

Blood urea nitrogen – independent marker of mortality in sepsis

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Background. This retrospective study examines the relationship between admission Blood Urea Nitrogen (BUN) levels and clinical outcomes in patients with sepsis from two separate cohorts in the Czech Republic and the United States.

Methods. The study included 9126 patients with sepsis between January 2014 and December 2018. Kaplan-Meier survival curves and Cox regression were used to analyse the data. An optimal cut-off was calculated by means of the Youden-Index.

Results. BUN at ICU admission was categorized as 10–20, 20–40 and >40 mg/dL. Comparing the group with the highest BUN levels to the one with lowest levels, we found HR for 28 days mortality 2.764 (CI 95% 2.37–3.20; $P<0.001$). We derived an optimal cut-off for prediction of 28 days mortality of 23 mg/dL. The association between BUN and 28 days mortality remained significant after adjusting for potential confounders – for APACHE IV (HR 1.374; 95%CI 1.20–1.58; $P<0.001$), SAPS2 (HR 1.545; 95%CI 1.35–1.77; $P<0.001$), eGFR (HR 1.851; 95%CI 1.59–2.16; $P<0.001$) and several other variables in an integrative model.

Conclusions. Our findings support the BUN level as an independent and easily available predictor of 28 days mortality in septic critically ill patients admitted to an ICU.

Key words: BUN, mortality, sepsis, big data, urea

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BACKGROUND

BUN is a readily available biomarker that has been demonstrated to be an independent risk factor for the prognosis across a broad spectrum of patient populations including decompensated heart failure, acute myocardial infarction, aortic dissection, acute pancreatitis and general critical illness¹⁻⁸. Of note, several studies documented that BUN levels are associated with adverse outcome independently of renal function⁹⁻¹¹. Although the exact pathophysiological mechanism underlying this association is unclear, biologically plausible hypotheses have been postulated and BUN has been labelled as a sensitive index of neurohormonal activation over and above any decline in renal filtration functions¹². Thus, the value of BUN as a strong indicator of prognosis and its role as a surrogate marker of key pathogenetic factors are emerging but more experimental, epidemiological and clinical data are required¹³. In this context, this retrospective study is the first by a large clinical database to evaluate the prognostic value of BUN on admission in critically ill patients with sepsis.

METHODS

Study subjects

The multi-centre study included patients from the medical ICU at Teaching Hospital Pilsen (Czech Republic), and publicly available data from the eICU Collaborative Research Database¹⁴. We collected data from eICU-CRD v2.0 in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Helsinki declaration and its later amendments. eICU-CRD covers 200,859 ICU admissions in 2014 and 2015 of 139,367 patients at 208 U.S. hospitals. The database is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. For the Czech cohort, adult patients admitted to ICU for sepsis between January 2014 and December 2018 were included. Data were extracted from computerized medical database (Medicalc, version 5.86, Plzen, Czech Republic). Only the first episode of sepsis was included to account for increased mortality associated with recurrent sepsis¹⁵. 8366 patients were enrolled in this study. Inclusion criteria were ICD code A41.9 and a documented BUN at admission. The primary endpoint of the study was 28 days mortality. We excluded repeat ICU stays and patients under 18.

Statistical analysis

Values reported are means \pm standard deviations. Differences between independent groups were calculated using one-way ANOVA. Independent Student's *t*-test and the Mann-Whitney U test were used to compare continuous parameters. Pearson's χ^2 was used to evaluate categorical variables. Correlation coefficients represent Spearman's rho.

28 days mortality was assessed by both univariate and multivariate logistic regression. Univariate and multivariate

Cox regression analysis was used to evaluate and to adjust for confounding factors for long-term mortality. Candidate covariates for multivariable modelling were obtained by screening all baseline variables with missing data $<5\%$ and a univariate association with mortality ($P \leq 0.001$). Elimination criterion was a *P* of more than 0.20. Two-tailed $P < 0.05$ were considered significant. Kaplan-Meier curves for death from any cause were plotted for the 3 combinations of BUN groups and significance was tested using the log-rank statistic.

