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ORIGINAL ARTICLE

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The model for end-stage liver disease excluding the international normalized ratio (MELD-XI) predicts three-year mortality in patients with advanced heart failure

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ABSTRACT

Introduction: Accurate risk stratification is an important element of management in patients with advanced heart failure (adHF).

Aim of the study: The aim was to determine factors associated with three-year mortality in patients with adHF who underwent qualification for heart transplantation.

Material and methods: The data of 417 consecutive adult patients with adHF hospitalized in the Cardiology Department between 2011 and 2017 was retrospectively analysed. Patients with New York Heart Association classes III–IV with at least two episodes of proven congestion requiring high-dose intravenous diuretics in the last 12 months were included in the study. Exclusion criteria were acute HF, inotropic support, any previous heart surgery, inflammatory diseases, chronic kidney and liver disease, severe obstructive pulmonary disease and haematologic, autoimmune or neoplastic diseases. Prognostic value of the model for end-stage liver disease (MELD), which reflects multiorgan dysfunction was analysed. The primary endpoint was death during three years of follow-up.

Results: In the overall population of 293 patients the median age was 56 (51–61) years, and 92.8% of the patients were male. During the follow-up period, 160 patients reached the primary endpoint. The MELD-XI score hazard ratio (HR) 1.197; 95% CI (confidence interval) (1.131–1.267), $p < 0.001$), PLR value [HR 1.100; 95% CI (1.080–1.130), $p < 0.001$], uric acid [HR 1.013; 95% CI (1.002–1.024), $p = 0.0169$] and sodium HR 1.079; 95% CI (1.044–1.115), $p < 0.001$] serum concentrations were independent factors of three-year mortality.

Conclusions: Higher MELD-XI scores and PLR values as well as higher uric acid and lower serum sodium concentrations are associated with worse outcomes in patients with adHF.

Keywords: MELD-XI score, PLR, advanced heart failure, prognosis, biomarkers

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Introduction

Accurate risk stratification is of utmost importance for the identification of patients with advanced heart failure (adHF) who require treatment, especially eligible candidates who may benefit from advanced interventions at adHF centres [1]. If standard methods of treatment, such as guideline-directed drugs and implantable devices, are insufficient, patients may benefit from long-term mechanical circulatory support (MCS) devices or heart transplantation (HT). Of equal importance is identifying patients who are not eligible

for treatment at an adHF centre and require palliative and symptom-focused therapies such as inotropic infusions, ultrafiltration, or end-of-life comfort care [2, 3]. Biomarkers that reflect different pathophysiological processes occurring in patients with heart failure (HF) are useful tools for risk stratification. There is no single test that can accurately identify patients at the highest risk because the clinical course of HF is unpredictable due to different influencing factors, such as sudden decompensations, diuretic refractoriness associated with worsening renal function, and individual responses to pharmacological treatment. From a pathophysiological point of view, the main area of interest in the population of patients with adHF refractory to the standard treatment is the degree of end-organ impairment, especially kidney or liver dysfunction, which influences the candidacy for MCS or HT [1–3]. A simple, cost-effective and readily available tool that reflects multiorgan dysfunction is the model for end-stage liver disease (MELD), which evaluates cardio–hepatic and cardio-renal interactions simultaneously [4–6]. The MELD scoring system can be used to measure the degree of renal and liver dysfunction based on creatinine and bilirubin serum concentrations and the international normalized ratio (INR), but it can be inaccurate in patients receiving oral anticoagulants [4]. Heuman et al. developed the model for end–stage liver disease excluding INR (MELD-XI) score, which is based only on creatinine and bilirubin levels, to predict mortality in patients with cirrhosis [7]. The MELD-XI scoring system omits the INR from the calculation and remains accurate even in patients with HF receiving oral anticoagulants. Considering the frequent use of anticoagulant therapy in patients with advanced HF, the authors sought to analyse the prognostic value of the MELD-XI score during the three-year follow-up. Furthermore, the aim was to analyse other factors independently associated with the primary end-point in the analysed group of patients during the three-year follow-up.

Material and methods

The data from 417 patients with adHF [New York Heart Association (NYHA) classes III–IV] who underwent planned hospitalization in the Cardiology Department between March 2011 and March 2017 [1] was retrospectively analysed.

For the analysis, patients on optimal guideline-directed therapy with reduced left ventricular ejection fraction (LVEF) < 30% and with at least two episodes of documented pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combination) within the last 12 months were included [1–3].

