THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Deep Dive into the Cardio-Pulmonary-Renal Interactions in Patients with Pulmonary Hypertension: Serum Creatinine Levels Even Within the Normal Range Related to Long-Term Survival

ABSTRACT

Background: Renal function in patients with pulmonary hypertension (PH) can be disrupted due to hypotension, low cardiac output, and venous pressure overload because of the its dependency on the pressure gradient between systemic arterial and venous circulations. The aim was to investigate whether measures of venous and pulmonary circulations determine renal function in patients with PH.

Methods: The single-center study group comprised 1071 patients with a hemodynamically confirmed PH diagnosis. Serum creatinine level was used for surrogate of renal perfusion status. Echocardiographic measures included left ventricle ejection fraction (LVEF), tricuspid annular plane excursion (TAPSE), and right atrial area (RAA). Hemodynamic parameters included mean aortic and pulmonary pressures (MAP and PAMP), pulmonary capillary wedge (PCWP) and right atrial pressure (RAP), transsystemic and transpulmonary pressure gradients (TSG and TPG), and pulmonary and systemic vascular resistances (PVR and SVR), respectively.

Results: Serum creatinine was significantly associated with TSG, RAP, TPG, PAMP, PVR, PVR/SVR ratio, cardiac index, stroke volume index, mixed venous O2 Sat %, TAPSE, RAA, LVEF%, pericardial effusion and BNP/NT-ProBNP levels ($P < .05$ for all), but not with MAP, PCWP, and SVR. According to the creatinine tertiles, survival rates were significantly different between groups 1 vs. 3, and 2 vs. 3 ($P = .001$ for both).

Conclusion: An integrative approach regarding cardio-pulmonary-renal interactions seems to provide a comprehensive perspective for circulatory status and renal function in patients with PH and congestive heart failure. More importantly, even small increases of serum creatinine levels within the normal range seems to be associated long-term survival differences.

Keywords: Cardiorenal syndrome, pulmonary hypertension, right heart failure

INTRODUCTION

Severe pulmonary hypertension (PH) is a progressive and potentially lethal condition which may be due pre-capillary and/or post-capillary pulmonary vascular diseases clinically classified as 5 main groups resulting in right- and/or left-sided circulatory failure.[1,2] Because maintenance of renal perfusion depends on a gradient between mean pressure renal artery and peritoneum or inferior vena cava, cardio-renal axis may be disturbed by systemic arterial hypotension, low-cardiac output, and venous pressure overload in patients with PH.[1-6] However, deleterious effect of systemic venous hypertension concomitant with low or even near-normal systemic arterial pressures in this setting seems to be ignored.

In this study, the aim was to evaluate the echocardiographic and hemodynamic determinants of cardio-pulmonary-renal interactions in patients with PH as assessed by serum creatinine level.

ORIGINAL INVESTIGATION

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Received: August 8, 2023
Accepted: May 5, 2025
Available Online Date: May 26, 2025

Cite this article as: Tokgöz HC, Hakgör A, Tanyeri Üzel S, et al. Deep dive into the cardio-pulmonary-renal interactions in patients with pulmonary hypertension: serum creatinine levels even within the normal range related to long-term survival. *Anatol J Cardiol.* 2025;XX(X):1-9.

DOI:10.14744/AnatolJCardiol.2025.3759

METHODS

The study group of this retrospective analysis comprised of 1,071 patients (age 55.8 (38.4-69) years, female 62.3%) with PH who enrolled in the single-center EUPHRATES (EvalUation of Pulmonary Hypertension Rise fActors associaTEd with Survival) study between 2006 and 2023. The diagnostic algorithm and hemodynamic definitions have been based on the recommendations of the European Society of Cardiology (ESC) / European Respiratory Society (ERS) 2009 and 2015 PH guidelines before September 2022, and revised criteria recommended by ESC/ERS 2022 PH guidelines thereafter.[1,2] There were no exclusion criteria. All patients who diagnosed PH and underwent right and left heart catheterization were included in the study.

Serum creatinine level was used for surrogate of renal perfusion status. Echocardiographic measures included left ventricle ejection fraction (LVEF %), tricuspid annular plane excursion (TAPSE), planimetric area of right atrium (RAA) measured at systole and on apical 4-chamber view.[1,2] Hemodynamic parameters included mean aortic and pulmonary pressures (MAP and PAMP), pulmonary capillary wedge (PCWP) and right atrial pressure (RAP), transsystemic and transpulmonary pressure gradients (TSG and TPG), pulmonary and systemic vascular resistances (PVR and SVR), respectively.[1,2] Brain natriuretic peptide (BNP) or NT-proBNP levels were also included in the analysis.

A written informed consent was obtained from each participant and the study protocol of EUPHRATES was reviewed and approved by the local Institutional Ethics Committee in accordance with the Declaration of Helsinki.

