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Ratio of Estimated Right Atrial Pressure with Pulmonary Capillary Wedge Pressure and Estimated Plasma Volume Status as Predictor of Major Adverse Cardiovascular Event During Hospitalization in Patients with Acute Heart Failure

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ABSTRACT

Background: Major cardiovascular events (MACE) in acute heart failure (AHF) are relatively high. The role of Estimated Right Atrial Pressure to Pulmonary Capillary Wedge Pressure (ERAP/EPCWP) and Estimated Plasma Volume Status (EPVS) as predictors of MACE during AHF hospitalization needs to be clarified. ***Objective:*** To determine whether ERAP/EPCWP and EPVS are predictors of MACE during AHF hospitalization. ***Methods:*** This prospective cohort study of AHF patients from February to April 2024. The independent variables are ERAP/EPCWP and EPVS. MACE outcomes consist of all-cause mortality, cardiogenic shock, malignant arrhythmias, and the incidence of renal replacement therapy. Samples were selected by consecutive sampling that met the inclusion and exclusion criteria and then observed during hospitalization. ***Results:*** A total of 62 AHF patients were included in the study. The MACE occurred in 45.2% of cases. The ERAP/EPCPWP cut-off point based on the ROC curve was ≥0.535 (95% CI 0.767-0.961; p<0.001; AUC 0.864). The EPVS cut-off point was ≥4.895 (95% CI 0.656-0.89; p<0.001; AUC 0.773). The cumulative survival on the fifth day in the ERAP/EPCWP ≥0.535 and <0.535 groups was 19.6 and 86.5%, respectively (p<0.001), while in the EPVS ≥0.4895 and <0.4895 groups, 29.6% and 71.7% respectively (p<0.001). The ERAP/EPCWP ≥0.535 and EPVS ≥0.4895 each were independent predictors of MACE during hospitalization (adjusted HR ERAP/EPCWP 8.89; 95% CI 2.936-26.972; p<0.001 and adjusted HR EPVS 5.046; 95% CI 1.893 -13.449; p<0.001). ***Conclusion:*** The ERAP/EPCWP and EPVS are independent predictors of MACE during AHF hospitalization.

Keywords: ERAP/EPCWP; EPVS; acute heart failure; major cardiovascular events

INTRODUCTION

Acute heart failure (AHF) is a rapid worsening of signs and symptoms of heart failure, which causes urgency to obtain rapid clinical treatment in the emergency room or inpatient setting [1]. Heart failure is still a global issue with high prevalence and all-cause mortality [1,2]. AHF's intrahospital mortality reached 6% [3]. This had implications for the health sector's high economic burden and resources due to AHF [4]. Better prognostication is important to provide comprehensive management and reduce mortality and major adverse cardiovascular events (MACE), especially during hospitalization.

The ratio of right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) invasively had clinical significance in terms of short—and long-term mortality [5,6]. An increase in the RAP/PCWP ratio correlates with a decrease in renal function, increased pulmonary vascular resistance (PVR), lower cardiac index, and lower RV stroke work index[1].

Both RAP and PCWP were developed noninvasively by echocardiography. They strongly correlated with invasive measurement with low interobserver variability [7,8].

Plasma Volume Status (PVS) value was a marker of congestion in AHF. The radiolabeled albumin dilution technique is the standard for accurate quantification of plasma volume status [9]. Unfortunately, this technique was not widely available and was relatively expensive. Duarte developed a formula for estimating plasma volume status (EPVS) through hemoglobin and hematocrit from simple blood counts [10]. It had a good correlation with the radiolabeled albumin dilution technique [11]. Duarte's formula was associated with cardiovascular mortality and rehospitalization of AHF within 30 days [12].

The use of ERAP/EPCWP noninvasively and EPVS in AHF is still controversial. This research aimed to determine whether ERAP/EPCWP measured by echocardiography and EPVS measured from hemoglobin-hematocrit are predictors of MACE during hospitalization in AHF populations.

METHODS

This is a prospective cohort study of AHF patients that hospitalized from February until April 2024 at Prof. dr. I.G.N.G Ngoerah Hospital, Bali, Indonesia. The independent variables are the ratio ERAP/EPCWP and EPVS. Outcomes MACE consist of all-cause mortality, cardiogenic shock, malignant arrhythmias, and the incidence of renal replacement therapy.