The exclusion criteria from the study were acute HF, inotropic support or inflammatory disease at presentation, haematologic disorders, any previous heart surgery, device implantation within the previous 6 months (MCS, implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy-defibrillator [CRT-D]), irreversible renal dysfunction (glomerular filtration rate < 30 ml/min/1,73 m^2), chronic liver disease, severe chronic obstructive pulmonary disease, haematologic, autoimmune or neoplastic disorders and incomplete clinical and laboratory data. Patients who underwent HT or MCS (N = 124) during the follow-up were excluded from the analysis. Data on patient medical history, physical examination, clinical characteristics, anthropometric measurements, laboratory, echocardiographic and haemodynamic results obtained at the time of index hospitalization were collected by reviewing the electronic records.

Optimal medical therapy, including beta-blockers, mineralocorticoid receptor antagonists and angiotensin–converting enzyme inhibitors or angiotensin receptor blockers, was carried out in all patients for at least 3 months. The primary endpoint of the study was the all-cause mortality during the three-year follow-up.

The study was conducted in line with GCP and the Declaration of Helsinki. Approval for this study was obtained from the Institutional Review Board at the Medical University of Silesia (approval number: PCN/CBN/0052/KB/194/22). This work was supported by an internal grant from the Medical University of Silesia (grant No PCN–1–089/N/2/K; to BS–J).

Laboratory measurements

The complete blood count, including haemoglobin (HGB), platelets (PLT) and white blood cell count (WBC) with differential count, was determined using automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). Cholesterol, creatinine, urea, uric acid, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyltranspeptidase (GGTP) plasma levels were measured using a COBAS Integra 800 analyser (Roche Instrument Center AG, Rotkreuz, Switzerland). Plasma C-reactive protein (CRP) was detected using a highly sensitive latex-based immunoassay with a Cobas Integra 70 analyser (Roche Diagnostics, Ltd.). A commercially available kit from Roche Diagnostics (Mannheim, Germany) on

an Elecsys 2010 analyser with an analytical sensitivity of < 5 pg/mL was used to measure the plasma concentration of N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP).

The platelet-to-lymphocyte ratio (PLR) was determined by dividing the platelet count by the absolute lymphocyte count. The MELD-XI was calculated using the following formula [8]:

MELD-XI = 5.11 × ln total bilirubin [mg/dL] + 11.76 × ln creatinine [mg/dL] + 9.44

Statistical analysis

Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC). Categorical data are described as numbers with percentages. Continuous data are presented as the means (standard deviations) for normally distributed variables or medians with upper and lower quartiles for nonnormal distributions. Differences between groups were compared using the Student's t-test or the Mann-Whitney U test for continuous variables or chi-square analysis for noncontinuous variables. P-value < 0.05 was considered statistically significant.

Cox proportional hazard regression analysis was used to select factors associated with three-year mortality. Cox univariate proportional analysis was used to select potential independent predictive factors of death for inclusion in the multivariate analysis. The examined covariables included ischaemic aetiology of HF, NYHA class, hyperlipidaemia, lymphocytes, platelets, creatinine, total bilirubin, urea, ALT, ALP, body mass index, PLR, urea, uric acid, sodium, MELD-XI, GGTP, hs-CRP, NT-proBNP, $V0_2max$ and statin use. The univariate predictors of death with p-value < 0.2 were entered into the multivariate Cox regression model with stepwise backward elimination. The tolerance and variance inflation factors were used to assess the correlation between explanatory variables and to assess multicollinearity. Schoenfeld residuals were used to check the proportional hazards assumption. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and the corresponding values of statistical significance.

Receiver operator characteristics (ROC) curves were plotted and the Youden index was used to determine the cut-off for the parameters that were significant in the multivariate analysis. The prognostic strength of biomarkers for predicting three-year mortality was evaluated by calculating each area under the ROC curve (AUC), sensitivity, specificity, negative predictive value, positive predictive value, negative likelihood ratio, positive likelihood ratio, and accuracy. Kaplan-Meier curves with the log-rank test were performed to compare mortality rates in patients dichotomized according to the cut-off values from the ROC curves for biomarkers. P-value < 0.05 was considered statistically significant.

Results

The final study population included 293 patients with adHF. The median age of the participants was 56.00 (51.00–61.00) years, and 272 of them (92.8%) were male. Patients were classified as profiles 4 to 6 according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale and NYHA class III to IV. All of them were on optimal medical and device therapy in accordance with the guidelines of the European Society of Cardiology [2, 3]. The mortality rate during the three-year follow-up was 54.6%. The baseline characteristics of all the patients as well as the survival and nonsurvival groups are presented in Table 1. The results of the univariate and multivariate analyses are presented in Table 2.

