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Original Article

Blood urea nitrogen has additive value beyond estimated glomerular filtration rate for prediction of long-term mortality in patients with acute myocardial infarction

Bernhard Richter[a], Patrick Sulzgruber[a], Lorenz Koller[a], Matthias Steininger[a], Feras El-Hamid[a], David J. Rothgerber[a], Stefan Forster[a], Georg Goliasch[a], Benjamin I. Silbert[b], Elias L. Meyer[c], Christian Hengstenberg[a], Johann Wojta[a], Alexander Niessner[a,*]

[a] Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria
[b] Department of Intensive Care Medicine, Fiona Stanley Hospital, Murdoch, Australia
[c] Section for Medical Statistics, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Austria

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ABSTRACT

Objectives: Blood urea nitrogen (BUN) has been shown to independently predict short- and intermediate-term outcomes in patients with acute myocardial infarction (AMI). We aimed to assess the additive predictive value of BUN beyond estimated glomerular filtration rate (eGFR) in AMI patients with an 8.6-year follow-up.

Methods: This retrospective, observational single-centre study included 1332 consecutive AMI patients (median age 64 years, 58.4% male). BUN, creatinine and eGFR were determined at hospital admission.

Results: During a median follow-up of 8.6 years (interquartile range [IQR] 4.0–11.6), 408 patients (30.6%) experienced the study endpoint of cardiovascular mortality. BUN (median 17.0 mg/dL [IQR 13.5–22.7]) was a significant predictor of cardiovascular mortality in univariate Cox regression (hazard ratio (HR) per 1 standard deviation increase 2.10, 95% confidence interval [CI] 1.94–2.28, $p < .001$). This association remained significant after multivariable adjustment for demographics, clinical variables and eGFR (adjusted HR 1.52 [CI 1.16–2.00, $p = .003$]). The association between BUN and outcome was more pronounced in patients with eGFR > 60 mL/min/1.73m^2 (HR 2.81 [CI 2.20–3.58, $p < .001$]). The discriminatory abilities (Harrell's C-statistic) for BUN, eGFR and creatinine were 0.75, 0.76 and 0.67, respectively. The addition of BUN to eGFR significantly improved the C-statistic (0.78, p for comparison = 0.017), net reclassification (23.7%, $p < .001$) and integrated discrimination (2.9%, $p < .001$).

Conclusions: Circulating BUN on admission is an independent predictor of long-term cardiovascular mortality in AMI patients and adds predictive power beyond eGFR. BUN reflects not only kidney function, but also acute haemodynamic and neurohumoral alterations during AMI, and may help to identify high-risk patients.

1. Introduction

The association between kidney function and outcome in patients with acute myocardial infarction (AMI) is well established [1–6]. Although prior studies predominantly examined creatinine-based estimates of kidney function [1–3], there is also growing evidence linking elevated blood urea nitrogen (BUN) levels to short- and intermediate-term mortality in patients with AMI [4–7]. BUN is an interesting marker in this setting as it not only reflects glomerular filtration rate (GFR), but is also influenced by other factors such as systemic and renal hypoperfusion, low cardiac output and neurohumoral activation, all of which frequently occur in the acute phase of myocardial infarction [4, 7–9]. Acute changes in renal function during AMI may therefore be better reflected by BUN compared to creatinine-based measures, and its superior prognostic value in cardiovascular patients has been reported by several authors [6, 9, 10]. However, the association between BUN and long-term outcomes in AMI patients has not previously been examined. In addition, some of the previous studies excluded patients

Abbreviations: AMI, acute myocardial infarction; BUN, blood urea nitrogen; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IDI, integrated discrimination improvement; IQR, interquartile range; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; STEMI, ST-elevation myocardial infarction

* Corresponding author at: Division of Cardiology, Department of Internal Medicine II, Waehringer Guertel 18-20, 1090 Vienna, Austria.
E-mail address: alexander.niessner@meduniwien.ac.at (A. Niessner).

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with poor kidney function [4], included only patients with ST-elevation myocardial infarction (STEMI) [7] or did not adjust results for important clinical parameters such as left ventricular systolic function [4, 6, 7] or N-terminal pro B-type natriuretic peptide (NT-proBNP) [5–7]. Furthermore, prior studies used GFR-estimating equations that have since been superseded due to their inaccuracy [1, 4, 5].

We aimed to assess the value of BUN for long-term mortality prediction in a comprehensive cohort of AMI patients. We were particularly interested in whether BUN provides additive predictive value beyond estimated GFR (eGFR) and whether the predictive value of BUN is modified by eGFR.