Table 1. Demographics of eICU patients.

eICU	BUN 0–20		BUN 20–40		BUN > 40		all		<i>P</i>
n	2778	std	3099	std	2489	std	8366	std	
Age (year)	58.6	17.3	68.2	14.9	69.4	14.1	65.4	16.2	< 0.001
Weight (kg)	80.0	26.9	83.5	31.7	84.9	28.4	82.8	29.3	< 0.001
APACHE IV (pts)	55.2	22.0	72.7	24.6	86.0	26.7	70.8	27.4	< 0.001
SAPS II (pts)	44.7	20.4	58.2	23.9	71.1	25.6	57.6	25.6	< 0.001
MAP (mmHg)	79.6	40.5	76.1	42.5	75.7	44.8	77.1	42.6	< 0.001
HR (/min)	114.0	27.6	111.5	29.2	109.6	29.6	111.8	28.8	< 0.001
WBC ($\times 10^9/L$)	13.6	8.5	15.1	10.6	16.9	13.5	15.1	11.0	< 0.001
BUN (mg/dL)	12.8	4.2	28.9	6.0	64.7	25.0	34.2	25.4	< 0.001
Creatinine (mg/dL)	75.9	43.7	145.9	103.1	305.4	211.6	170.1	162.8	< 0.001
BUN/creatinine (mmol/mmol)	91.2	46.7	123.1	72.4	133.8	87.9	115.7	72.7	< 0.001
Male gender	1267		1640		1422		4329		< 0.001
eGFR MDRD (mL/min/1.73m ²)	102.1	62.7	54.8	45.9	25.1	20.3	61.7	56.0	< 0.001

Significant *P* values (<0.001) are highlighted in bold text.

SAPS II, Simplified Acute Physiology Score; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

Table 2. Demographics of Czech patients.

mICU	BUN 0–20		BUN 20–40		BUN > 40		All		<i>P</i>
n	147	std	279	std	334	std	760	std	
Age (year)	59.0	16.9	65.4	14.3	67.4	13.9	65.1	14.9	< 0.001
Weight (kg)	80.9	22.6	83.0	20.5	87.3	22.2	84.5	21.7	< 0.001
APACHE II (pts)	21.8	7.9	24.2	8.8	27.4	8.6	25.1	8.8	< 0.001
admission SOFA (pts)	8.2	4.1	9.0	4.3	10.3	4.1	9.4	4.3	< 0.001
MAP (mmHg)	80.5	21.3	77.3	21.2	76.2	19.5	77.4	20.5	0.103
HR (/min)	100.3	27.1	104.8	26.9	104.9	28.9	103.9	27.7	0.204
WBC ($\times 10^9/L$)	15.0	32.9	14.6	13.7	18.8	26.2	16.5	23.8	0.0728
CRP (mg/mL)	138.0	114.0	173.7	117.1	192.4	124.6	175.1	121.4	< 0.001
Lactate (mmol/L)	2.7	3.0	3.5	3.7	3.4	3.8	3.3	3.6	0.063
BUN (mg/dL)	14.1	3.5	29.1	6.0	75.1	33.5	46.4	34.3	< 0.001
Creatinine ($\mu\text{mol/L}$)	104.8	98.1	177.5	114.5	358.8	217.1	241.0	195.3	< 0.001
BUN/creatinine (mmol/mmol)	61.1	27.8	77.7	64.7	88.9	49.6	79.4	53.6	< 0.001
Male gender	90		162		193		445		0.764
eGFR MDRD (mL/min/1.73m ²)	81.62	47.7	43.9	40.7	19.5	14.7	42.4	47.4	< 0.001

Significant *P* values (<0.001) are highlighted in bold text.

SAPS II, Simplified Acute Physiology Score; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

All computation was conducted in Python version 3.7 and IBM SPSS Statistics v23. For data cleaning and pre-processing, NumPy and Pandas were used.

RESULTS

Study population

The baseline characteristics for both cohorts are presented in Table 1–2. A total of 9126 patients diagnosed with sepsis were included in the study. These included 760 patients from the Czech cohort, and 8366 patients from the eICU cohort. Patients with elevated BUN were older, had greater severity of acute illness, higher prevalence of cardiovascular comorbidities.

Survival data

Patients in eICU cohort with BUN above 40 mg/dL had significantly higher 28 days mortality compared to

the 10–20 mg/dL group (HR 2.764; 95%CI 2.37–3.20; $P<0.001$) and to the 20–40 mg/dL group (HR 1.932 95%CI 1.64–2.23; $P<0.001$; Table 5, Fig 1). Admission BUN level was associated with adverse 28 days mortality (HR 1.013; 95%CI 1.012±1.014; $P<0.001$) in univariate analysis (Table 3).

