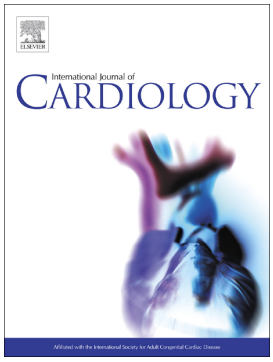

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Alberto Palazzuoli, Gaetano Ruocco, Pierpaolo Pellicori, Eufemia Incampo, Cristina Di Tommaso, Roberto Favilli, Isabella Evangelista, Ranuccio Nuti, Jeffrey M. Testani

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The prognostic role of different renal function phenotypes in patients with acute heart failure

Alberto Palazzuoli MD, PhD, FESC[1], Gaetano Ruocco MD[1], Pierpaolo Pellicori MD[2], Eufemia Incampo MD[3], Cristina Di Tommaso MD[3], Roberto Favilli MD[3], Isabella Evangelista MD[1], Ranuccio Nuti MD[1], Jeffrey M. Testani MD[4].

[1] *Department of Internal Medicine, Cardiovascular Diseases Unit, University of Siena, Siena, Italy.*

[2] *Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow, G12 8QQ.*

[3] *Cardiothoracic Department, Le Scotte Hospital, Siena Italy.*

[4] *Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT, USA.*

Address for correspondence

Alberto Palazzuoli MD, PhD, FESC

Department of Internal Medicine, Cardiovascular Disease Unit, Le Scotte Hospital,

University of Siena Viale Bracci 53100 Siena Italy

Fax: +39577233480

Phone: +39577585363-+39577585461

Email:palazzuoli2@unisi.it

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Abstract

Objective: Worsening renal function (WRF) is common in patients treated for acute heart failure (AHF) and might be associated with a significant increase in blood nitrogen urea (BUN). Although many patients develop WRF during hospitalization, its prognostic role is still unclear. Thus, we aimed to evaluate the prognostic relevance of WRF according to BUN changes during hospitalisation.

Methods: We studied patients with AHF screened for Diur-HF Trial (NCT01441245). WRF was defined as an in-hospital rise in serum creatinine ≥ 0.3 mg/dl or estimated glomerular filtration rate (GFR) reduction ≥ 20%. BUN increase was defined as a rise in BUN ≥ 20% during admission. Effective decongestion was defined as complete resolution of two, or more, signs of HF, or absence of clinical signs of congestion at discharge.

Results: Of 247 patients enrolled, 59 (23%) patients experienced WRF, 107 (43%) had a BUN increase ≥20%, and 111 (45%) were effectively decongested during hospitalization.

During 180 days of follow-up, 136 patients died or were re-hospitalised for AHF. An increase in BUN was an independent predictor of adverse outcome, regardless of WRF (HR = 2.19 [1.35-3.54], p =0.002 and 1.71 [1.14-2.59], p =0.010; with and without WRF, respectively) or congestion at discharge. WRF was not an independent predictor of outcome if BUN did not increase or when congestion was effectively relieved.

Conclusions: an increase in BUN≥20% during hospitalization for AHF predicts a poor outcome independently from renal function deterioration and decongestion. WRF predicts adverse outcome only if BUN increases substantially or clinical congestion persists.

Key Words: acute heart failure, outcome, renal dysfunction, blood urea nitrogen.

Introduction

Around 50% of patients admitted with acute heart failure (AHF) will die within 5 years from diagnosis. [1,2] Thus, there is a need to identify with more precision those clinical phenotypes at higher risk of adverse outcome. [3,4] Chronic kidney disease (CKD) is one of the most potent contributing factors aggravating prognosis of patients with AHF. [5] CKD is common, and it might affect more than 50% of hospitalized patients with AHF, 10-15% of whom will have advanced stages of renal dysfunction. [6,7] Many studies showed that WRF during HF admission usually complicates a poorer cardiac, or renal, function and has a prognostic impact similar to that of CKD [8-10]. However, other studies did not confirm this association between WRF and prognosis: a transient WRF might be the results of aggressive decongestion and temporary kidney overload. [11-14]

Blood nitrogen urea (BUN) is not only a marker of renal function, but it also reflects neurohormonal activation, that enhances reabsorption of urea in the terminal inner medullary collecting duct. [15] Thus, changes in BUN in the context of minor fluctuation or renal function can be valuable to understand when a relative intravascular volume reduction is taking place in a patient with congestive status. [16] With the present study, we evaluate the prognostic relevance of worsening renal function and BUN changes in patients admitted with AHF.