The areas under the curves of PLR (AUC 0.8795) and MELD-XI (AUC 0.8052) have good sensitivities and specificities, which allows for the prediction of mortality during a three-year follow-up. According to the Kaplan-Meier analysis higher PLR value, higher uric acid concentrations, higher MELD-XI score and lower serum sodium concentrations were associated with a significantly worse three–year survival. Table 3 presents a summary of ROC curve analysis for selected biomarkers. Figure 1A–H presents ROC Curves (left) and Kaplan-Meier survival curves (right) for: A, B — PLR values; C, D — uric acid serum concentration; E, F — sodium serum concentrations; G, H — MELD-XI values.

Discussion

Based on this single-centre study, it was found that the MELD-XI score was the strongest predictor of three-year mortality in the analysed group of patients. The MELD-XI score outperforms classical parameters of assessing renal and liver function regardless of anticoagulation. Other factors associated with three-year mortality were PLR, uric acid and sodium serum concentrations.

The MELD-XI scoring system reflecting congestive hepatopathy and altered renal function is a modification of the classical MELD score and is calculated utilizing

Table 1. Baseline characteristics of the study population

	All the patients N = 293	Survival N = 133	Nonsurvival N = 160	P-value
Age, years	56.0 (51.0–61.0)	57.0 (50.0–61.0)	56.0 (51.0–60.0)	0.3965
Male, n (%)	272 (92.8)	126 (94.7)	146 (91.3)	0.2493
Ischaemic aetiology of HF, n (%)	147 (50.2)	81 (60.9)	66 (41.3)	< 0.001
BMI, kg/m^2	26.6 (3.8)	27.9 (3.6)	25.5 (3.6)	< 0.001
NYHA III, n (%)	220 (75.1)	118 (88.8)	102 (63.7)	< 0.001
NYHA IV, n (%)	73 (24.9)	15 (11.3)	58 (36.3)	< 0.001
Hypertension, n (%)	143 (48.8)	70 (52.6)	73 (45.6)	0.2323
Type 2 diabetes, n (%)	131 (44.7)	57 (42.9)	74 (46.3)	0.5609
Hyperlipidaemia, n (%)	142 (48.5)	79 (59.4)	63 (39.4)	< 0.001
Persistent AF, n (%)	133 (45.4)	60 (45.1)	73 (45.6)	0.9301
WBC, × 10^9/L	7.7 (6.6–8.9)	7.7 (6.6–8.9)	7.9 (6.6–9.1)	0.7932
Lymphocytes, × 10^9/L	1.7 (1.3–2.1)	1.9 (1.5–2.2)	1.5 (1.2–1.9)	< 0.001
Platelets, × 10^9/L	222.0 (179.0–275.0)	190.0 (161.0–226.0)	258.0 (209.5–287.0)	< 0.001
PLR	137.3 (105.9–174.4)	104.1 (81.6–129.8)	165.4 (136.7–205.9)	< 0.001
Haemoglobin, mmol/L	8.8 (8.1–9.5)	8.80 (8.3–9.5)	8.8 (8.0–9.6)	0.3601
Creatinine, μmol/L	107.0 (92.0–130.0)	99.0 (89.0–117.0)	119.0 (99.0–136.0)	< 0.001
Total bilirubin, μmol/L	20.6 (14.2–28.6)	15.5 (11.2–20.2)	25.5 (20.1–35.9)	< 0.001
Uric acid, μmol/L	495.6 (146.9)	451.1 (133.7)	532.6 (147.5)	< 0.001
Urea, μmol/L	8.8 (6.4–12.2)	8.1 (6.1–10.7)	9.3 (7.1–13.0)	0.0046
AST, U/L	25.0 (21.0–33.0)	25.0 (21.0–33.0)	25.0 (20.0–32.0)	0.4893
ALT, U/L	23.0 (18.0–35.0)	27.0 (18.0–36.0)	22.0 (16.0–33.0)	0.0116
ALP, U/L	86.0 (68.0–122.5)	81.0 (63.0–105.0)	94.0 (74.0–130.0)	0.009
GGTP, U/L	102.0 (54.0–182.0)	89.0 (45.5–154.0)	115.0 (60.0–210.0)	0.0471
LDL, mmol/L	2.4 (1.9–3.1)	2.3 (1.9–2.8)	2.5 (1.8–3.3)	0.3050
Hs-CRP, mg/L	4.1 (1.7–11.1)	3.6 (1.6–8.2)	5.2 (1.9–13.2)	0.0457
MELD-XI	11.7 (11.1–15.8)	11.6 (9.9–13.7)	14.9 (13.1–17.3)	< 0.001
Sodium, mmol/L	137.0 (133.0–141.0)	140.0 (137.0–142.0)	134.0 (131.0–138.0)	< 0.001
NT-proBNP, pg/mL	3688.0 (2076.0–6876.0)	3239.0 (1421.0–5470.0)	4099.5 (2544.0–8137.5)	< 0.001
LA, mm	51.0 (46.0–55.0)	51.0 (47.0–54.0)	51.0 (46.0–56.0)	0.5762
LVEDd, mm	74.0 (67.0–81.0)	73.9 (10.2)	74.25 (10.9)	0.8191
LVEF, %	20.0 (16.0–23.0)	20.0 (17.0–23.0)	20.0 (16.0–22.0)	0.4367
B-blockers, n (%)	282 (96.2)	130 (97.7)	152 (95)	0.2186
ACEI/ARB, n (%)	281 (95.9)	128 (96.2)	153 (95.6)	0.7912
Loop diuretics, n (%)	293 (100)	133 (100)	160 (100)	0.6076
MRA, n (%)	280 (95.6)	128 (96.2)	152 (95)	0.6076
Statin, n (%)	203 (69.3)	104 (78.2)	99 (61.9)	0.0026
ICD/CRT-D, n (%)	293 (100)	133 (100)	160 (100)	
VO_2 max, mL/kg/min	13.00 (11.1–15.4)	14.1 (12.1–16.5)	12.1 (10.5–14.4)	< 0.001