HIGHLIGHTS

- The measures of pulmonary circulation and right ventricle and atrial dysfunction, pressure and volume status in venous circulation, and systemic arterio-venous pressure gradient seem to be as important as left ventricle function in patients with pulmonary hypertension and congestive heart failure.
- This study yielded significant insights into the overall correlations between the serum creatinine levels and various hemodynamic, echocardiographic, and neurohumoral measures such as right atrial pressure, PAPM, pulmonary vascular resistance, transsystemic gradient, transpulmonary pressure gradient, mixed venous oxygen saturation, left ventricle ejection fraction %, tricuspid annular plane excursion, and brain natriuretic peptide levels.
- The findings emphasized the critical importance of the dynamic interplay between systemic arterial and venous circulations at the renal level, and the term "cardio-pulmonary-renal syndrome" appears to offer a more comprehensive perspective within this context.
- Even small increases of serum creatinine levels within the normal range seems to be associated long-term survival differences in this setting.

Statistical Methods

Continuous data were presented as median and interquartile range or mean and SD, as appropriate, and categorical data were expressed as frequency and percentage. All statistical analyses were performed using "rms," "mgcv," "survival," "survminer," "Hmisc," "coin," and "ggplot2" packages with R-Software v. 3.5.1 (R statistical software, Institute for Statistics and Mathematics).

Outcome variables: Continuous creatinine level.

Candidate predictors: TSG, RAP, MAP, TPG, PAPM, PCWP, SVR, PVR, PVR/SVR, CI, SVI, mix venous O2 (MVO_2) saturation, TAPSE, RA area, LVEF, pericardial effusion, and BNP/NT-ProBNP were included in the model as along with age/sex (adjusted model). Proportional odds (PO) logistic regression method was used to examine the relationship between outcome (continuous creatinine) and candidate predictors.[7] Effects of individual predictors on Creatinine were reported by using odds ratio and 95% CI. Odds ratio and 95% CI were presented as change in interquartile change. All candidate predictors were included in the model as flexible smooth parameters using with restricted cubic spline and non-linearity *P*-value was also presented. The comparison between models was made with assessment of area under the curve (AUC) and R^2.

Patients were divided into 3 groups according to creatinine tertiles, and Kaplan–Meier survival analysis was performed based on these groups. Pairwise comparisons between the groups were conducted using the log-rank and Gehan tests.

RESULTS

The study included 1071 consecutive patients in accordance with the inclusion criteria. Overall, the median age (IQR) was 55.8 (38.4-69) years and 667 (62.3%) were female. Mean creatinine was 0.76 ± 0.62 mg/dL (IQR: 0.62-0.92). Patient characteristics, clinical groups, laboratory, echocardiographic and hemodynamic measures of study group were presented in Table 1A-C. In study population, 55.9% of patients had World Health Organization group 1 PH, 4.4% had group 2, 11.3% had group 3 and 26.9% had group 4 PH.

The relationship between each candidate predictor (age-sex adjusted) and creatinine was evaluated with PO logistic regression analysis (Table 2). Transsystemic gradient, RAP, TPG, PAPM, PVR, PVR/SVR, CI, SVI, % saturation of MVO_2, TAPSE, RA area, LVEF, pericardial effusion and BNP or NT-ProBNP levels were significantly associated with serum creatinine levels ($P < .05$ for all) (Figures 1-5). However, MAP, PCWP and SVR were not related to creatinine level (Figures 1-3). The relationship with serum creatinine levels was linear for BNP/NT-ProBNP, LVEF %, and CI, but nonlinear for other variables (Figure 5). The baseline model consisting only of age and gender had AUC = 0.672 and $R^2 = 0.232$. Model performances (AUC and R2) of the variables added to this baseline model are presented in Table 2. Accordingly, only the performance metrics for NT-Pro-BNP, BNP, TAPSE, MAP, RAP and CI were numerically higher than the baseline model. Statistically, while the performance metrics of NT-ProBNP, BNP, TAPSE and CI were higher than

Table 1A. Patients' Characteristics and Laboratory Parameters

Characteristics	n = 1071
Age (years)	55.8 (38.4, 69)
Sex (female) (n)	667 (62.3%)
Group 1 PAH (n)	599 (55.9%)
APAH-congenital heart disease	289 (27%)
IPAH	248 (23.2%)
APAH-connective tissue disease	48 (4.5%)
APAH-drug	3 (0.3%)
Heritable PAH	8 (0.3%)
Portopulmonary hypertension	3 (0.3%)
Group 2 PH (n)	47 (4.4%)
Group 3 PH (n)	121 (11.3%)
Group 4 PH (CTEPH) (n)	288 (26.9%)
Group 5 PH* (n)	8 (0.7%)
Follow up period (day)	368 (71, 1214)
6MWD (m)	220 (60, 340)
Mortality (n)	441 (41.2%)
Laboratory Parameters	
Serum creatinine level (mg/dL)	0.76 ± 0.62 (0.62;0.92)
EGFR (mL/min/1.73 m^2)	96.6 ± 37.8 (73, 118)
Na (mmol/L)	138 ± 6.85 (136, 140)
Alb (g/L)	40 ± 6.95 (36, 43)
WBC (10^3/μL)	7.9 ± 3.36 (6.4, 9.6)
Hgb (g/dL)	13.5 ± 4.07 (11.8, 15.2)
Plt (10^3/μL)	221 ± 89.8 (175, 281)
BNP (pg/mL)	411 ± 2958 (140, 1267)
Nt-Pro BNP (pg/mL)	679 ± 3594 (176, 2214)