2. Materials and methods

2.1. Study design, setting and population

The present trial is a retrospective, observational single-centre cohort study. The study population consisted of 1332 consecutive patients admitted to the Vienna General Hospital (Austria) for STEMI or Non-STEMI. AMI, STEMI and Non-STEMI were defined according to the third universal definition of myocardial infarction [11]. In short, AMI was defined as evidence of cardiomyocyte necrosis characterized by a rise and/or fall of cardiac biomarkers, preferably cardiac troponin (with at least one value above the 99th percentile upper reference limit) in a clinical setting consistent with acute myocardial ischaemia. STEMI was defined as AMI with presence of new prolonged ($>$ 20 min) ST-segment elevation at the J point in two contiguous leads with age- and sex-dependent cut-points (leads V2–V3: $\geq$0.25 mV in men $<$ 40 years, $\geq$0.2 mV in men $\geq$40 years, and $\geq$ 0.15 mV in women; all other leads: $\geq$0.1 mV), true posterior MI (ST-segment elevation in leads V7–V9 $\geq$ 0.1 mV in men $<$ 40 years and $\geq$ 0.05 mV in men $\geq$40 years and women, usually combined with ST depression in V1–3) or new left bundle branch block. All AMIs not meeting the criteria for STEMI were classified as non-STEMI. There were no exclusion criteria except age $<$ 18 years. The Vienna General Hospital is a large university-affiliated tertiary centre with a high-volume 24-h cardiac catheter laboratory. The study protocol complies with the Declaration of Helsinki and was approved by the ethics committee of the Medical University of Vienna. In accordance with the requirements of the local ethics committee, informed consent was not required due to the retrospective nature of the study.

2.2. Laboratory analysis

Kidney function parameters were determined immediately after hospital admission and before any acute intervention (i.e. percutaneous coronary intervention, thrombolysis or coronary artery bypass surgery) was performed as part of the routine laboratory measurements. Blood samples were processed immediately using the hospital's standard procedures. In short, serum BUN levels were analyzed by the Urease-GLDH-method (coefficient of variation = 2.6%) and serum creatinine levels by the Jaffe method (coefficient of variation = 7.7%). The currently recommended Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. [12] was used to calculate eGFR.

2.3. Outcome measures

The study endpoint of cardiovascular mortality was determined by screening the Austrian register of death (statistics Austria; https://www.statistik.at/web_en/statistics/index.html).

2.4. Statistical analysis

Continuous data are reported as median (interquartile range [IQR]), since they were not normally distributed according to the Kolmogorov-Smirnov-Test and the Shapiro-Wilk-Test. Differences between continuous variables and tertiles of BUN were assessed using the Kruskal-Wallis test. Spearman-Rho correlation coefficient was used to assess correlations between continuous variables. Categorical data are presented as counts and percentages. Differences between categorical data were analyzed using a test for linear association (Mantel-Haenszel-χ^2 test). Univariate and multivariable Cox proportional hazard regression models were used to assess the influence of estimates of kidney function (BUN, eGFR and creatinine) on cardiovascular mortality. We adjusted for demographics, clinical parameters and the respective other kidney function parameters in multivariable models as described in Table 2. Continuous variables were log-transformed before analysis. First-degree interactions between BUN and eGFR, BUN and creatinine and BUN and the type of AMI (STEMI versus Non-STEMI) were tested using interaction terms. Furthermore, we built separate Cox regression models for subgroups of eGFR and subgroups of creatinine as well as for STEMI and Non-STEMI patients. Cumulative survival in BUN tertiles was examined by Kaplan-Meier curves (log-rank test).

The discriminatory abilities of BUN, eGFR and creatinine for prediction of cardiovascular mortality were assessed using Harrell's C-statistic. The incremental prognostic impact of BUN in addition to eGFR (and in addition to creatinine) was further examined using the category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Reclassification was further illustrated by reclassification plots as described by Steyerberg et al. [13]. For these plots predicted probabilities for 5-year mortality were calculated from Cox regression models including one predictor (BUN, eGFR or creatinine) or two predictors (BUN and eGFR; BUN and creatinine). Time-dependent receiver operating characteristic (ROC) curves [14] were used to calculate measures of diagnostic accuracy (likelihood ratios, sensitivity, specificity, positive and negative predictive value, area under the curve). SPSS 24.0 (SPSS Inc., Chicago, Illinois, USA), STATA 12 (Stata Corp, USA) and R (version 3.4.4, the R foundation for statistical computing, Vienna, Austria https://www.r-project.org) were used for statistical analyses. $P \leq .05$ (two-sided) was considered statistically significant.