ACEI — angiotensin-converting enzyme inhibitor, AF — atrial fibrillation, ALP — alkaline phosphatase, ALT — alanine aminotransferase, ARB — angiotensin II receptor blocker, AST — aspartate aminotransferase, BMI — body mass index, CRT-D — cardiac resynchronization therapy-defibrillator, GGTP — γ-glutamyl transpeptidase, HF — heart failure, hs-CRP — high-sensitivity C-reactive protein, ICD — implantable cardioverter-defibrillator, LA — left atrium, LDL — low-density lipoprotein, LVEDd — left ventricular end-diastolic dimension, LVEF — left ventricular ejection fraction, MELD-XI — model for end-stage liver disease excluding INR, MRA — mineralocorticoid receptor antagonists, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, NYHA — New York Heart Association, PLR — platelet to lymphocyte ratio, VO2max — maximal oxygen uptake, WBC — white blood cell

Table 2. Univariate and multivariate analyses of factors

Parameter	Univariate data		Multivariate data	
	HR [95% CI]	P-value	HR [95% CI]	P-value
BMI[a]	1.131 [1.085–1.181]	< 0.0001		
PLR[b]	1.140 [1.120–1.160]	< 0.001	1.100 [1.080–1.130]	< 0.001
Urea[b], μmol/L	1.046 [1.021–1.072]	0.0002		
Uric acid[b], mmol/L	1.020 [1.010–1.040]	< 0.001	1.013 [1.002–1.024]	0.0169
Sodium[a], mmol/L	1.139 [1.253–1.388]	< 0.001	1.079 [1.044–1.115]	< 0.001
MELD-XI	1.319 [1.253–1.388]	< 0.001	1.197 [1.131–1.267]	< 0.001
GGTP, U/L	1.001 [1.000–1.002]	0.0870		
Hs-CRP, mg/L	1.013 [1.002–1.023]	0.0176		
NT-proBNP[c], pg/mL	1.100 [1.098–1.115]	< 0.0001		
VO2max, mL/kg/min	1.145 [1.089–1.203]	< 0.0001		
Statin[d]	1.618 [1.174–2.232]	0.0033		

[a]per 1 unit decrease, [b]per 10 unit increase, [c]per 100 unit increase, [d]no therapy, CI — cardiac index, CI — confidence interval, other abbreviations — see Table 1

Table 3. A summary of receiver operating characteristic curves analysis for analysed biomarkers

	AUC [± 95% CI]	P-value	Cut-off	Sensitivity [± 95% CI]	Specificity [± 95% CI]	PPV [± 95% CI]	NPV [± 95% CI]	Accuracy
PLR	0.8795 [0.8422–0.9168]	< .001	≥ 126.9	0.84 [0.77–0.89]	0.73 [0.65–0.80]	0.79 [0.72–0.85]	0.79 [0.71–0.86]	0.79 [0.74–0.83]
Uric acid	0.657 [0.5944–0.7189]	< .001	≥ 529	0.51 [0.43–0.59]	0.76 [0.68–0.83]	0.72 [0.63–0.80]	0.56 [0.49–0.64]	0.62 [0.57–0.68]
Sodium	0.7487 [0.6926–0.8047]	< .001	≤ 136	0.65 [0.57–0.72]	0.75 [0.67–0.82]	0.76 [0.68–0.83]	0.64 [0.56–0.72]	0.70 [0.64 –0.75]
MELD-XI	0.8052 [0.7565–0.8538]	< 0.05	≥ 13.7	0.70 [0.63–0.78]	0.74 [0.66–0.82]	0.77 [0.69–0.83]	0.68 [0.60–0.75]	0.72 [0.67–0.77]