Continuous variables given as both median - interquartile range (25th to 75th) and mean ± SD.
6MWD, 6 minute walking distance; Alb, albumin; APAH, associated pulmonary arterial hypertension; BNP, brain natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; EGFR, estimated glomerular filtration rate; Hgb, hemoglobin; IPAH, idiopathic pulmonary arterial hypertension; IPAH, idiopatic pulmonary arterial hypertension; m, meter; Na, Sodium; Nt-ProBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; Plt, platelets; TAPSE, tricuspid annular plane systolic excursion;TR, tricuspid regurgitation; Wbc, white blood cell; WBC, white blood cell; yr, years.
*One of the patients had histiocytosis, others had segmental PAH due to truncus arteriosus or complex congenital heart disease like single ventricle.

Table 1B. Patients' Echocardiographic Parameters

Echocardiographic Parameters	
TR Vmax (m/sec)	4 ± 1.41 (3.5, 4.6)
sPAP (mm Hg)	75 ± 26.2 (56, 95)
mPAP (mm Hg)	50 ± 14.9 (41, 61)
TR grade	
0	15 (1.5%)
1	269 (25.1%)
2	307 (28.7%)
3	277 (25.9%)
4	203 (18.9%)
RA area (cm^2)	22 ± 9.83 (17.5, 28)
PA diameter (cm)	3.1 ± 0.8 (2.8, 3.5)
RV TDI, St (cm/sec)	12 ± 3.13 (10, 14)
D-septum (n)	706 (65.9%)
IAS bulding (n)	166 (15.4%)
Pericardial effusion (n)	162 (15.1%)
TAPSE (cm)	1.8 ± 0.9 (1.5, 2.2)
LVEF (%)	62.7 ± 6.9

Continuous variables given as both median - interquartile range (25th to 75th) and mean ± SD.
IAS, interatrial septum; LVEF, left ventricle ejection fraction; mPAP, pulmonary artery mean pressure; PA, pulmonary artery; RA, right atrium; RV, right ventricle; sPAP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TR Vmax, tricuspid regurgitation maximal velocity; TR, tricuspid regurgitation.

Table 1C. Patients' Hemodynamic Parameters

Heart Catheterization Parameters	
Aortic systolic pressure (mm Hg)	131 ± 25.9 (116, 150)
Aortic diastolic pressure (mm Hg)	71 ± 13.6 (64, 80)
RV diastolic pressure (mm Hg)	10 ± 7.7 (7, 14)
sPAP (mm Hg)	76 ± 28.8 (58, 100)
mPAP (mm Hg)	44 ± 19.8 (35, 60)
PCWP (mm Hg)	12 ± 4.79 (10, 15)
TPG (mm Hg)	31 ± 20.7 (21,48)
TSG (mm Hg)	85 ± 19.2 (75, 96)
CO (L/min)	4.2 ± 1.25 (3.5, 5)
CI (L/min/m^2)	2.4 ± 0.71 (2, 2.8)
PVR (WU)	6.5 ± 6.23 (4.3, 11)
SVR (WU)	20 ± 7.6 (16, 25)
PVR/SVR ratio	0.33 ± 0.26 (0.22, 0.50)
Sat MVO_2 (%)	63 ± 10.1 (57, 69)
Sat Aort	93 ± 7.68 (88, 96)

Continuous variables given as both median - interquartile range (25th to 75th) and mean ± SD.
6MWD, 6 minute walking distance; CI, cardiac index; CO, cardiac output; mPAP, pulmonary artery mean pressure; MVO_2, mixed venous oxygen; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; Sat, saturation; sPAP, pulmonary artery systolic pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TR Vmax, tricuspid regurgitation maximal velocity; TR, tricuspid regurgitation; TSG, transsystemic gradient; WU, woods units.

the baseline model, MAP and RAP were found to be similar ($P = .315$).

According to the creatinine tertiles from lowest to highest levels as 1st, 2nd, and 3rd, the estimated probability of survival for 12 months, 36 months and beyond 60 months were 75.5% [70.7%-80.5%, 95% CI], 63.3% [57.8%-69.4%, 95% CI], and 57.4% [51.5%-64.1%, 95% CI] in the first tertile; 77.2% [72.5%-82.1%, 95% CI], 59.9% [53.9%-66.7%, 95% CI], and 52.3% [45.7%-59.8%, 95% CI] in the second tertile; and 64.4% [58.9%-70.3%, 95% CI], 45.9% [39.9%-52.9%, 95% CI], and 33.9% [27.7%-41.4%, 95% CI] in the third tertile, respectively. Survival rates were significantly different between groups 1 and 3, and between groups 2 and 3 according to both the

Table 2. Correlation Co-efficients, AUC, OR (95% CIs), Significance for Relations and for Non-linearity