3. Results

A total of 1332 consecutive patients admitted to the General Hospital of Vienna for AMI were included in the study. Patient characteristics of the entire cohort and stratified according to tertiles of BUN on admission are depicted in Table 1. The study cohort comprised 677 patients with STEMI (50.8%) and 655 patients with Non-STEMI (49.2%). A total of 134 patients (10.1%) presented with cardiogenic shock. With regard to acute revascularization therapy, 987 patients (74.1%) were treated with immediate percutaneous coronary intervention (PCI), 186 patients (14.0%) with thrombolysis and 50 patients (3.8%) with acute coronary artery bypass grafting (CABG), respectively. The study cohort comprised a substantial proportion of patients with abnormal renal function. In detail, 40.7% of patients had normal or high eGFR ($\geq$90 mL/min/1.73 m^2), 22.6% mildly decreased eGFR (60 to 89 mL/min/1.73 m^2), 30.9% moderately decreased eGFR (30 to 59 mL/min/1.73 m^2) and 5.8% severely decreased eGFR or kidney failure ($\leq$29 mL/min/1.73 m^2) at hospital admission.

3.1. BUN and correlations with baseline characteristics

The median BUN level on admission was 17.0 mg/dL [IQR 13.5–22.7]. Table 1 displays correlations between BUN and other variables. In short, elevated BUN showed highly significant associations with older age and cardiovascular risk factors such as hypertension and diabetes mellitus, whilst current smoking and hypercholesterolemia were associated with lower BUN levels. Furthermore, BUN levels were higher in patients with STEMI than Non-STEMI. BUN levels were also higher in patients presenting with cardiogenic shock and in patients with poor left ventricular systolic function. Concordant with these

Table 1
Patient characteristics.

	All	Tertiles of BUN Correlation All			Correlation		
		1	2	3	p	r	q
n	1332	444	444	444			
BUN on admission, mg/dL	17.0 (13.5–22.7)	11.9 (10.3–13.5)	17.0 (15.9–18.5)	27.1 (22.7–33.6)			
Clinical Presentation							
Age, years	64 (43–81)	44 (40–64)	58 (42–80)	81 (72–86)	< 0.001	0.510	< 0.001
Male gender, n (%)	778 (58.4)	271 (61.0)	262 (59.0)	245 (55.2)	0.077		
Body mass index, kg/m2	26.2 (24.0–29.1)	26.4 (24.0–29.3)	26.6 (24.4–29.6)	25.8 (23.7–28.4)	0.002	−0.070	0.013
Current smoker, n (%)	696 (52.3)	319 (71.8)	241 (54.3)	136 (30.6)	< 0.001		
Heart rate on admission, bpm	76 (66–88)	75 (65–85)	77 (67–88)	77 (65–90)	0.300	0.046	0.112
Systolic BP on admission, mmHg	125 (111–140)	125 (113–140)	127 (110–140)	125 (110–145)	0.771	0.003	0.925
Cardiogenic Shock, n (%)	134 (10.1)	28 (6.3)	53 (11.9)	53 (11.9)	0.005		
STEMI, n (%)	677 (50.8)	187 (42.1)	221 (49.8)	269 (60.6)	< 0.001		
Acute revascularization, n (%)	1085 (81.5)	392 (88.3)	375 (84.5)	318 (71.6)	< 0.001		
PCI, n (%)	987 (74.1)	352 (79.3)	346 (77.9)	289 (65.1)	< 0.001		
Thrombolysis, n (%)	186 (14.0)	72 (16.2)	66 (14.9)	48 (10.8)	0.020		
Coronary artery bypass grafting, n (%)	50 (3.8)	16 (3.6)	16 (3.6)	18 (4.1)	0.724		
Comorbidities							
Hypertension, n (%)	895 (67.2)	258 (58.1)	300 (67.6)	337 (75.9)	< 0.001		
Diabetes mellitus, n (%)	279 (20.9)	56 (12.6)	94 (21.2)	129 (29.1)	< 0.001		
Hypercholesterolemia, n (%)	837 (62.8)	296 (66.7)	293 (66.0)	248 (55.9)	0.001		
Previous myocardial infarction, n (%)	255 (19.1)	67 (15.1)	84 (18.9)	104 (23.4)	0.002		
Family history of CVD, n (%)	459 (34.5)	196 (44.1)	155 (34.9)	108 (24.3)	< 0.001		
LVEF < 35%, n (%)	162 (12.2)	29 (6.5)	56 (12.6)	77 (17.3)	< 0.001		
Biomarkers and eGFR							
Peak Troponin T, µg/L	1.9 (0.6–4.7)	1.8 (0.6–4.1)	2.0 (0.7–4.9)	2.1 (0.6–5.0)	0.303	0.045	0.113
Peak creatine kinase, U/L	646 (241–1672)	716 (256–1766)	767 (248–1852)	548 (214–1439)	0.022	−0.050	0.069
NT-proBNP, pg/mL	1112 (296–4011)	479 (169–1734)	904 (224–2746)	3101 (776–7790)	< 0.001	0.418	< 0.001
Creatinine on admission, mg/dL	1.1 (0.9–1.3)	0.95 (0.82–1.08)	1.04 (0.92–1.19)	1.29 (1.07–1.60)	< 0.001	0.495	< 0.001
eGFR, mL/min/1.73 m2	78.3 (48.4–109.6)	105.1 (80.9–126.3)	83.8 (58.3–109.5)	45.8 (34.7–64.0)	< 0.001	−0.567	< 0.001
Medication on admission Aspirin, n (%)	300 (22.5)	66 (14.9)	88 (19.8)	146 (32.9)	< 0.001		
Beta-blocker, n (%)	254 (19.1)	71 (16.0)	82 (18.5)	101 (22.7)	0.010		
Statin, n (%)	190 (14.3)	49 (11.0)	66 (14.9)	75 (16.9)	0.013		
RAAS inhibitor, n (%)	328 (24.6)	68 (15.3)	100 (22.5)	160 (36.0)	< 0.001		
ACE inhibitor, n (%)	250 (18.8)	56 (12.6)	77 (17.3)	117 (26.4)	< 0.001		
ARB, n (%)	85 (6.4)	13 (2.9)	24 (5.4)	48 (10.8)	< 0.001		
Diuretics, n (%)	92 (6.9)	7 (1.6)	18 (4.1)	67 (15.1)	< 0.001		