A total of 62 samples were selected by consecutive sampling that met the inclusion and exclusion criteria. The samples were observed during hospitalization. The inclusion criteria were: a) Aged ≥18 years and willing to participate by signing a consent form after explanation; b) Acute heart failure (decompensated, *de novo*, and isolated right ventricular failure). The exclusion criteria were: a) AHF patients with moderate-severe mitral stenosis or prosthetic mitral valve; b) Presentation of cardiogenic shock on admission; c) Patients with atrial fibrillation; d) Patients with congenital heart disease; e) Use of a ventilator at the beginning of admission; f) Patients with end-stage chronic kidney disease on hemodialysis; g) Inadequate echocardiography picture; h) Refuse to participate.

The research implementation process follows: 1) Research ethics to the Ethics Commission of the Faculty of Medicine, Udayana University/Prof. dr. I.G.N.G Ngoerah Hospital; 2) A sample of 62 AHF patients undergoing hospitalization were selected who met the inclusion and exclusion criteria; 3) Echocardiography measurements at the beginning of admission (emergency room) to assess ERAP and EPCWP, according to American Society of Echocardiography (ASE) guidelines [13] and Nagueh formula [14], respectively.

The ERAP was determined from the inferior vena cava's expiratory diameter and collapsibility index (IVC) during inspiration and respiration [14]. It was categorized into 3 groups: regular (ERAP 3 mmHg, IVC diameter ≤ 2.1 cm and collapsibility index >50%), intermediate (ERAP 8 mmHg, IVC diameter ≤ 2.1 cm and collapsibility index <50%), and high (ERAP 15 mmHg, IVC diameter >2.1 cm and collapsibility index <50%). The EPCWP was measured by formula 1,24 [E/e'] + 1,9. The echocardiographic measurement was using GE Vivid IQ (GE Healthcare, US) and verified by two echocardiography consultants that were independently and blindly to clinical data; 4) Measurement of EPVS using the Duarte's formula [15] using hemoglobin and hematocrit parameters at the beginning of admission (emergency room). Haemoglobin and hematocrit are routine blood tests and conducted at the laboratory of Prof. dr. I.G.N.G Ngoerah Hospital; 5) Reliability of ERAP/EPCWP was examined using Bland-Altman test; 6) Patients are divided into groups with high ERAP/EPCWP and EPVS based on the cut-off point of Receiver Operating Characteristic (ROC); 7) The patients were followed for MACE during hospitalization.

Comparison of each proportion was analyzed using chi-square (x^2) for categorical data and independent t-test for numerical data. Survival analysis was using the Kaplan-Meier curve and Cox regression test. The data were analyzed using SPSS 26. The confidence level in this study was set at 95%. Ho is rejected if the p-value <0.05.

RESULTS

Data characteristics are presented in Table 1. Most of the samples were male, with a mean age of 57.6 ± 11.9 years. Most clinical presentations of AHF were decompensated AHF (59.7%) with decreased ejection fraction (69.4%). The MACE was found in 28 cases (45.2%), which consisted of cardiogenic shock (22.6%), all-cause mortality (16.1%), malignant arrhythmias (3.2%), and severe acute renal failure requiring renal replacement therapy (RRT) (3.2%).

TABLE 1: Basic Characteristics of the Research Sample.

Basic Characteristics	Total (N=62)
Gender	
Male, n (%)	42 (67.7)
Female, n (%)	20 (32.3)
Age, mean standard deviation	57.6±11.9
Body mass index, mean ± standard deviation	26.50±5.75
Obesity, n (%)	28 (45.2)
Smoking, n (%)	41 (66.1)
Acute Heart Failure	
De novo, n (%)	25 (40.3)
Decompensation (ADHF), n (%)	37 (59.7)
Ejection Fraction (EF)	
EF ≤40%, n (%)	43 (69.4)
EF >40%, n (%)	19 (30.6)
Comorbidities, n (%)	57 (91.9)
Hypertension, n (%)	32 (51.6)
Diabetes mellitus, n (%)	20 (32.3)

Basic Characteristics	Total (N=62)
Coronary heart disease, n (%)	21 (33.9)
Kidney disorders, n (%)	18 (29)
Chronic obstructive pulmonary disease, n (%)	4 (6.5)
Infection/sepsis, n (%)	31 (50)
Major Cardiovascular Events, n (%)	28 (45.2)
Total mortality, n (%)	10 (16.1)
Malignant arrhythmia, n (%)	2 (3,2)
Cardiogenic shock, n (%)	14 (22.6)
Severe acute renal failure, n (%)	2 (3,2)

All numerical data are presented as mean standard deviation.
Categorical data are presented as frequencies (%).