Variables	Adjusted by	R-squared (model)	AUC (model)	OR, 95 % CI (from Q1 to Q3)	*P*-value (ANOVA) and *P*-value for non-linearity
Base	age and sex	0.232	0.672	-	-
TSG	None	0.020	0.543	1.43 (1.07 – 1.91)	0.002 and 0.001
TSG	age-sex	0.236	0.673	1.06 (0.79 – 1.43)	<0.001 and 0.006
RAP	age-sex-map	0.249	0.677	1.49 (1.13 – 1.97)	<0.001 and 0.919
MAP	age-sex-rap	0.249	0.677	0.86 (0.64 – 1.14)	0.458 and 0.948
TPG	none	0.022	0.543	0.83 (0.62 – 1.11)	<0.001 and 0.010
TPG	age-sex	0.230	0.669	1.59 (1.17 – 2.17)	0.007 and 0.038
PAPM	age-sex-PCWP	0.239	0.672	2.03 (1.48 – 1.78)	<0.001 and 0.003
PCWP	age-sex-PAPM	0.239	0.672	0.93 (0.70 – 1.24)	0.137 and 0.367
PVR	age-sex	0.235	0.672	1.61 (1.23 - 2.11)	<0.001 and 0.166
SVR	age-sex	0.216	0.664	0.94 (0.71 – 1.23)	0.400 and 0.390
PVR/SVR	age-sex	0.236	0.669	1.36 (1.03 – 1.78)	<0.001 and 0.659
CI	age-sex	0.236	0.673	0.67 (0.51 – 0.89)	<0.001 and 0.248
SVI	age-sex	0.225	0.668	0.82 (0.61 – 1.09)	0.001 and 0.025
Mix venous	age-sex	0.219	0.665	0.91 (0.67 – 1.23)	<0.001 and 0.240
TAPSE	age-sex	0.248	0.678	0.67 (0.50 – 0.91)	<0.001 and 0.309
RA area	age-sex	0.222	0.671	2.39 (1.42 – 4.03)	0.012 and 0.014
LVEF	age-sex	0.224	0.672	9.30 (0.11 - 0.83)	0.022
BNP	age-sex	0.303	0.695	1.50 (1.08 – 2.08)	<0.001 and 0.416
NT-pro-BNP	age-sex	0.385	0.725	3.89 (2.50 – 6.07)	<0.001 and <0.001
Pericardial eff.	age-sex	0.234	0.671	2.54 (1.40 – 4.63)	0.002

TSG, Trans-systemic gradient, RAP, Right atrial pressure, MAP, Mean arterial pressure, TPG, Trans-pulmonary gradient, PAPM, Mean pulmonary arterial pressure, PCWP, Pulmonary capillary wedge pressure, PVR, Pulmonary vascular resistance, SVR, Systemic vascular resistance, CI, Cardiac index, SVI, Stroke volume index, TAPSE, Tricuspid annular plane systolic excursion, RA, Right atrium, LVEF, Left ventricle ejection fraction, BNP, Brain natriuretic peptide.

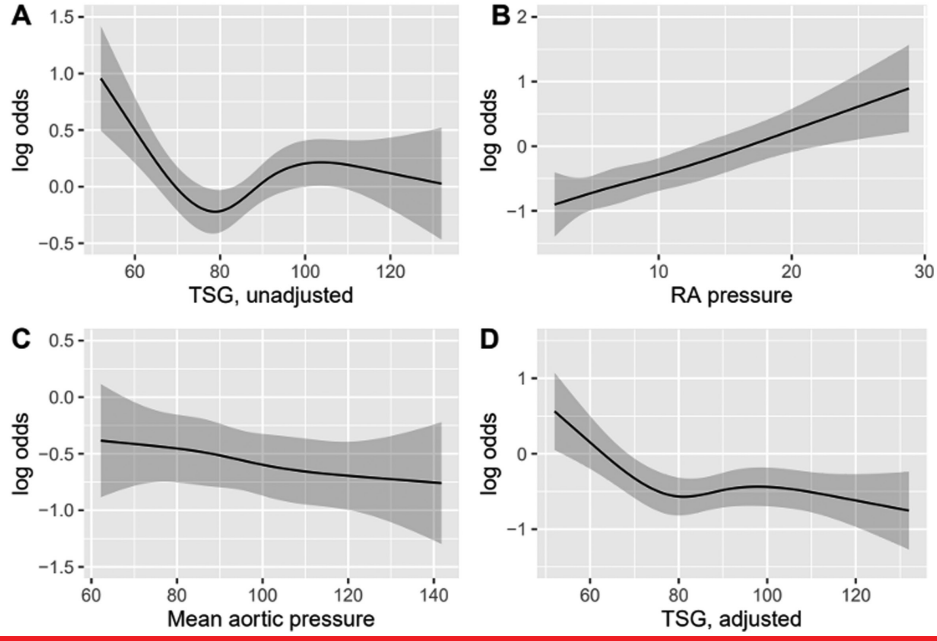

Figure 1. Relationship of serum creatinine level and transsystemic gradient (TSG) in unadjusted model (A), right atrial pressure (B), mean aortic pressure (C), and TSG in adjusted model (D).