Methods

Study Design

This is a retrospective, post-hoc analysis of a prospective single-centre study including 247 patients admitted with AHF who were screened for the Diur-HF Trial (clinicaltrials.gov: NCT01441245) between September 2013 and July 2015.

Diur-HF is an ongoing prospective, open-label, study comparing continuous with intermittent infusion of furosemide in patients admitted with a diagnosis of AHF conducted at the Departments of Internal Medicine and Cardiology of the University of Siena, Italy. [17] We screened patients over the age of 18 years admitted with dyspnoea, evidence of volume overload and/or clinical signs of HF (peripheral oedema, rales, third heart sound, jugular turgor, lung congestion on chest X-ray), in whom a diagnosis of AHF was confirmed by elevated (>100 pg/ml) levels of B-type natriuretic peptide [BNP].Patients with end-stage (serum creatinine levels >4.0 mg/dL) renal disease or the need for renal replacement therapy (dialysis or ultrafiltration), a recent myocardial infarction (within thirty days of screening) or a systolic blood pressure< 80 mm Hg were excluded. We did not screen patients with known liver or neoplastic disease or concurrent infective disease. All patients gave their written informed consent.

Clinical assessment and evaluation of congestion

Two physicians assessed patients at admission and graded congestion by giving one point for the presence of each of the following clinical signs, regardless of their severity: pulmonary crepitations, third heart sound, jugular venous distention, peripheral oedema and hepatomegaly, for a total of maximum 5 points. [18]. Effective decongestion was defined as complete resolution of two, or more, clinical signs of HF, or absence of clinical signs of congestion at discharge.

Laboratory analysis

Blood tests, including creatinine, BUN and BNP were measured from blood samples taken within 24 hours post-admission and prior to discharge; Renal function was monitored every 48 hours .The estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of

Diet in Renal Disease (MDRD) formula. [19] CKD was defined by creatinine > 1,4 mg/dl and/or eGFR < 60 ml/min/1,73 m^2 .[20] A rise in serum creatinine ≥ 0.3 mg/dl or eGFR reduction ≥ 20% from admission to discharge were used according to conventional criteria to define WRF [21] BUN increase was defined as a rise in BUN ≥20% from admission to discharge. [22]

End Points

1- To evaluate BUN changes with respect to WRF occurrence during hospitalization. 2- To study associations of isolated BUN increase, WRF and their combination with outcome 3- To analyze the relationship existing among BUN, WRF and relief from congestion.

Follow-up

Patients were followed for 180 days after discharge with clinical visits and telephone contacts. The primary outcome of interest was a composite of all-cause mortality (ACM) or HF hospitalization (HFH).

Statistical analysis

Categorical data are presented as number and percentages; normally distributed continuous data as mean ± SD and non-normally distributed continuous variables as median and interquartile range. Patients with AHF were grouped by phenotypes according to WRF, BUN increase ≥ or < 20% or by effective, or not, decongestion during hospitalisation. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Different multivariable Cox proportional hazard regression models were used to investigate the relationship between WRF, BUN and outcome. Multivariable models were adjusted for clinical

variables of interest (age, gender, hypertension, diabetes, dyslipidemia, coronary artery disease, CKD and smoking habits) chosen prospectively a priori. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. All analyses were performed using SPSS 20.0 for Windows (SPSS Inc, Chicago IL). A 2-sided P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 267 patients with AHF enrolled, 12 were excluded because of end-stage renal failure and 8 were lost to follow-up, leaving a final cohort of 247 patients. Median age was 83[76-88] years and 123 (49%) were male; CKD at admission was prevalent in 101 patients (41%), median creatinine was 1.30[1.00-1.69] mg/dL, BUN 66[47-91] mg/dL and BNP 749[429-1150] pg/mL. [Table 1] During hospitalisation, 59 (24%) patients developed WRF and 107 (43%) an increase in BUN $\geq$20%. According to development of BUN increase and/or WRF patients were divided in 4 groups: 37 patients (15%) had both BUN increase and WRF (Group A), 70 (28%) had isolated BUN increase (Group B), 22 (9%) had isolated WRF (Group C) and 118 (48%) patients had neither WRF nor BUN increase (Group D).