There is a high level of agreement of ERAP/EPCWP between the first and second observer, with a slight mean difference and statistically insignificant (mean difference 0.0002; CI 95% -0.0008 - 0.0011; p=0.742). The best cut-off of ERAP/EPCWP was 0.535 (AUC 0.864; 95% CI 0.767-0.961; p<0.001). The sensitivity and specificity were 92.6% and 78.4%, respectively. The best cut-off of EPVS was 4.895 (AUC 0.773; 95% CI 0.656-0.89; p<0.001). The sensitivity and specificity were 74.1% and 78.4%, respectively. The ERAP/EPCWP ratio ≥ 0.535 and EPVS value ≥ 4.895 are each categorized as risk factors.

The ERAP/EPCWP ≥ 0.535 tend to have mechanical ventilation during hospitalization (22.6% vs. 3.2%; p=0.023), shorter length of stay (3 .29±1.18 vs. 5.00±3.04 days; p=0.005), lower LV stroke volume (45.48±24.20 vs. 55.19±18.99 ml, p=0.034), and lower hemoglobin (12.20±2.49 vs.13.48±2.14 mg/dL, p=0.035).

The EPVS ≥ 4.895 had lower diastolic blood pressure at admission (70.40±14.97 vs. 80.11±16.79; p=0.021). Lower red blood cell (RBC), hemoglobin, hematocrit, and platelet levels were seen in the EPVS ≥4.895 (p<0.05).

ERAP/EPCWP ratio ≥ 0.535 had higher ERAP (13.03 ± 3.49 vs. 9.77 ± 3.94 mg/dL; p = 0.001), as well as the EPVS ≥ 4.895 (12.92 ± 3.25 vs. 10.22 ± 4, 24; p=0.008). Both ERAP/EPCWP ≥ 0.535 or < 0.535 had clinically high ECPWP values (> 15 mmHg). There was no difference in mean EPCWP based on the ERAP/EPCWP ratio group or EPVS value (p>0.05).

TABLE 2: Distribution Table of Sample Characteristics Based on ERAP/EPCWP and EPVS Categories.