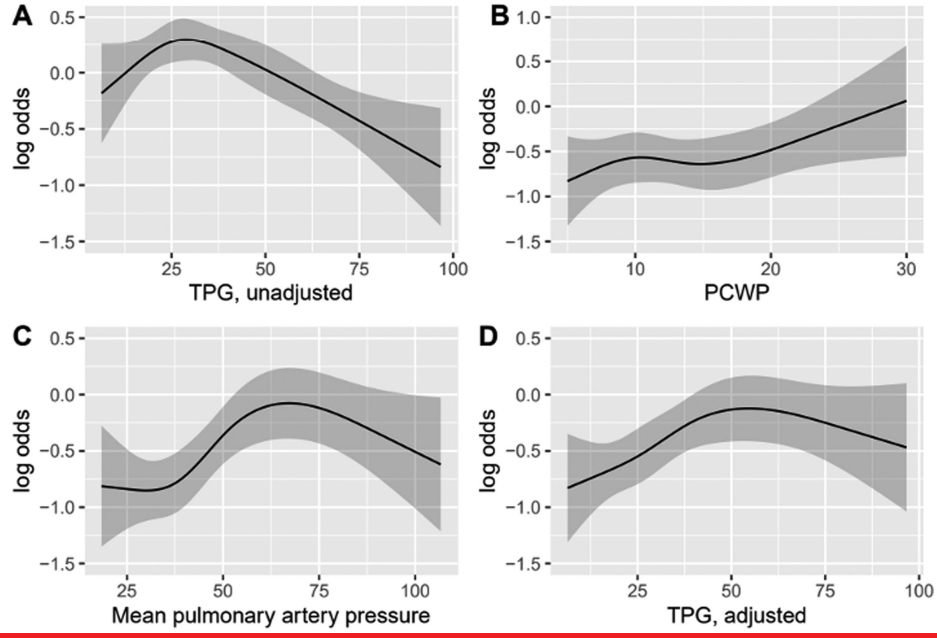

Figure 2. Relationship of log-odds of creatinine level and transpulmonary gradient (TPG) in the unadjusted model (A), pulmonary capillary wedge pressure (B), mean pulmonary artery pressure (C), and TPG in the adjusted model (D).

log-rank test and Gehan's test ($P < .001$) (Supplementary Table 1D and Figure 6).

DISCUSSION

This study evaluating the measures of left-sided and right-sided circulatory status as potential determinants of renal perfusion in patients with precapillary and/or post-capillary PH, depicted meaningful associations regarding the dynamic interaction between systemic and venous circulations in this setting.

The serum creatinine level showed significant relations with LVEF %, grade of pericardial effusion, adjusted measures of mixed venous O2 Sat %, RAP, TSG (as a surrogate of renal perfusion pressure gradient), PAPM, TPG, PVR, PVR/SVR ratio, BNP or NT-ProBNP, CI, and SVI, but not with SVR, MAP or PCWP. The relationship with serum creatinine levels was linear for BNP/NT-ProBNP, LVEF %, and CI, but non-linear for other variables. More importantly, even small increases of serum creatinine levels within the normal range seems to be associated long-term survival differences in this setting.

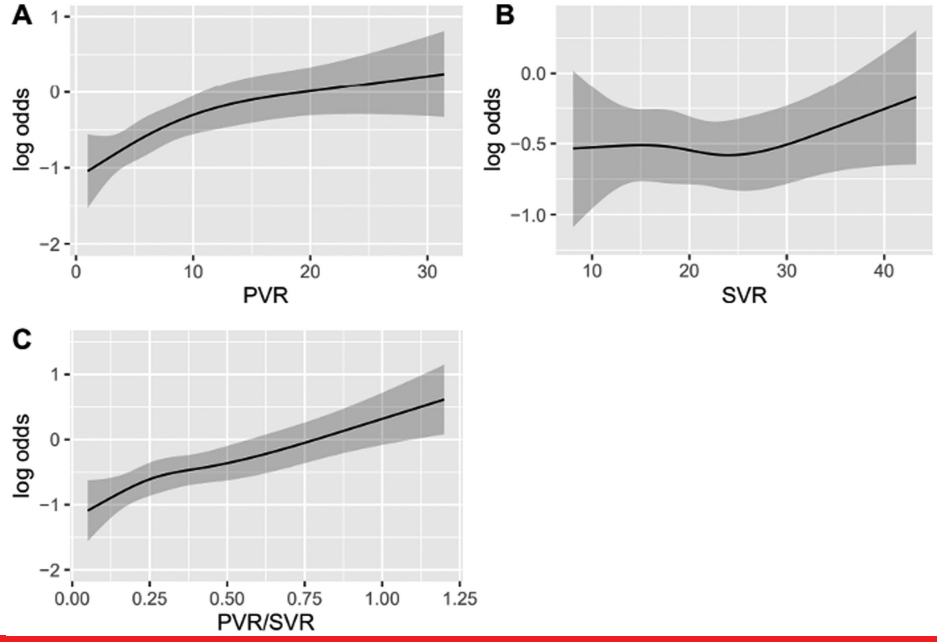

Figure 3. Relationship of serum creatinine level and pulmonary vascular resistance (PVR) (A), systemic vascular resistance (SVR) (B), and PVR/SVR (C).