Patients who developed both WRF and BUN increase and those with isolated WRF had the highest levels of BNP at admission, and a lower left ventricular ejection fraction (LVEF) compared to other two groups. [Supplementary Table 1]

Outcome

During 180 days of follow-up, 136 (55%) patients died or were re-hospitalised for AHF. In univariable analysis, both WRF and BUN increase were associated with poor prognosis. An increase in BUN$\geq$20% was independently associated with an increased risk of ACM or HFH,

regardless of incident WRF (U-HR 1.64 [1.09-2.45], p=0.017; M-HR 1.71 [1.14-2.59], p=0.01); incident WRF was not an independent predictor of outcome if BUN did not increase (U-HR 1.60 [0.87-2.95], p=0.13; M-HR 1.66 [0.88-3.10], p=0.12.). Those with both WRF and BUN increase had the worst outcome (U-HR 2.38 [1.50-3.77], p<0.001; M-HR 2.19 [1.35-3.54], p=0.002.). [Table 2 and Figure 1]

Renal function trajectories and congestion

To evaluate the impact of congestion, we divided our patients according to the BUN changes and persistence or not of congestion at discharge. Univariate analysis showed that BUN increase ≥ 20% at discharge was related to poor outcome either without effective decongestion (HR = 2.58 [1.51-4.40]; p <0.001) and with effective decongestion (HR = 1.91 [1.11-3.29]; p =0.02). After adjustment for potential confounders, multivariable analysis confirmed the previous findings (HR = 2.70 [1.57-4.63]; p <0.001. HR=1.81 [1.04-3.14]; p=0.035). [Supplementary Table 2 and Figure 2]

We performed a further analysis evaluating the associations of incident WRF, congestion and outcome, and we observed that WRF was related to poor prognosis only if an effective decongestion was not achieved (Univariate HR = 2.14 [1.31-3.51]; p =0.001. Multivariable HR=2.20 [1.32-3.68]; p=0.003). [Supplementary Table 2 and Supplementary Figure 1]

Discussion

Our study, conducted in a daily life clinical scenario, shows that WRF is common in patients treated for AHF, but an increase in BUN≥20% from baseline is even more common. Importantly, we found that an increase in BUN≥20% during admission is a powerful predictor of adverse outcome; WRF has a significant prognostic impact only if associated with an increase in BUN or with the inability to control clinical congestion. Interestingly, our results suggest that caution is needed when relief from congestion causes a disproportionate increase in BUN.

The bidirectional relation existing between heart and kidneys is well known, however the prevalence, and incidence, of renal dysfunction in patients with chronic and AHF is poorly reported in clinical trials and observational studies. Studies rarely provide a definition of renal dysfunction, and different specific phenotype of renal dysfunction might be contemplated, with different impact on clinical outcomes [23]. Importantly, no universal agreement exists to what blood marker has to be used to define, and monitor, renal function. Our findings demonstrated that patients experiencing BUN increase have also an higher prevalence of unfavorable condition such as CAD, atrial fibrillation and advanced CKD stage that could potentially impair outcome, although multivariable analysis showed that BUN is independently related to adverse event.

Otherwise, some might argue that BUN is not a specific renal marker, as it might reflect an increased neurohormonal activity and the effects of vasopressin (AVP) enhancing reabsorption of urea at the distal tubule. [16] Acute arterial underfilling and overdiuresis, occurring during aggressive treatment with diuretics, could further activate the sympathetic and AVP systems, and subsequently increase BUN levels. Importantly, circulating BUN is also elevated secondary to an increased protein catabolism, as it might happen during cachexia, which could further contribute to an adverse outcome.

Our results appears confirmatory of previous multicenter trials conducted in the acute and chronic heart failure setting: in the OPTIME trial, a significant increase (>25%) in BUN was frequent (40%) during hospitalisations for HF, and was strongly related to increased mortality. [24] Similarly, in the ACTIV in CHF trial, BUN, but not creatinine, was an independent predictor of morbidity and mortality. [25] Moreover, the RELAX trial suggested that WRF was not a powerful predictor of poor outcome. [26] In line with the current study, Kajimoto and colleagues studied >4000 patients with AHF enrolled in a national registry in Japan, and showed that a reduced eGFR at discharge (<45 ml/min per 1.73 m^2) was associated with a significantly higher risk of all-cause mortality only if there was a concomitant elevation in BUN (≥25 mg/dl) [27]. Elevated levels of BUN are also powerful predictors of adverse outcome in ambulatory patients with heart failure. [28].

