and is explained by the phenomenon of arterial underfilling.[18,19] Similarly, normotensive patients having APE with a low cardiac index have also been identified.[20] The presence of normotension (normal arterial blood pressure), despite decreased CO appears to result from NHA including sympathetic overactivity. As with HF, APE has been shown to be associated with elevated neuroendocrine markers.[21-23] In addition to estimating renal function, BUN is accepted as a biomarker of neurohormonal activation and is reported to be a better predictor of survival than is eGFR in patients with HF.[24] In the present study, increased BUN and heart rate in patients with adverse outcomes indicates an existing NHA. However, BUN was not a better predictor of adverse outcome compared with eGFR, in the univariate or multivariate analyses. Second, accumulating evidence suggests that poor forward flow alone does not explain the decrease in GFR. Renal venous congestion seems to be secondary to increased CVP and could have a significant impact on GFR. This view is supported by previous studies performed in patients with HF.[14-16] Similar observations were also made in studies investigating the relationship between APE and GFR.[6-8] These studies suggest a significant correlation between GFR and various radiological and echocardiographic right ventricular functional parameters, since $eGFR_{MDRD}$ is significantly correlated with the RV–LV ratio, PAOI, and SVC diameter. These findings support the hypothesis that this may be a predominant mechanism.

Estimated Glomerular Filtration Rate Calculations

There are a number of methods used to estimate GFR in daily practice; however, the simplified MDRD equation is the most popular. This method was derived from individuals with renal disease and has been criticized due to its underestimation of GFR in healthy individuals.[2] The $eGFR_{CKD\text{-}EPI}$ equation was developed in a study involving healthy individuals, and it includes the same 4 variables as MDRD years but uses a 2-slope "spline" model.[25] Currently, the CKD-EPI equation is considered to be the most accurate method for estimating GFR.[2] Interestingly, in the present study, the $eGFR_{CKD\text{-}EPI}$ equation classified more patients as having intermediate RD. Similar findings have already been reported in patients with multiple myeloma,[26] but the advanced age of the patients in this study (>70) may be the reason for this discrepancy.[27]

Renal Disease and Mortality

Chronic kidney disease and chronic renal failure are associated with increased APE risk.[28] However, there is conflicting evidence about the relationship between APE mortality and CKD, especially in patients undergoing dialysis. Autopsy studies suggest that APE-related mortality rates in patients with end-stage renal disease (ESRD) are lower than those in the general population.[29,30] A variety of reasons have been suggested to explain these observations, including platelet dysfunction, bleeding tendency, and anticoagulation therapy during dialysis. In a recent study, Fabbian et al found no relationship between APE-related mortality and CKD or ESRD,[31] yet other studies contradict these findings.[32] Several studies have shown an association between low eGFR levels and CKD; however, it is not clear whether the observed low eGFR levels were due to preexisting renal impairment or kidney injury. To clarify these findings, 2 studies by Kost et al were performed. In the first study, neutrophil gelatinase-associated lipocalin (N-GAL), an accepted marker of acute kidney injury, and cystatin C levels were evaluated in patients with APE.[7] Serum N-GAL levels were significantly higher in patients who died from APE; however, cystatin C levels were a significant predictor of all-cause mortality both in univariate and in multivariate analyses. In the second study, eGFR was measured at admission and 72 hours later, and it was found that eGFR levels improved in patients with a good prognosis but remained low in patients with a poor prognosis.[8] As a result, low GFR levels in patients with APE seem to be an outcome of multiple pathophysiological processes including CKD and hemodynamic dysfunction.

According to the current guidelines, risk stratification of APE is based on cardiac biomarkers.[1] Although the NPV of these biomarkers for APE mortality is high, the PPV is quite low.[1,33] In this study, combination of cTn and $eGFR_{CKD\text{-}EPI}$ has been shown to improve the risk stratification based on cTn only by increasing PPV.

Limitations

This study was retrospective, and the patient population was relatively small. Our laboratory switched from measuring troponin I to troponin T during the study; however, previous reports have shown that both troponins have a similar ability to predict the prognoses of patients with APE. In this study, we found a relatively higher adverse event rate (22%), although similar rates have been reported in the literature.[34-37] Our study population was comprised of a relatively more advanced age and high comorbidity group including CLD and diabetes mellitus, which might have contributed to higher rate of adverse outcomes. Variation in creatinine assays may be a source of bias in eGFR measurement. Isotope dilution mass spectrometry is a standard method to measure reference levels of sCr; however, our laboratory does not have this capability. In this study, the prevalence of renal disease was lower relative to that in other studies, which may be result of recall bias. It may also indicate the presence of subclinical kidney disease, since patients with adverse outcomes had a higher incidence of comorbidities (HF, DM, and CVD), although this did not reach significance. However, in daily practice, it is difficult to determine whether low eGFR values in patients with APE are dependent on hemodynamic changes or CKD. Regardless of the reason, decreased eGFR seems to be closely associated with APE prognosis.

Conclusion

There is a close relationship between RD and the prognosis of APE. $eGFR_{CKD\text{-}EPI}$, but not BUN, predicts adverse outcomes

better than does $eGFR_{MDRD}$. $eGFR_{CKD-EPI}$ seems to be a potential marker for risk stratification in normotensive patients with APE.

Authors' Note

In this article, the English language has been checked by at least 2 professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/kVdHvN

Declaration of Conflicting Interests

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