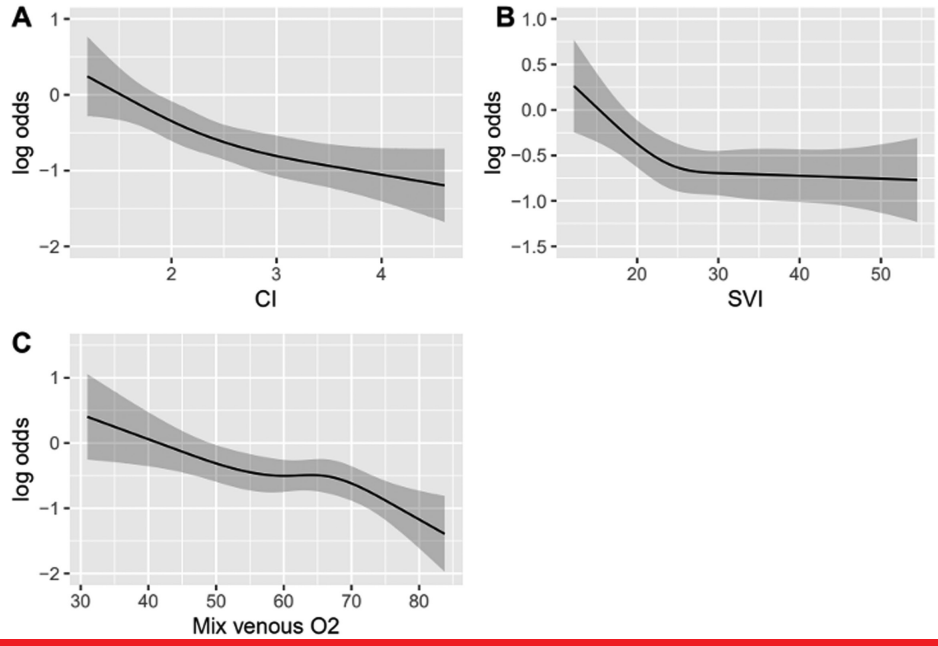

Figure 4. Relationship of serum creatinine level and cardiac index (CI) (A), stroke volume index (SVI) (B), mixed venous O2 saturation (C).