Worsening congestion is one of the key reasons for admission for patients with heart failure, and the failure of its treatment it is one of the main drivers of outcome. Metra et al. showed that WRF during AHF hospitalisations is associated with increased morbidity and mortality only when clinical congestion persists at discharge, suggesting that effective decongestion might be more important than changes in renal function. [29] We expanded this data, and we identified a population of patients with AHF in whom the risk of adverse outcome remains high even when clinical congestion is effectively relieved but at the expenses of a substantial rise in BUN levels. A proof of these concepts, appears to be confirmed by two recent post hoc analysis from PROTECT and RELAX-AHF trials examining diuretic response during hospitalization phase. [26,30,31] Both studies showed a strict relation among poor diuretic response, renal dysfunction and congestion. In the RELAX-AHF trial, WRF was not a predictor of poor outcome, conversely BUN increase was strictly related to reduced diuretic response confirming the hypothesis that the primarily driver of Cardio-Renal Syndrome indwells at tubular level. [26] Higher levels of BUN were also one of the strongest predictors of reduced diuretic response in the PROTECT trial, supporting the concept that sustained activation of the neuro-hormonal system might increase urea reabsorption in the kidneys,

which might precede a detectable deterioration in renal function due to hypoperfusion. [31] . Finally, creatinine and eGFR are the two biomarkers currently involved in WRF diagnosing, unfortunately both parameters are not useful to precociously recognize WRF. In addition, they are not able to identify the causes of the underlying sudden renal deterioration (i.e tubular, glomerular, or collector duct). [23] Most of patients with reduced natriuretic and diuretic response experienced some degree of tubular damage and renal sodium avidity. Interestingly, patients with CKD displayed a better diuretic response compared to patients with preserved renal function. [32,33]

This peculiar finding confirms that previously described by Testani and colleagues in a population of stable patients with heart failure and reduced LVEF. [34] They found that use of high doses of loop diuretics is only associated with mortality in patients with elevated BUN (>21.0 mg/dl), which might reflect a significant activation of the neuro-endocrine system.

In patients with acute heart failure, cardio-renal dysfunction and neuro-hormonal activation are relevant features together with systemic congestion. Although loop diuretic are the main drug to reduce congestion, they could potentially contribute to activate neuro-hormonal with both increase in sodium concentration in the macula densa and afferent arterial vasoconstriction. An optional strategy balancing volume status with modulation of sympathetic and RAA tone could lead to a better diuretic dose optimization. [35]

Limitations

This is a relatively small, single center, retrospective, observational study, with limited power. It was conducted in a tertiary hospital where patients admitted with AHF are usually older and with

more comorbidities than those enrolled in clinical trials and recent registries, which might explain the high morbidity and mortality during follow-up. [36] Also, only consenting patients considered suitable for the Diur-HF trial were screened and enrolled in this study, which introduces further selection bias. In addition, treating physicians were not blinded to clinical congestion, renal function or BUN modifications occurred during hospitalization and different therapeutic choices might have influenced results.

Clinical assessment of congestion is highly subjective and it is frequent to observe disagreement amongst colleagues assessing congestion, particularly when this is not obvious; importantly, a comprehensive clinical evaluation might also take time and all these factors might have influenced how congestion was clinically assessed.

Moreover, there is no specific algorithm to assess or grade congestion, and there is no guidance for an objective use of loop diuretics. The use of ultrasound, for instance by measuring the inferior vena cava or jugular vein diameters, or other non-invasive technologies such as spectroscopy or bio-impedance, could provide more robust methods to quantify congestion and its responses to administration of diuretics. [37,38] Importantly, we did not serially assess weight changes and we did not measure invasively central venous pressure, right atrial pressure and left ventricle filling pressure, all of which would have provided further insight on the complex interactions between WRF, BUN and congestion.

For all these reasons, our findings should be interpreted with caution and need to be confirmed in larger, less selective, prospective cohorts.

Conclusions

Blood urea nitrogen (BUN) increase≥20% during hospitalization for AHF predicts a higher rate of adverse events after discharge, regardless of changes in renal function or clinical congestion.

Conversely, isolated WRF did not demonstrate any association with adverse outcome. If our findings will be confirmed in larger sample size, the role of WRF during hospitalization should be reviewed taking into the account BUN variability. Whether combining measurements of BUN levels with other ultrasound and biochemical methods quantifying congestion might be useful to improve outcomes, requires further investigations.