Categorical data are presented as counts and percentages and are analysed using a test for linear association (Mantel–Haenszel-chi-square-test). Continuous data are presented as median (interquartile range (IQR)) and analysed using the Kruskal-Wallis test. Additionally, the Spearman-Rho correlation coefficient was used to assess associations between BUN and continuous variables (two right columns). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (CKD-EPI equation); LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone-system; STEMI, ST-elevation myocardial infarction.

findings, BUN levels showed a significant association with NT-proBNP levels ($r = 0.418$, $p < .001$). As expected, BUN levels were strongly associated with eGFR ($r = -0.567$, $p < .001$) and creatinine levels ($r = 0.495$, $p < .001$). Of note, patients with elevated BUN were less likely to receive acute revascularization therapies.

3.2. Follow-up and risk prediction

During a median follow-up time of 8.6 years [IQR: 4.0–11.6] equal to 10,826 patient-years of follow-up, 408 patients (30.6%) experienced the primary endpoint of cardiovascular mortality. BUN levels significantly predicted long-term cardiovascular mortality in univariate Cox regression analysis (hazard ratio (HR) per one standard deviation (1-SD) increase 2.10, confidence interval [CI] 1.94–2.28, $p < .001$, Table 2). Fig. 1 shows Kaplan-Meier survival curves of tertiles of BUN. BUN remained a significant predictor of cardiovascular mortality (HR per 1-SD increase 1.52 [CI 1.16–2.00, $p = .003$]) after multivariable adjustment for eGFR and a comprehensive set of covariates as listed in the legend of Table 2. In a second multivariable model in which eGFR was replaced by creatinine, BUN retained its independent predictive value of cardiovascular mortality (HR per 1-SD increase 1.62 [CI 1.23–2.11, $p < .001$]).

Interestingly, the effect of BUN on cardiovascular mortality was significantly modified by eGFR (p for interaction < 0.001). This was also evident in stratified analysis with a more pronounced association between BUN and cardiovascular mortality in the subgroup with eGFR > 60 mL/min/1.73 m^2 (HR per 1-SD increase 2.81 [CI 2.20–3.58, $p < .001$]) than in the subgroup with eGFR < 60 mL/min/1.73 m^2 (HR per 1-SD increase 1.54 [CI 1.37–1.73, $p < .001$]). Similar results were found in strata of creatinine with a stronger association between BUN and outcome in patients with creatinine < 1.2 mg/dL (HR per 1-SD increase 2.70 [CI 2.29–3.19, $p < .001$]) than in those with creatinine > 1.2 mg/dL (HR per 1-SD increase 1.84 [CI 1.63–2.08, $p < .001$]; p for interaction < 0.001). The predictive value of BUN did not significantly differ between the STEMI group (HR per 1-SD increase 1.97 [CI 1.78–2.17, $p < .001$] and the Non-STEMI group (HR per 1-SD increase 2.25 [CI 1.93–2.61, $p < .001$], p for interaction = 0.106). There was also no difference in the predictive value of BUN between the subgroup of patients treated with acute PCI or CABG (HR per 1-SD increase 2.18 [CI 1.95–2.43, p < .001]) and the

Table 2
The influence of blood urea nitrogen (BUN) levels and other kidney function parameters on long- term cardiovascular mortality in patients with acute myocardial infarction in univariate and multivariable Cox proportional hazards models.