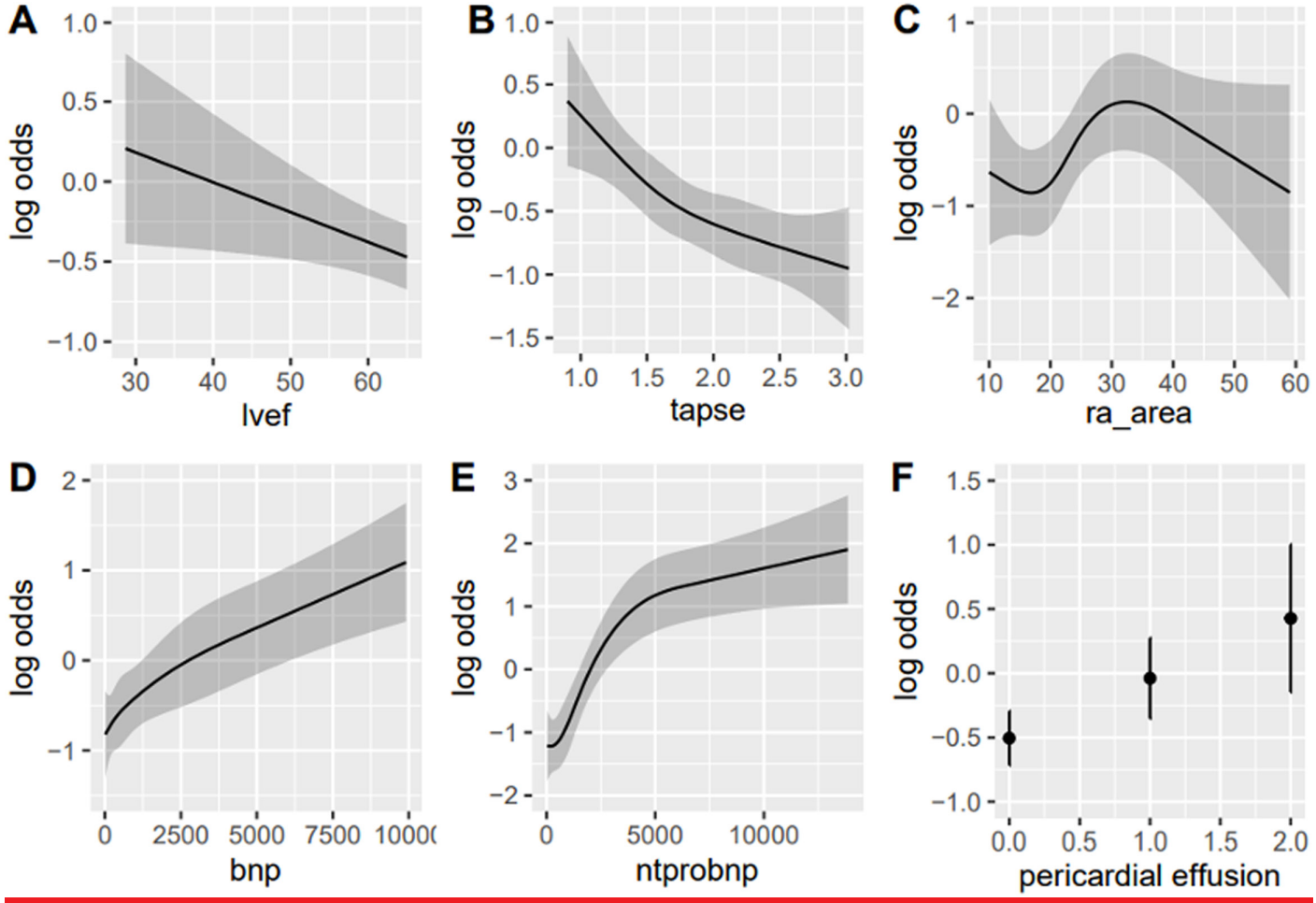

Figure 5. Relationship of serum creatinine level and left ventricle ejection fraction (LVEF) (A), tricuspid annular systolic excursion rate (TAPSE) (B), RA area (C), brain natriuretic peptide (BNP) and NT-pro-BNP (D and E), pericardial effusion (F).

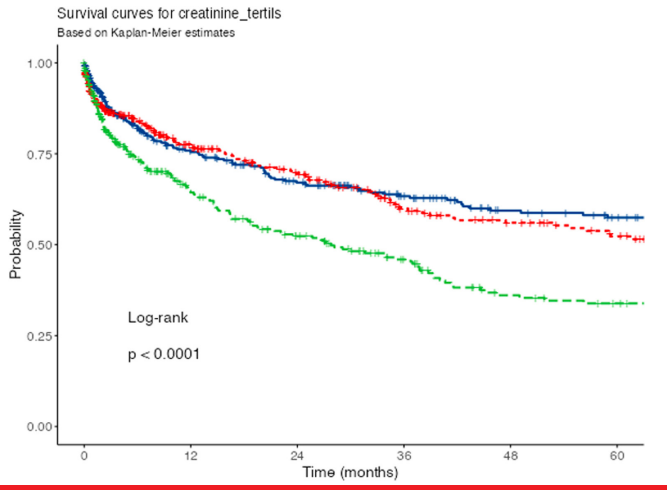

Figure 6. Survival in groups based on creatinine tertiles 1, 2, and 3 is shown in blue, red, and green, respectively. Survival rates were significantly different between groups 1 and 3, and between groups 2 and 3.

Cardiorenal syndrome (CRS) is defined as "any acute or chronic problem in the heart or kidneys that could result in an acute or chronic problem of the other," and is subdivided into 5 subtypes according to the underlying triggering pathology, chronicity, prognosis, and need for targeted management strategies.[8-13] Type 1 represents the most commonly analyzed type of CRS, where a sharp decline in cardiac function is responsible for acute worsening in renal function.[8,9] Type 2 is characterized by chronic heart failure related to a persistent reduction in renal function.[8,9] In types 3 and 4, the direction of the causal relation is inverse, with an abrupt decline in renal function leading to acute heart failure in type 3, whereas progressive decline in kidney function results in chronic heart failure in type 4.[8,9] These last 2 forms of CRS are usually caused by acute or chronic volume overload due to renal dysfunction, cardiac failure added to metabolic abnormalities, and neurohormonal activation.[8-13] Finally, systemic diseases affecting both cardiac and renal function such as sepsis, systemic lupus erythematosus, diabetes mellitus, decompensated cirrhosis, or amyloidosis are classified as type 5 CRS.[8-13] In a large database including patients admitted with acutely decompensated heart failure, normal renal function was noted in 9.0% of patients, whereas mild, moderate, and severe renal dysfunction, and end-stage disease needing chronic dialysis were documented in 27.4%, 43.5%, 13.1%, and 7.0% of patients, respectively.[13]

Although type 1 CRS has been considered to be due to decrease in cardiac output leading to a decrease in the glomerular filtration rate, recent data showed that increased central venous pressure due to pressure and fluid overload transmitting the pressure back to the efferent arterioles and decreasing glomerular filtration pressure seems to be a more critical factor in the pathogenesis of CRS.[13-25] Moreover, elevated intraabdominal pressure, activation of renin-angiotensin-aldosterone and sympathetic nervous systems, and increased inflammatory damage to the kidney are other factors involved in the pathogenesis of types 1 and 2 CRS's.[8,9,13-25] Therefore, re-optimizing this cycle with fluid removal, either with diuretics or ultrafiltration, is the goal of therapy for type 1 CRS.[8-12,26-30] The most potent loop diuretics have been utilized in fluid removal in type 1 CRS.[8-12,26-30] On the other hand, ultrafiltration can be useful in cases of diuretic resistance.[8-12,26-30] Although noradrenaline and low-dose dopamine can also be utilized for refractory cases to restore glomerular filtration pressure, no conclusive data have supported their use in CRS.[8-12,26-30] Overall prognosis is poor in CRS.[8-12] There are multiple mortality and readmission calculators, including blood urea nitrogen, systolic blood pressure, serum creatinine, BNP/NT-ProBNP, and response to diuretics to predict in-hospital mortality and readmission rates in CRS.[8-12]