AUC — area under the curve, CI — confidence intervals, MELD-XI — model for end-stage liver disease excluding INR, NPV — negative predictive value, PLR — platelet to lymphocyte ratio, PPV — positive predictive value

the serum bilirubin and creatinine concentrations. The pathophysiology of renal and liver dysfunction due to adHF is associated with poor organ perfusion and passive venous congestion, which develops following right ventricular failure and elevated right atrial pressures [8]. Biochemical markers of cholestasis, including bilirubin and ALP concentrations, are increased in the serum of patients with systemic congestion and elevated right–sided filling pressure and reflect the first stage of liver dysfunction in HF — congestive hepatopathy [9]. Long-term congestive hepatopathy leads to liver cell necrosis, cirrhosis and higher transaminase serum concentrations. Furthermore, the reason for transaminase elevation in HF is hypoperfusion due to hypotension and tachycardia. This stage of liver failure is a contraindication to HT.

Several studies have evaluated the prognostic utility of the MELD-XI score in patients with acute and chronic HF [5, 6, 11]. In the study of Gotou et al., MELD-XI scores predicted a worse postdischarge prognosis during a median follow–up of 19 months in hospitalized patients with HF and reduced LVEF [10]. Lin et al. [11] showed that the MELD-XI score can be used to assess three-year prognosis in hospitalized patients with chronic HF. Analysed patients in their study group were older (median age 76 years) than in the following study; furthermore, only in 20% of patients reduced LVEF was observed. Saito et al. found that a higher MELD-XI score was associated with all–cause mortality during 30 (9–67) months of follow–up in patients with HF undergoing CRT-D [12]. Hepatorenal impairment in this study group was associated with the severity of