An optimal admission BUN cut-off for eICU cohort was calculated at 23 mg/dL. This cut-off was associated with 28 days mortality (HR 2.318; 95%CI 2.033–2.643; $P<0.001$).

The association of admission BUN>23 mg/dL with 28 days mortality remained even after correction for APACHE IV (HR 1.374; 95%CI 1.20–1.58; $P<0.001$), SAPS2 (HR 1.545; 95%CI 1.35–1.77; $P<0.001$), eGFR(MDRD) (HR 1.851; 95%CI 1.59–2.16; $P<0.001$) and several parameters (creatinine, age, gender, chronic heart failure class IV, CKD 5) in an integrative model (HR 2.103; 95%CI 1.79–2.48; $P<0.001$; Table 7). These findings are consistent with the data analysis of Czech cohort (Table 4,6).

Table 3. Univariate analysis eICU patients.

Factor	HR	95% CI	<i>P</i>
Male gender	0.99	0.89	0.858
age	1.028	1.024	<0.001
BUN	1.010	1.008	<0.001
SAPS II	1.024	1.022	<0.001
APACHE IV	1.026	1.025	<0.001
HR	1.005	1.003	<0.001
MAP	0.998	0.996	<0.001
Creatinine	1.077	1.053	<0.001
eGFR (MDRD)	0.992	0.991	<0.001

Table 4. Univariate analysis Czech patients.

Factor	HR	95% CI	<i>P</i>
gender	0.92	0.80	0.196
age	1.007	0.997	0.156
BUN	1.005	1.002	0.002
APACHE II	1.071	1.056	<0.001
HR	1.005	1.000	0.036
MAP	0.981	0.973	<0.001
Creatinine	1.001	1.000	0.002
eGFR (MDRD)	0.995	0.991	0.010

Table 5. Hazard ratios for eICU patients.

BUN	HR	95% CI	<i>P</i>
<20	1.0		
20–40	1.932	1.651	<0.001
>40	2.764	2.372	<0.001
23	2.318	2.033	<0.001

Table 6. Hazard ratios for Czech patients.

BUN	HR	95% CI	<i>P</i>
<20	1.0		
20–40	1.697	1.098	0.017
>40	2.009	1.324	<0.001

DISCUSSION

Although the prognostic value of admission BUN has been well established in different patient population, this is the first study to report that BUN is an independent prognostic predictor of 28 day overall mortality for

Table 7. Multivariate Analysis eICU patients.

Multivariate model 1			
Factor	HR	95% CI	<i>P</i>
BUN > 23	1.374	1.197	<0.001
APACHE IV	1.025	1.023	<0.001
Multivariate model 2			
BUN > 23	1.545	1.348	<0.001
SAPS II	1.022	1.020	<0.001
Multivariate model 3			
BUN > 23	1.850	1.603	<0.001
Creatinine	1.040	1.011	0.0059
Age	1.025	1.021	<0.001
Gender	0.950	0.853	0.3507
Multivariate model 4			
BUN > 23	1.844	1.598	<0.001
Creatinine	1.039	1.021	0.0072
Age	1.039	1.010	<0.001
Multivariate model 5			
BUN > 23	2.103	1.786	<0.001
Age	1.023	1.019	<0.001
Gender	0.978	0.858	0.7374
CHF IV	1.222	0.305	0.7775
CKD 5	0.961	0.240	0.9553
Multivariate model 6			
BUN > 23	1.970	1.724	<0.001
Age	1.024	1.020	<0.001
Multivariate model 7			
BUN > 23	1.851	1.589	<0.001
eGFR (MDRD)	0.996	0.994	<0.001

critically patients with sepsis and BUN seems to have a prognostic value beyond kidney function also in this population. Even mild elevation in BUN is associated with increased risk for death. Indeed, BUN cut-off of 23 mg/dL differentiated between survivors and non-survivors, a finding supporting existing literature in general medical ICU population⁸.