Variable	Hazard ratio per 1-SD increase (95% confidence interval)	*p*
BUN on admission		
Univariate	2.10 (1.94–2.28)	< 0.001
Multivariable-adjusted*	1.52 (1.16–2.00)	0.003
Multivariable-adjusted#	1.62 (1.23–2.11)	< 0.001
eGFR on admission		
Univariate	0.51 (0.47–0.54)	< 0.001
Multivariable-adjusted**	0.71 (0.53–0.97)	0.032
Multivariable-adjusted##	0.85 (0.58–1.24)	0.384
Creatinine on admission		
Univariate	1.42 (1.32–1.53)	< 0.001
Multivariable-adjusted**	1.24 (1.02–1.52)	0.031
Multivariable-adjusted##	1.08 (0.84–1.40)	0.547

SD, standard deviation. All multivariable models were adjusted for the following set of variables: age, gender, body-mass-index, hypertension, diabetes mellitus type II, hypercholesterolemia, history of myocardial infarction, current smoking, systolic blood pressure on admission, heart rate on admission, ST-Elevation myocardial infarction, acute revascularization, peak troponin T, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, renin-angiotensin-aldosterone-system inhibitor therapy and diuretic therapy.

* Adjusted for the abovementioned set of variables + estimated glomerular filtration rate (eGFR).

** Adjusted for the abovementioned set of variables.

Adjusted for the abovementioned set of variables + creatinine.

adjusted for the abovementioned set of variables + BUN.

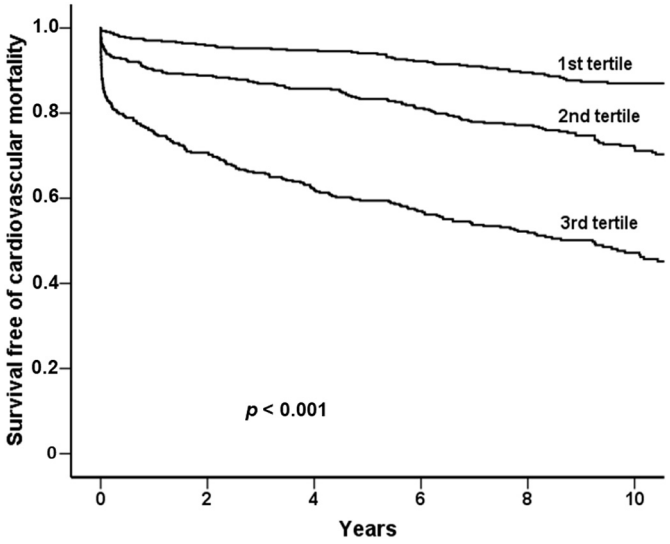

Fig. 1. Kaplan-Meier plots showing the crude cumulative survival free from cardiovascular mortality according to blood urea nitrogen (BUN) tertiles. *P*-value derived from log-rank test.

subgroup of patients treated with medication only (HR per 1-SD increase 1.82 [CI 1.60–2.06, p < .001], p for interaction =0.223).

Although eGFR significantly predicted long-term mortality in univariate analysis and after multivariable adjustment for demographics and clinical variables (Table 2), eGFR lost its independent predictive power after additional adjustment for BUN (adjusted HR per 1-SD increase 0.85 [CI 0.58–1.24, $p = .384$], Table 2). Similarly, the association between creatinine and long-term mortality did not remain significant after controlling for BUN (adjusted HR per 1-SD increase 1.08 [CI 0.84–1.40, $p = .547$], Table 2).