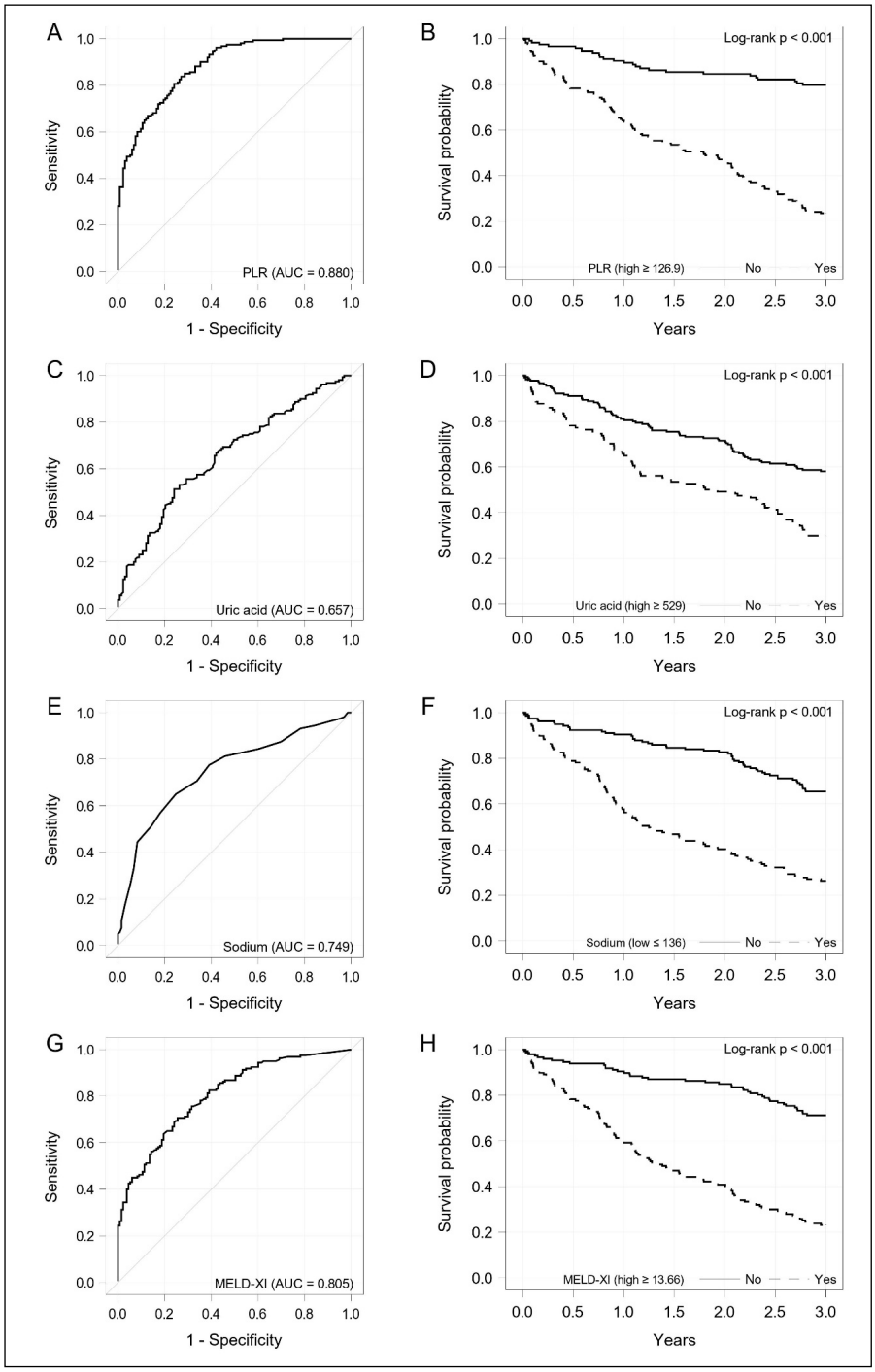

Figure 1. Receiver operating characteristic curves (left) and Kaplan-Meier survival curves (right) for: A, B — PLR values, C, D — uric acid serum concentrations, E, F — sodium serum concentrations, G, H — MELD-XI values

HF, lower CRT-D response rate, older age and multiple comorbidities [12]. It must be emphasized that the patients were older (median age 67 years) and the LVEF was higher (median 30%) than in the current study group, and only 8% of patients presented with NYHA IV functional class.

Another factor associated with three-year mortality in the analysed study group was PLR, a systemic inflammatory marker that has been used in recent years in many studies for risk assessment in cardiovascular diseases [13]. PLR, which reflects inflammation and is calculated from lymphocyte and platelet counts, is easy

to detect and can be obtained through routine blood testing in each patient. Chronic inflammation, in which WBCs and their subtypes play major roles, is associated with HF development, progression and poor outcomes [14]. A higher PLR reflects thrombocytosis caused by intensified proliferation and maturation of megakaryocytes, activation of platelets by cytokines and lymphopenia [13, 14]. In turn, lymphopenia in HF is caused by activation of the hypothalamic-pituitary-adrenal axis and increased apoptosis of lymphocytes. The stimulation of inflammation causes the release of some proteolytic enzymes and proinflammatory cytokines, which leads to the activation of platelets [14]. Furthermore, chronic inflammation is associated with megakaryocyte proliferation and maturation, which leads to relative thrombocytosis [15]. In turn, platelets interact with endothelial cells and leukocytes and release inflammatory substances, leading to the adhesion of monocytes to the vascular wall in macro- and micro-circulation [16]. High cytokine levels, disturbances in microcirculation and increased inflammation lead to ischaemia and myocardial remodelling [17]. Thus, increased platelet count and lymphocytopenia may result in cardiac adverse events and decreased survival [18].

The current study also demonstrated that the sodium serum level reflecting neurohormonal activation with a leading role of arginine vasopressin (AVP) is an independent predictor of mortality in the current study group. In HF patients, the neurohormonal axis acts in a maladaptive way, generating excessive retention of sodium and water and perpetuating systemic congestion [19]. Reduced baroreceptor stimulation due to decreased cardiac output and systemic hypoperfusion along with activation of the sympathetic nervous system and renin-angiotensin-aldosterone axis leads to increased secretion of AVP [19]. The release of AVP causes reabsorption of free water in the renal collecting ducts and dilution of plasma sodium concentration and increases systolic and diastolic cardiac wall tension. There is a close association between serum sodium levels and plasma neurohormone concentrations, such as angiotensin II, norepinephrine and renin, which cause cardiac myocyte hypertrophy and necrosis and influence poor outcomes in HF patients [19]. Lower serum sodium levels may be a marker of neurohormonal activation, reflecting systemic congestion and the severity of HF [20]. Several studies have identified the relationship between hyponatremia and outcomes in HF patients [21, 22]. Adrogué showed that hyponatremia represented the most common electrolyte disorder among HF patients and was associated with the severity of HF, morbidity and hospital readmissions [21]. In a meta-analysis, Rusinaru et al. showed that lower serum sodium concentrations were associated with mortality in a population of patients with HF [22]. Lee and Packer, in a group of patients with adHF, found that lower serum sodium concentrations were associated with higher mortality rates [23]. Deubner et al. performed an analysis of 1000 consecutive HF patients showing that hyponatremia was associated with a significantly increased risk of mortality [24]. Yoo et al. found that hyponatremia represented an independent predictor of 12-month mortality in patients with HF [25].