The mechanistic implications of elevated BUN in patients with sepsis are potentially important. Although the link between elevated BUN and neurohormonal response has almost exclusively been derived from population of patients with cardio-renal problems^{1,2}, we believe that elevated BUN independent of GFR may sensitively reflect

complex underlying pathological processes directly implicated in the pathophysiology of sepsis. First, in sepsis an arterial underfilling due to systemic inflammation-induced arterial vasodilatation is a potent stimulus for the activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone axis (RAAS), and the nonosmotic release of vasopressin (AVP) (ref.^{16,17}). Such an endocrine overdrive contributes to the disproportionate renal reabsorption of urea by modulating three major mechanisms of urea reabsorption: (1) concentration-dependent in proximal tubules (RAAS); (2) flow-dependent in distal tubules (SNS) and (3) up-regulation of urea transporters in inner medullary and collecting duct (VP)

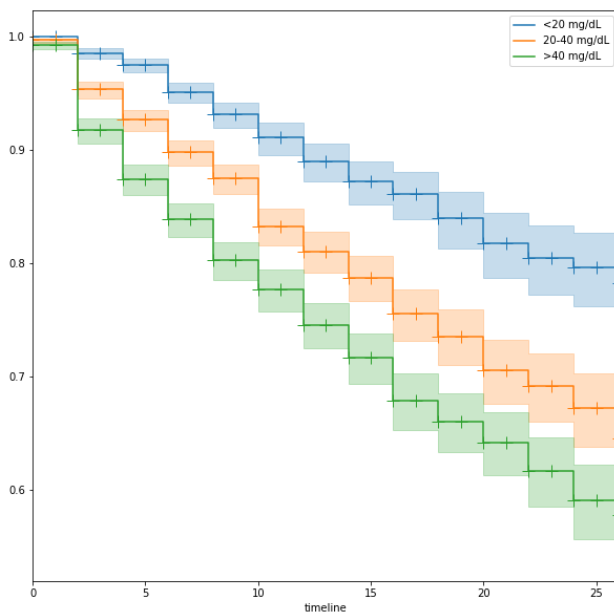


Fig. 1. Kaplan-Meier curves for 28 days all cause mortality of eICU patients according admission BUN level. group comparison by log-rank test, $P<0.001$

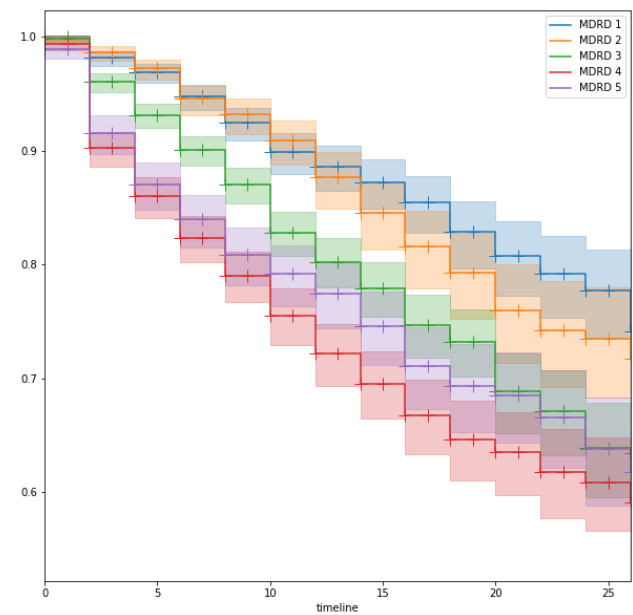


Fig. 2. Kaplan-Meier curves for 28 days all cause mortality of eICU patients according admission estimated GFR (MDRD). group comparison by log-rank test, $P<0.001$