As assessed by Harrell's C-statistic, the discriminatory abilities of

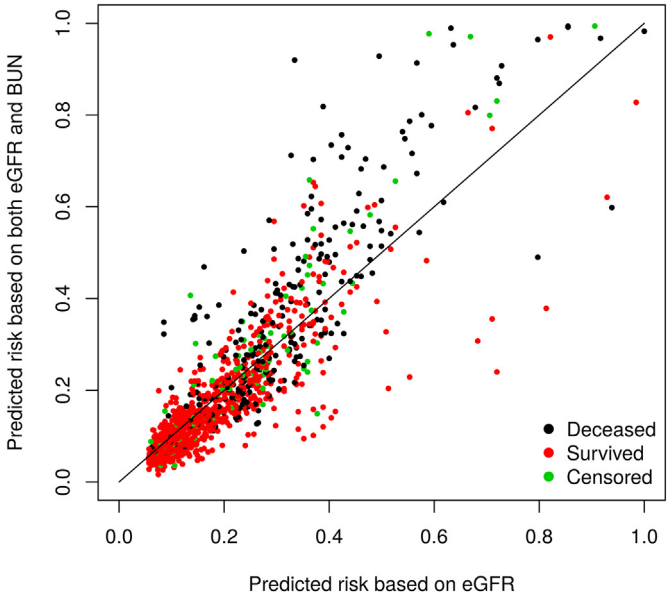

Fig. 2. Reclassification plot showing predicted probabilities of 5-year cardiovascular mortality calculated from a univariable Cox model containing estimated glomerular filtration rate (eGFR) as predictor (x-axis) plotted against the predicted risk from a multivariable Cox model containing eGFR and blood urea nitrogen (BUN) as predictors (y-axis). Red dots: alive at 5-year follow-up. Black dots: deceased due to cardiovascular disease within 5 years. Green dots: censored cases. The model containing eGFR and BUN correctly up-classified risk in 145 deceased cases and incorrectly down-classified risk in 104 deceased cases, correctly down-classified risk in 595 survivors and incorrectly up-classified risk in 338 survivors (as compared to eGFR alone). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

BUN, eGFR and creatinine for prediction of long-term cardiovascular mortality were 0.75 [95% CI 0.70–0.81, $p < .001$], 0.76 [95% CI 0.71–0.81, p < .001] and 0.67 [95% CI 0.60–0.73, p < .001], respectively. The addition of BUN to eGFR significantly improved discrimination, with a C-statistic of 0.78 [95% CI 0.73–0.82, p < .001] (p for comparison = 0.017 versus eGFR alone). The incremental prognostic impact of BUN and eGFR in combination (versus eGFR alone) was further affirmed by a significant improvement in category-free NRI (23.7%, p < .001) and IDI (2.9%, p < .001). Fig. 2 shows the respective reclassification plot. We observed similar results when BUN was added to creatinine (versus creatinine alone) with a significant improvement of the C-statistic, NRI and IDI (reclassification plot shown in Fig. 3, remaining data not shown). Table 3 displays measures of diagnostic accuracy for all assessed kidney function parameters with regard to predicted 5-year cardiovascular mortality.

4. Discussion

The present study suggests that circulating BUN levels at hospital admission have the potential to independently predict long-term cardiovascular mortality in AMI patients. BUN continued to provide additional prognostic information after adjusting for either eGFR or creatinine in multivariable analysis. Interestingly, this association between BUN and outcome was modified by eGFR with a greater predictive value of BUN in those patients with normal or only mildly deceased eGFR. Moreover, the discriminatory power of BUN and eGFR in combination was significantly higher than that of eGFR alone.

The present study extends current knowledge on BUN and adverse outcomes amongst patients with AMI. With a median follow-up of 8.6-years, this is the first study to provide long-term outcome data. To the best of our knowledge, the longest follow-up presented in prior

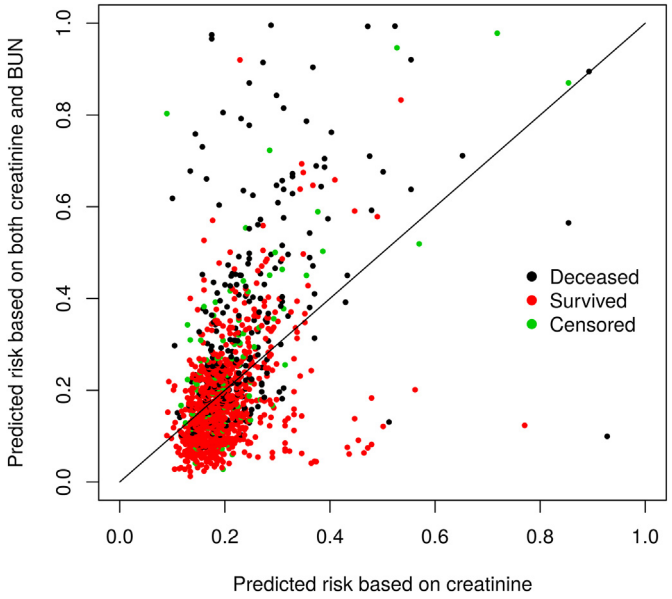

Fig. 3. Reclassification plot showing predicted probabilities of 5-year cardiovascular mortality calculated from a univariable Cox model containing creatinine as predictor (x-axis) plotted against the predicted risk from a multivariable Cox model containing creatinine and blood urea nitrogen (BUN) as predictors (y-axis). Red dots: alive at 5-year follow-up. Black dots: deceased due to cardiovascular disease within 5 years. Green dots: censored cases. The model containing creatinine and BUN correctly up-classified risk in 178 deceased cases and incorrectly down-classified risk in 90 deceased cases, correctly down-classified the risk in 667 survivors and incorrectly up-classified the risk in 304 survivors (as compared to creatinine alone). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