Our results should be considered to provide important insights into overall relations between log-odds of serum creatinine level and several hemodynamic, echocardiographic, and neurohumoral measures that have been considered valuable surrogates in PH and heart failure. Serum creatinine level showed significant relations with TSG, RAP adjusted for age and sex, PAPM, mixed venous oxygen saturation, TPG, PVR, and PVR/SVR ratio, but not with SVR, MAP or PCWP. The relationship with serum creatinine levels was linear for BNP/NT-ProBNP, LVEF %, and CI, but non-linear for other variables. The results seem to address that glomerular filtration status was dependent on the dynamic pressure gradient between systemic arterial and venous pressures at the renal level, working as a driving force as reflected by TSG, rather than absolute levels of mean arterial pressure and systemic vascular resistance, especially in cases of PH and congestive heart failure characterized by elevated venous pressures. In accordance with results from recent studies demonstrating the importance of elevated central venous and intraabdominal pressure in the pathogenesis of some subtypes of CRS,[14-25] this study also confirmed the importance of hemodynamic status of pulmonary circulation and systemic venous return, central venous pressure and volume overload, and right and left-ventricle functions in maintaining the renal function in these patients.

More importantly, mean creatinine was 0.76 ± 0.62 mg/dL (IQR: 0.62-0.92) in the study group, and first time this study revealed that even small increases of serum creatinine levels within the normal range seems to be associated with long-term survival differences in this setting.

Study Limitations

Serum creatinine level has been adopted as a universal surrogate representing glomerular filtration rate (GFR) status, and showed more robust and linear relations to echocardiographic and hemodynamic measures as compared to e GFR which is a product of estimation. Therefore, the relations with GFR have remained inconclusive in the analyses. Although retrospective nature of this study might be considered as a weakness, serum creatinine and other blood biochemistry, neurohumoral, echocardiographic and hemodynamic measures have been obtained at same day or 1 day before invasive evaluation without change in treatment strategies that may change blood pressures, pressures in left and right heart chambers and intravascular volume status or

intraabdominal pressure. However, this cross-sectional analysis provides no prospective data to assess these relations in acute or chronic subtypes of CRS, except the prognostic impact of serum creatinine levels, and a significant association was found between serum creatinine levels within normal range and long-term survival in this setting. No data was given on whether the patients used diuretics, and if so, which molecule they used, by which route (intravenous or orally) and in what dosage. Relations with baseline creatinine levels of patients and hemodynamic and echocardiographic characteristics of patients with PH diagnosis were evaluated. When the effects of pulmonary hemodynamics and cardiac status on creatinine level are examined, other parameters affecting renal functions (diuretic use, hypertension, diabetes, primary renal disease, etc.) should be taken into consideration. Different studies should be designed for evaluation of these interactions.

CONCLUSION

Our results pointed out the pivotal role of dynamic interaction between systemic arterial and venous circulations throughout the renal level, and measures indicating the severity of pre-capillary PH, right heart failure and volume overloading should be taken into consideration in patients with PH. The term cardio-pulmonary-renal syndrome seems to provide a more holistic approach, and even small increases of serum creatinine levels within the normal range seems to be associated long-term survival differences in this setting.

Ethics Committee Approval: This study was approved by Ethics Committee of Koşuyolu High Specialization Education and Research Hospital (Approval No.: 2013.3/4; Date: 12 Jul 2013).

Informed Consent: Not applicable due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.C.T., C.K.; Design – A.H, S.T.Ü.; Supervision – C.K., İ.H.T.; Resources – B.Kültürsay, B.Keskin.; Materials – A.T., .B.Keskin; Data Collection and/or Processing – Ş.K., S.T.Ü.; Analysis and/or Interpretation – İ.H.T., A.K., B.Kültürsay.; Literature Search – A.S., D.S.; Writing – C.K., H.C.T., N.O.; Critical Review – C.K., N.O.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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Supplementary Table 1D. Survival status according to creatinine tertiles

1, 3, 5 year Survival - Creatinine Tertils

					95% Confidence Interval	
Levels	**time**	**Number at Risk**	**Number of Events**	**Survival**	**Lower**	**Upper**
1	12	199	75	75.5%	70.7%	80.5%
1	36	124	29	63.3%	57.8%	69.4%
1	60	85	10	57.4%	51.5%	64.1%
2	12	181	69	77.2%	72.5%	82.1%
2	36	99	34	59.9%	53.9%	66.7%
2	60	68	11	52.3%	45.7%	59.8%
3	12	143	101	64.4%	58.9%	70.3%
3	36	76	38	45.9%	39.9%	52.9%
3	60	43	18	33.9%	27.7%	41.4%