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TABLES AND FIGURES LEGEND

Table 1. Baseline characteristics

Table 2. Univariate and Multivariable analysis for composite outcome prediction considering BUN increase and WRF groups.

Figure 1. Kaplan Meier curves showing adverse events occurrence according BUN and WRF groups.

Figure 2. Kaplan Meier curves showing adverse events occurrence according BUN increase and decongestion.

Table 1. Baseline characteristics

	All Patients
Age (years)	83[76-88]
Gender (n)	
Female	124
Male	123
Admission creatinine (mg/dl)	1.30[1.00-1.69]
Creatinine at discharge(mg/dl)	1.40[1.00-1.74]
eGFR at admission (ml/min/1,73 m^2)	49[37-65]
eGFR at discharge (ml/min/1,73 m^2)	47[33-66]
Admission BUN (mg/dl)	66[47-91]
BUN at discharge (mg/dl)	74[49-104]
Admission BNP (pg/ml)	749[429-1150]
BNP at discharge (pg/ml)	441[155-781]
Ejection fraction (%)	35[25-43]
Risk factors %/(n)	
Chronic Kidney Disease	41/(101)
Diabetes Mellitus	36/(90)
Hypertension	37/(92)
Dyslipidemia	35/(88)
Smokers	23/(57)
Ischemic heart disease	41/(101)
Atrial fibrillation	28/(70)
WRF %/(n)	24/(59)
BUN increase ≥ 20% %/(n)	43/(107)
BNP decrease ≥ 30% %/(n)	66/(165)

Medication at admission %/(n)	
Beta-Blockers	66%/(164)
Aldosterone antagonists	19%/(48)
Ace inhibitors	73%/(180)
Angiotensin receptors blockers	27%/(67)
Nitrates	39%/(95)
Digoxin	10%/(37)
Statins	52%/(129)
Thiazides	6%/(14)
Loop diuretics	94%/(233)

Abbreviations: BNP, B-type natriuretic peptide; BUN , Blood urea nitrogen; eGFR, Estimated glomerular filtration rate;

REHOSPITALIZATION or DEATH						
	Univariable analysis		***Multivariable analysis[1]***			
Variable	***HR (95% CI)***	***p-value***	***HR (95% CI)***	***p-value***	***HR (95% CI)***	***p-value***
BUN increase ≥20% and WRF	2.38 (1.50-3.77)	<0.001	-	-	2.19 (1.35-3.54)	0.002
BUN increase ≥20% without WRF	1.64 (1.09-2.45)	0.017	-	-	1.71 (1.14-2.59)	0.010
BUN increase <20% with WRF	1.60 (0.87-2.95)	0.13	-	-	1.66 (0.88-3.10)	0.12
BUN increase <20% without WRF	Ref		-	-	Ref	
Effective decongestion (yes vs no)	0.76 (0.54-1.08)	0.12	-	-	-	
CKD (yes vs no)	1.33 (0.95-1.87)	0.09	1.24 (0.85-1.79)	0.27	1.25 (0.89-1.82)	0.24
BUN increase≥20% (vs <20%)	1.72 (1.23-2.41)	0.002	1.60 (1.13-2.27)	0.009	-	
WRF(yes vs no)	1.69 (1.17-2.44)	0.005	1.41 (0.95-2.10)	0.09	-	
BNP decrease ≥ 30%	1.04 (0.73-1.49)	0.82	-	-	-	