literature was 2.3 years [7]. Most prior studies focused on short- or intermediate-term mortality, for example in-hospital mortality [6], and 30-day [15], 6-month [4] or 1-year mortality [5]. Furthermore, the generalizability of some of the previous findings was limited due to the exclusion of important patient groups. Kirtane et al., for instance, excluded all patients with creatinine > 1.6 mg/dL, an estimated creatinine clearance < 40 mL/min, or bleeding, as the study population was derived from an oral glycoprotein IIb/IIIa inhibitor trial [4]. Similarly, in Aronson et al. only a small proportion of patients had moderately or severely reduced kidney function [7]. Furthermore, Aronson et al. excluded all Non-STEMI patients [7]. The present study aimed to cover the full spectrum of AMI comprising patients with both STEMI and Non-STEMI and did not find a difference in the predictive value of BUN between both groups. This study also included a significant proportion of patients with substantially impaired kidney function. Interestingly, the predictive value of BUN was greater in patients with normal or only mildly decreased eGFR, defined as eGFR ≥ 60 mL/min/1.73 m^2, than in the subgroup of patients with moderately or severely decreased eGFR. The same phenomenon was found in strata of creatinine. In line with these observations, interaction term analysis showed significant effect modification of the association between BUN and mortality by eGFR and creatinine. According to these newly discovered findings, BUN seems to be of particular value for the identification of high-risk patients in the patient-group with normal or nearly normal GFR which might otherwise be misclassified.

In distinction to prior studies, the present study adjusted results for a comprehensive set of variables which also included important prognostic parameters such as NT-proBNP and left ventricular systolic function which previously were either not incorporated into analysis at all [6, 7, 15] or were only available in subgroups [4]. Another strength of the present study is that it used the currently recommended CKD-EPI equation for the estimation of GFR [12]. In former studies the Modification of Diet in Renal Disease (MDRD) formula [1, 4, 5, 7, 16] or other no longer recommended eGFR formulas [5, 7] were used. The MDRD formula in particular is known to give inaccurate estimates in patients with GFR > 60 ml/min/1.73 m^2 and should therefore not be used in AMI cohorts with predominantly normal or only mildly reduced renal function [12, 17].

Using the more accurate CKD-EPI equation, we could confirm previous observations that BUN continues to provide additional prognostic information after adjusting for eGFR. Furthermore, our data suggest that the addition of BUN to eGFR significantly, albeit modestly, improves indices of discrimination and reclassification such as the C-statistic, IDI and NRI. This additive predictive value of BUN might be explained by the fact that BUN levels during AMI not only reflect GFR and underlying renal disease, but also acute neurohumoral and systemic haemodynamic alterations [4, 6–8]. In the acute phase of myocardial infarction low cardiac output, hypotension and subsequent renal hypoperfusion are common, which results in activation of the sympathetic nervous and renin-angiotensin-aldosterone systems and

Table 3
Measures of diagnostic accuracy for predicting 5-year cardiovascular mortality.

Variable	LR +	LR-	Sensitivity	Specificity	PPV	NPV	AUC
Cut-offs at a specificity of 85%							
BUN ≥ 22.7 mg/dL	3.50	0.57	51.2	85.4	47.9	87.0	0.78
eGFR ≤ 48.4 mL/min/1.73 m2	3.64	0.54	53.8	85.2	47.9	87.9	0.80
BUN added to eGFR	4.25	0.43	63.3	85.1	51.8	90.2	0.83
Creatinine ≥ 1.35 mg/dL	2.45	0.76	35.0	85.7	39.0	83.5	0.67
BUN added to creatinine	3.59	0.55	53.6	85.1	48.4	87.5	0.78
Cut-offs at a sensitivity of 85%							
BUN ≥ 15.6 mg/dL	1.72	0.30	85.1	50.6	31.1	92.8	0.78
eGFR ≤ 80.6 mL/min/1.73 m2	2.22	0.22	86.4	61.0	35.9	94.7	0.80
BUN added to eGFR	2.63	0.22	85.1	67.6	39.9	94.7	0.83
Creatinine ≥ 0.91 mg/dL	1.27	0.44	85.9	32.1	24.9	89.7	0.67
BUN added to creatinine	1.75	0.29	85.4	51.2	31.4	93.0	0.78