Numerous studies have noted that hyperuricemia is a frequent metabolic derangement observed in HF [26–30]. The following data support prior analyses that have shown the association between higher uric acid serum concentrations and an increased risk of death in patients with HF during long-term follow up [26, 27]. Although the prognostic value of uric acid has been established in HF, the exact mechanisms behind the relationship between its levels and outcome have not yet been fully clarified. Hyperuricemia may be a result of increased uric acid production due to upregulated xanthine oxidase activity. Xanthine oxidase arises from xanthine dehydrogenase in conjunction with inflammatory cytokines. Xanthine oxidase can produce free oxygen radicals that can lead to cardiac and vascular tissue injury and contribute to cardiac remodelling and HF [27, 28]. Furthermore, plasma uric acid accumulation in HF patients is associated with diuretic–induced impaired uric acid excretion. Otherwise, angiotensin II also increases uric acid reabsorption, reducing its excretion. Additionally, noradrenaline increases serum uric acid levels through renal haemodynamic changes, but the mechanism is poorly understood [29]. Several other factors regulate the reabsorption of uric acid in the proximal tubule and influence its serum levels, such as decreased intravascular volume, low salt diet, and intake of alcohol or common medications (salicylates, diuretics). Moreover, some medical conditions, such as renal insufficiency, diabetes, obesity or hypertension, are associated with higher uric acid serum levels [30].

This study had several limitations which were mostly associated with its retrospective nature. First, the decision to collect laboratory data in the study population was based on individual physician decisions. Second, there was no complete data on all patients, so the data of some patients were omitted. In addition, the following analysis was performed before the introduction of new drugs, such as angiotensin receptor neprilysin inhibitors and sodium-glucose co-transporter-2 inhibitors. Furthermore, this was a single-centre study, which might have led to unmeasured selection bias. These

results will need to be replicated in a larger, prospective cohort of patients to verify the current findings. Notably, the analysed patients underwent HT evaluation, which is why the data on hepatitis serology was available, and the possibility that these patients were exposed to hepatotropic viruses and had an ongoing injury from chronic hepatitis could be excluded.

Conclusions

In conclusion, hepatorenal dysfunction, as measured using the MELD-XI score, predicts mortality in the analysed group of patients with adHF during the three-year follow-up. MELD-XI is an accurate measure of renal and liver dysfunction regardless of anticoagulation, which can augment the traditional MELD score and can be used when the INR is not available. Other factors associated with the three-year mortality rate in the analysed group of patients are higher PLR ratio values, higher uric acid and lower serum sodium concentrations.