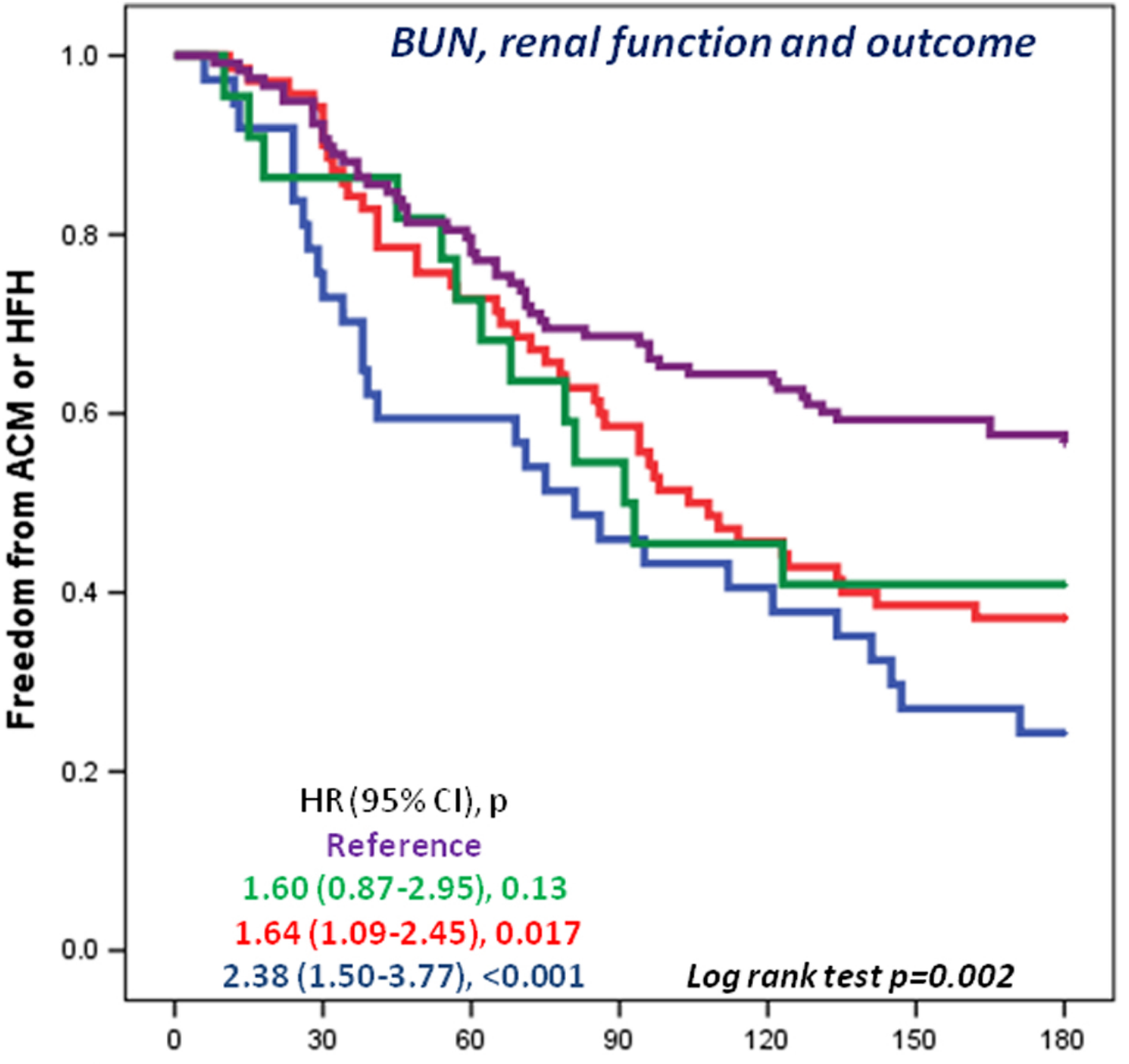
Table 2. Univariate and Multivariable analysis.

Abbreviations: B-type Natriuretic Peptide (BNP); Blood Urea Nitrogen (BUN); Coronary heart disease (CHD); Chronic Kidney Disease (CKD); Confidence Interval (CI); Hazard Ratio (HR); Worsening renal function (WRF). Two separate multivariable analyses are shown: in the first one (middle column) both BUN increase and WRF were simultaneously entered in the model, in the second (right column) we entered in the model the four patients' phenotypes (according to BUN increase (≥ or < 20%) and WRF).

[1]Models were adjusted for clinical variables of interest chosen prospectively (age, gender, and hypertension, diabetes, dyslipidemia, CHD, CKD and smoking habits).

Highlights

- The prognostic relevance of kidney function in acute heart failure has been investigated with contradictory results.
- The definition of worsening renal function may be challenged with introduction of blood urea nitrogen evaluation.
- Worsening renal function evaluation for blood urea nitrogen values could improve acute cardio-renal syndrome diagnosis and identify patients with increased risk.