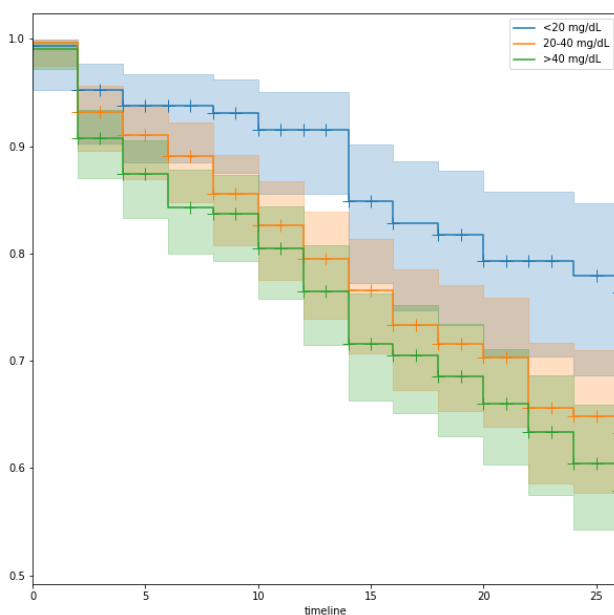


Fig. 3. Kaplan-Meier curves for 28 days all cause mortality of Czech patients according admission BUN level. group comparison by log-rank test, $P<0.01$

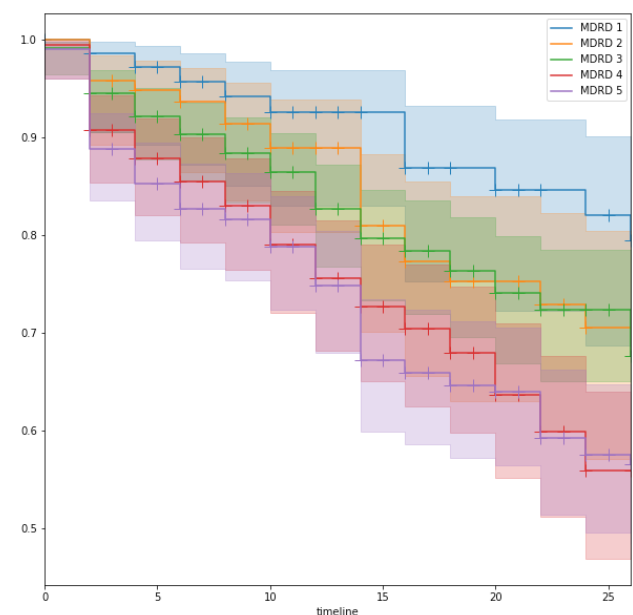


Fig. 4. Kaplan-Meier curves for 28 days all cause mortality of Czech patients according admission estimated GFR (MDRD). group comparison by log-rank test, $P<0.001$

(ref.^{12,18}). Although both SNS, RAAS and AVP represent key adaptive responses to stress, it is tempting to speculate that excessive and prolonged activation during sepsis may become maladaptive and exert adverse effects¹⁹⁻²¹. Furthermore, critical illness, and sepsis in particular, is characterized by profound and often persistent catabolic state, ultimately leading to loss of muscle mass and neuromuscular weakness²². In this context, elevated BUN may also serve as an index of severe catabolism in sepsis. In support of this notion, Haines et al. recently identified the urea over creatinine ratio as a promising biomarker of critical illness-associated catabolism²³.

This study has several limitations. Given the retrospective nature of our analysis, it is possible that the findings may have been affected by both known and unknown confounders despite the attempts to control for these variables through stratified and multivariable analyses. In addition, a number of non-renal factors that affect plasma BUN such as fluid and nutritional status, hepatic urea synthesis have not been taken into consideration. The design of the present study neither allows one to establish a causative link between observed BUN elevation and outcome nor provide mechanistic insights into the factors that determine BUN levels. Furthermore, the retrospective identification of septic patients is a complicated task; our selection was based on ICD-9 coding, which may not be entirely reliable. Finally, sepsis is a dynamic process and analyses from a single time-point at the time of ICU admission only provide a limited perspective, thus leaving the prognostic value of dynamic changes in BUN levels open to speculation.

On the other hand, our study has several strengths. 28 days all-cause mortality is considered an unbiased and clinically relevant outcome in observational studies in critically ill patients²⁴. We analysed sufficient numbers of patients to ensure the adequate reliability of our mortality estimates ($n = 9126$). Finally, we believe the analysis of 2 different cohorts using ICU big data provide external validity to the hypothesis that admission BUN may be a useful marker of 28-day adverse outcome in this group of patients.

CONCLUSION

In conclusion, these data support the concept that the BUN concentrations are independently associated with a poor prognosis in critically patients with sepsis. Prospective studies are needed to delineate the role of BUN as a surrogate of neurohormonal and metabolic signature of critical illness and understand the mechanisms underlying the observed associations and their clinical relevance.

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