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References

1. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018; 20(11): 1505–1535, doi: 10.1002/ejhf.1236, indexed in Pubmed: 29806100.
2. Dorrance A. Faculty Opinions recommendation of ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature. 2014, doi: 10.3410/f.718489795.793497182.
3. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the Diagnosis And Treatment of Acute And Chronic Heart Failure 2008. Revista Española de Cardiología (English Edition). 2008; 61(12): 1329, doi: 10.1016/s1885-5857(09)60059-1.
4. Szczurek W, Szyguła-Jurkiewicz B, Zakliczyński MW, et al. Prognostic value of selected risk scales in patients with end-stage heart failure. Kardiol Pol. 2018; 76(9): 1320–1326, doi: 10.5603/KPa2018.0090, indexed in Pubmed: 29633233.
5. Kim MS, Kato TS, Farr M, et al. Hepatic dysfunction in ambulatory patients with heart failure: application of the MELD scoring system for outcome prediction. J Am Coll Cardiol. 2013; 61(22): 2253–2261, doi: 10.1016/j.jacc.2012.12.056, indexed in Pubmed: 23563127.
6. Inohara T, Kohsaka S, Shiraishi Y, et al. West Tokyo Heart Failure Registry Investigators. Prognostic impact of renal and hepatic dysfunction based on the MELD-XI score in patients with acute heart failure. Int J Cardiol. 2014; 176(3): 571–573, doi: 10.1016/j.ijcard.2014.08.052, indexed in Pubmed: 25305701.
7. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl. 2007; 13(1): 30–37, doi: 10.1002/lt.20906, indexed in Pubmed: 17154400.
8. Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol. 2013; 61(24): 2397–2405, doi: 10.1016/j.jacc.2013.03.042, indexed in Pubmed: 23603231.
9. Myers RP, Cerini R, Sayegh R, et al. Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology. 2003; 37(2): 393–400, doi: 10.1053/jhep.2003.50062, indexed in Pubmed: 12540790.
10. Gotou M, Suzuki A, Shiga T, et al. Implication of modified MELD scores for postdischarge prognosis in hospitalized patients with heart failure. Heart Vessels. 2023; 38(4): 535–542, doi: 10.1007/s00380-022-02202-z, indexed in Pubmed: 36422651.
11. Lin Z, Liu X, Xiao Li, et al. The MELD-XI score predicts 3-year mortality in patients with chronic heart failure. Front Cardiovasc Med. 2022; 9: 985503, doi: 10.3389/fcvm.2022.985503, indexed in Pubmed: 36035923.
12. Saito Y, Nakai T, Ikeya Y, et al. Prognostic value of the MELD-XI score in patients undergoing cardiac resynchronization therapy. ESC Heart Fail. 2022; 9(2): 1080–1089, doi: 10.1002/ehf2.13776, indexed in Pubmed: 34983080.
13. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets. 2015; 26(7): 680–681, doi: 10.3109/09537104.2014.979340, indexed in Pubmed: 25549287.
14. Mann DL, Young JB. Basic mechanisms in congestive heart failure. Recognizing the role of proinflammatory cytokines. Chest. 1994; 105(3): 897–904, doi: 10.1378/chest.105.3.897, indexed in Pubmed: 8131560.
15. Ferroni P, Vazzana N, Riondino S, et al. Platelet function in health and disease: from molecular mechanisms, redox considerations to novel therapeutic opportunities. Antioxid Redox Signal. 2012; 17(10): 1447–1485, doi: 10.1089/ars.2011.4324, indexed in Pubmed: 22458931.
16. Lindemann S, Krämer B, Seizer P, et al. Platelets, inflammation and atherosclerosis. J Thromb Haemost. 2007; 5 Suppl 1: 203–211, doi: 10.1111/j.1538-7836.2007.02517.x, indexed in Pubmed: 17635728.
17. Prabhu S. Cytokine-Induced Modulation of Cardiac Function. Circulation Research. 2004; 95(12): 1140–1153, doi: 10.1161/01.res.0000150734.79804.92.
18. Azab B, Shah N, Akerman M, et al. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis. 2012; 34(3): 326–334, doi: 10.1007/s11239-012-0718-6, indexed in Pubmed: 22466812.
19. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation. 1986; 73(2): 257–267, doi: 10.1161/01.cir.73.2.257, indexed in Pubmed: 3002660.
20. Klein L, O'Connor CM, Leimberger JD, et al. OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation. 2005; 111(19): 2454–2460, doi: 10.1161/01.CIR.0000165065.82609.3D, indexed in Pubmed: 15867182.
21. Adrogué HJ. Hyponatremia in Heart Failure. Methodist Debakey Cardiovasc J. 2017; 13(1): 40, doi: 10.14797/mdcj-13-1-40, indexed in Pubmed: 28413584.
22. Rusinaru D, Tribouilloy C, Berry C, et al. MAGGIC Investigators. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis(†): Meta-Analysis Global Group in Chronic heart failure (MAGGIC). Eur J Heart Fail. 2012; 14(10): 1139–1146, doi: 10.1093/eurjhf/hfs099, indexed in Pubmed: 22782968.
23. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation. 1986; 73(2): 257–267, doi: 10.1161/01.cir.73.2.257, indexed in Pubmed: 3002660.
24. Deubner N, Berliner D, Frey A, et al. Dysnatraemia in heart failure. Eur J Heart Fail. 2012; 14(10): 1147–1154, doi: 10.1093/eurjhf/hfs115, indexed in Pubmed: 22820314.
25. Yoo BS, Park JJ, Choi DJ, et al. COAST investigators. Prognostic value of hyponatremia in heart failure patients: an analysis of the Clinical Characteristics and Outcomes in the Relation with Serum Sodium Level in Asian Patients Hospitalized for Heart Failure (COAST) study. Korean J Intern Med. 2015; 30(4): 460–470, doi: 10.3904/kjim.2015.30.4.460, indexed in Pubmed: 26161012.

26. Tamariz L, Harzand A, Palacio A, et al. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail. 2011; 17(1): 25–30, doi: 10.1111/j.1751-7133.2011.00200.x, indexed in Pubmed: 21272224.
27. Filippatos GS, Ahmed MI, Gladden JD, et al. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. Eur Heart J. 2011; 32(6): 712–720, doi: 10.1093/eurheartj/ehq473, indexed in Pubmed: 21199831.
28. Otaki Y, Watanabe T, Kinoshita D, et al. Association of plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure. Int J Cardiol. 2017; 228: 151–157, doi: 10.1016/j.ijcard.2016.11.077, indexed in Pubmed: 27865177.
29. Yamamoto T, Moriwaki Y, Takahashi S, et al. Effect of norepinephrine on the urinary excretion of purine bases and oxypurinol. Metabolism. 2001; 50(10): 1230–1233, doi: 10.1053/meta.2001.26709, indexed in Pubmed: 11586499.
30. Desai RV, Ahmed MI, Fonarow GC, et al. Effect of serum insulin on the association between hyperuricemia and incident heart failure. Am J Cardiol. 2010; 106(8): 1134–1138, doi: 10.1016/j.amjcard.2010.06.023, indexed in Pubmed: 20920653.