N. at risk:							
↑ BUN<20% without WRF	118	109	94	82	77	71	68
↑ BUN<20% and WRF	22	20	17	13	11	10	9
↑ BUN≥20% without WRF	70	66	52	42	33	28	26
↑ BUN≥20% and WRF	37	28	23	18	16	11	9

Figure 1

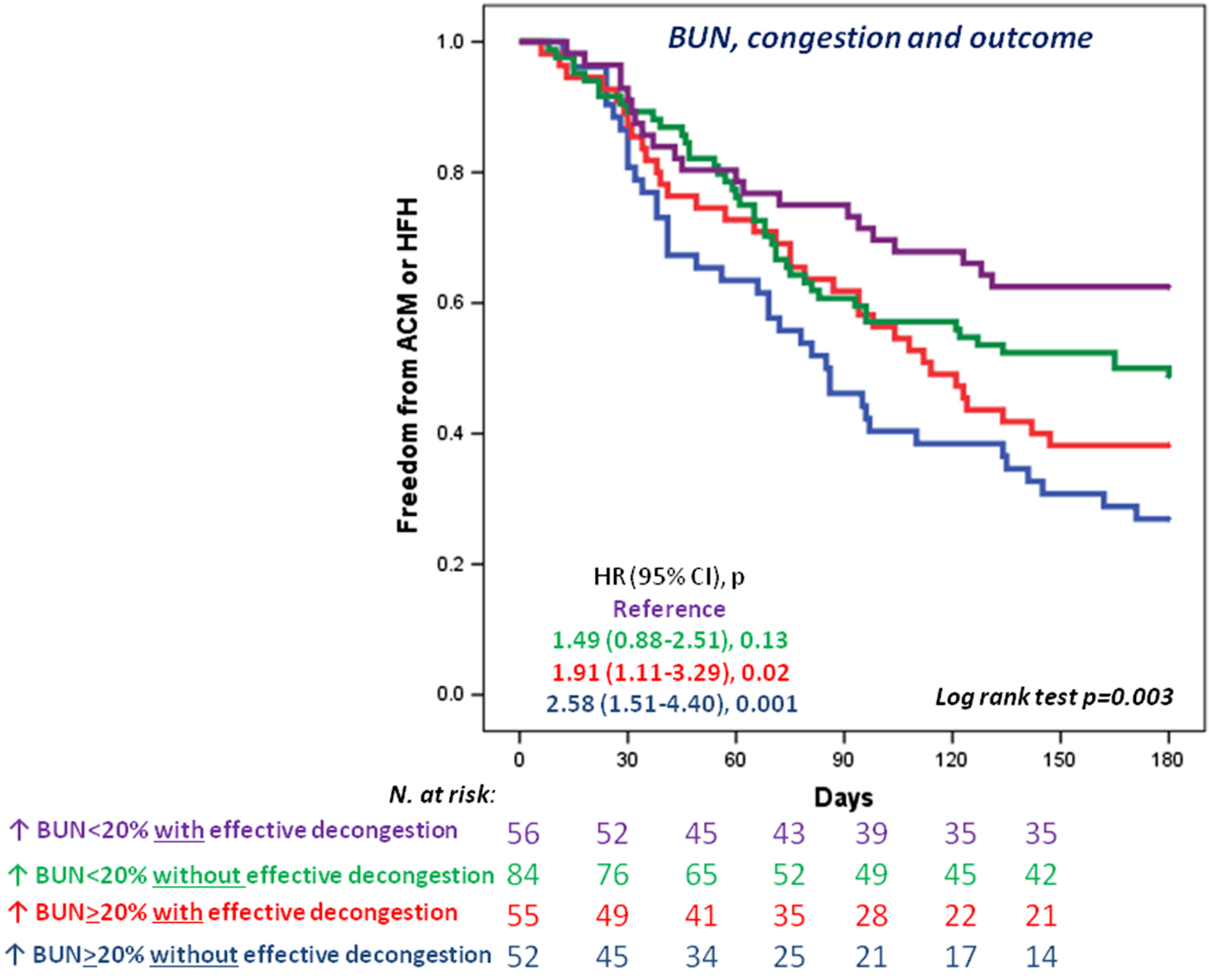
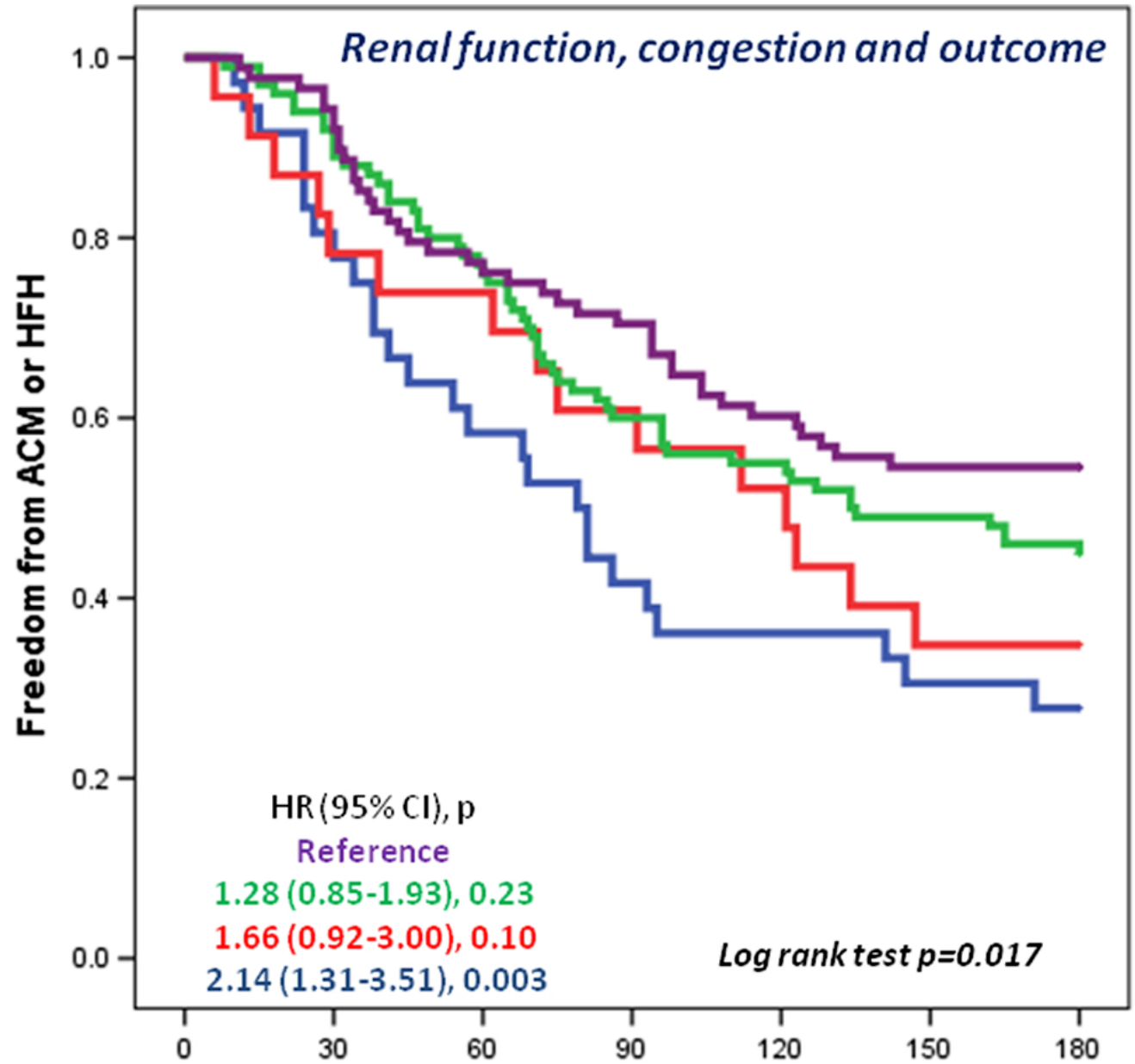

BUN, congestion and outcome
Freedom from ACM or HFH
1.0
0.8
0.6
0.4
0.2
0.0
HR (95% CI), p
Reference
1.49 (0.88-2.51), 0.13
1.91 (1.11-3.29), 0.02
2.58 (1.51-4.40), 0.001
Log rank test p=0.003
0
30
60
90
120
150
180
Days
N. at risk:
↑ BUN<20% with effective decongestion 56 52 45 43 39 35 35
↑ BUN<20% without effective decongestion 84 76 65 52 49 45 42
↑ BUN≥20% with effective decongestion 55 49 41 35 28 22 21
↑ BUN≥20% without effective decongestion 52 45 34 25 21 17 14

Figure 2



N. at risk:

No WRF with effective decongestion	88	83	68	63	54	49	48
No WRF without effective decongestion	100	92	77	61	56	50	46
WRF with effective decongestion	23	19	18	15	13	9	8
WRF without effective decongestion	36	29	22	16	14	12	10

Figure 3