AUC, area under the receiver operating characteristic (ROC) curve; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate (CKD-EPI equation); LR +, positive likelihood ratio defined as sensitivity/(1–specificity); LR-, negative likelihood ratio defined as (1–sensitivity)/specificity; NPV, negative predictive value; PPV, positive predictive value. Time-dependent ROC analysis (accounting for censored data) was used to calculate and compare measures of diagnostic accuracy at the two pre-specified cut-offs: (1) specificity set at 85%, (2) sensitivity set at 85%. Due to the discreteness of the ROC curve, in some analyses the actually achieved sensitivity or specificity is 86%. The predicted risk for 5-year cardiovascular mortality calculated from univariable or multivariable Cox models (univariable: BUN, eGFR, creatinine; multivariable: BUN added to eGFR, BUN added to creatinine) was used as predictor variable in the ROC analysis. Thus "BUN added to eGFR" and "BUN added to creatinine" describe the diagnostic ability of a risk prediction approach combining the predictive information of both parameters. Note that the AUCs are independent of the selected cut-offs.

enhanced proximal tubular reabsorption of urea, water and sodium [4, 7, 8, 10]. This mechanism of urea reabsorption leads to an increase of BUN levels which is disproportionate to the change in GFR [4, 8] and can be viewed as an appropriate renal response to hypoperfusion and/or volume depletion [7]. In support of these conclusions, in this study BUN was found to be higher in patients presenting with STEMI and/or cardiogenic shock, and was significantly associated with elevated NT-proBNP levels and poor left ventricular function. These parameters might indirectly reflect more severe haemodynamic alterations with consequential BUN elevation.

Although BUN might traditionally be regarded as an imperfect, non-specific measure of kidney function, its ability to signal the presence of unfavourable acute haemodynamic and neurohumoral alterations suggests it may be valuable for prognostication in AMI patients. This has been proposed previously by Saygitov et al., who concluded that BUN is a better marker for risk stratification in AMI patients than creatinine [6]. Creatinine is slow to change in response to acute alterations in GFR as may be seen in AMI [4, 7] and is known to underestimate renal dysfunction in elderly, malnourished and deconditioned patients due to muscle wasting [6, 18]. In the present study as well as in the study by Kirtane et al., creatinine and creatinine-based metrics lost their independent predictive power after controlling for BUN in multivariable analysis [4]. Furthermore, BUN was reported to be superior to creatinine-based measures for risk assessment of patients with decompensated heart failure [9, 10].

The present findings suggest that BUN and other kidney function parameters might be useful diagnostic tools in a multivariable risk assessment approach in AMI patients. BUN levels as well as other kidney function parameters might help to identify high-risk patients who may benefit from special care and aggressive risk factor modification. However, previous authors have shown that patients with impaired kidney function are less likely to receive appropriate medical treatment, revascularization therapy and risk factor modification than the general population, a concept known as “therapeutic nihilism” [1, 19]. Potential reasons for this phenomenon include concerns about worsening of kidney function caused by interventional or medical treatment and about treatment-related toxic effects secondary to insufficient renal clearance [1, 20, 21].

5. Limitations

A limitation of the present study is the retrospective single-centre design. As the clinical parameters were only assessed during the index hospital admission and were not reassessed during the follow-up period, we cannot exclude that changes in patient characteristics over time might have influenced the results of the multivariable analysis. Furthermore, unidentified confounders might have affected results. Future prospective studies are warranted to confirm the present results. Additionally, the present study has a smaller sample size than some previous studies. However, the number of patients achieving the primary endpoint and the long duration of follow-up adding up to 10,826 patient-years ensured sufficient statistical power.

BUN levels are altered by high-protein diets, gastrointestinal bleeding and corticosteroid therapy [22]. Although these factors were very rare in the present study population, they might have influenced results. Finally, BUN levels are known to be influenced by renin-angiotensin-aldosterone-system inhibitors and diuretics. We therefore included these medications as factors in our multivariable analysis, and still found a significant predictive value of BUN.

6. Conclusions

In the present study BUN levels on admission had independent value for predicting long-term cardiovascular mortality amongst patients with AMI and provided additive prognostic information beyond eGFR. BUN might be of particular value for the identification of high-risk patients in subjects with relatively normal eGFR who would be misclassified by eGFR alone. Apart from underlying kidney disease, BUN levels reflect multiple aspects of cardiorenal pathophysiological features and rise in response to hypoperfusion and neurohumoral activation which might explain their prognostic value in AMI patients. BUN and other routinely available kidney function parameters might help to identify AMI patients at increased risk of fatal cardiovascular events who need special attention, as unfortunately, it is these vulnerable patients with impaired kidney function who often may not receive optimum treatment.

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Declarations of interest

None.

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