Variable	ERAP/EPCWP			EPVS		
	≥ 0.535 (N=31)	< 0.535 (N=31)	p-value	≥ 4,895 (N=27)	< 4,895 (N=35)	p-value
Age, years, mean±SB	58.29±9.52	57.0±14.05	0.674	60.88±12.11	55.14±11.3	0.059
≥70 years, n(%)	5 (16.1)	7 (22.6)	0.520	8 (8)	4 (11.4)	0.072
<70 years, n(%)	26 (83.9)	24 (77.4)		19 (70.4)	31 (88.6)	
Gender						
Male, n(%)	24 (77.4)	18 (58.1)	0.103	18 (66.7)	24 (68.6)	0.874
Female, n(%)	7 (22.6)	13 (41.9)		9 (33.3)	11 (31.4)	
Acute Heart Failure						
De novo, n(%)	14 (45.2)	11 (35.5)	0.437	10 (37)	15 (42.9)	0.643
Decompensation, n(%)	17 (63)	20 (57.1)		17 (45.9)	20 (54.1)	
Comorbidity						
Hypertension, n(%)	18 (58.1)	19 (61.3)	0.796	16 (59.3)	21 (60)	0.953
DM, n(%)	13 (41.9)	14 (45.2)	0.798	14 (51.9)	13 (37.1)	0.247
COPD, n(%)	4 (12.9)	6 (19.4)	0.490	4 (14.8)	6 (17.1)	0.805
CHD, n(%)	10 (32.3)	11 (35.5)	0.788	9 (33.3)	12 (34.3)	0.937
Kidney disorders, n(%)	8 (25.8)	7 (22.6)	0.767	8 (29.6)	7 (20.0)	0.38
Infection/Sepsis, n(%)	16 (51.6)	15 (48.4)	0.799	17 (63)	14 (40)	0.073
BMI, kg/m2, mean±SB	26.65±5.77	26.34 ± 5.83	0.834	25.43±6.16	27.32 ± 5.36	0.204
Obesity, n(%)	17 (54.8)	18 (58.1)	0.798	14 (51.9)	21 (60)	0.521
Smoking, n(%)	23 (74.2)	18 (58.1)	0.180	18 (66.7)	23 (65.7)	0.937
Systolic blood pressure, mmHg, mean ± SB	113.9 ± 28.06	121.4 ± 33.43		109.8 ± 25.36	123.8 ± 33.57	
≤100 mmHg, n(%)	8 (25.8)	10 (32.3)	0.342	10 (37)	8 (22.9)	0.076
>100 mmHg, n(%)	23 (74.2)	21 (67.7)	0.576	17 (63)	27 (77.1)	0.223
Diastolic blood pressure mmHg, mean ± SB	74.12 ± 16.42	77.64 ± 16.89		70.40±14.97	80.11±16.79	
< 60 mmHg, n(%)	9 (29)	7 (22.6)	0.409	9 (33.3)	7 (20)	0.021*
≥ 60 mmHg, n(%)	22 (71.0)	24 (77.4)	0.562	18 (66.7)	28 (80)	0.234
Heart rate, times/minute, mean ± SB	91.3 ± 22.52	93.2 ± 19.70		93.1 ± 23.51	91.6 ± 19.1	
>100 x/minute, n(%)	23 (74.2)	23 (74.2)	0.720	20 (74.1)	26 (74.3)	0.790
≤100 x/minute, n(%)	8 (25.8)	8 (25.8)	1,000	7 (25.9)	9 (25.87)	0.985

Variable	ERAP/EPCWP			EPVS		
	≥ 0.535 (N=31)	< 0.535 (N=31)	p-value	≥ 4,895 (N=27)	< 4,895 (N=35)	p-value
respiratory rate, times/minute, mean ± SB	21.87±2.70	23.48±5.63	0.156	22.66±4.54	22.68±4.45	0.987
Peripheral oxygen saturation %, mean±SB	97.22±2.21	96.67±3.21	0.438	97.33 ± 1.88	96.65±3.27	0.342
Therapy before hospitalization						
RAAS blockers, n(%)	24 (77.4)	27 (87.1)	0.319	24 (88.9)	27 (77.1)	0.230
Diuretics, n(%)	30 (96.8)	29 (93.5)	0.554	25 (92.6)	34 (97.1)	0.408
Beta-blockers n(%)	22 (71)	22 (71)	1,000	17 (63)	27 (77.1)	0.223
MRA, n(%)	28 (90.3)	24 (77.4)	0.167	23 (85.2)	29 (82.9)	0.805
CCB, n(%)	1 (3,2)	5 (16.1)	0.086	1 (3.7)	5 (14.3)	0.162
Oxygen, n(%)	13 (41.9)	16 (51.6)	0.445	13 (48.1)	16 (45.7)	0.849
Mechanical ventilation, n(%)	7 (22.6)	1 (3,2)	0.023*	5 (18.5)	3 (8.6)	0.247
Length of stay, days, mean±SB	3.29 ± 1.18	5.00±3.04	0.005*	3.48 ± 1.36	4.65±2.95	0.060
Echocardiography						
ERAP, cm, mean±SB	13.03±3.49	9.77±3.94	0.001*	12.92±3.25	10.22±4.24	0.008*
EPCWP, mmHg, mean±SB	23.09 ± 8.12	25.83±9.13	0.216	23.28±6.43	25.37±10.08	0.350
SV, ml, mean±SB	45.48±24.20	55.19±18.99	0.034*	48.88±15.69	51.40±19.06	0.581
CO, liters/minute, mean±SB	4.132 ± 2.53	4.98 ± 1.75	0.129	4.48 ± 1.61	4.65±1.95	0.713
SVR, dynes/sec/cm5, mean±SB	1694.0±719	1563.6±748	0.487	1412.9±591	1705.1±687	0.083
TAPSE, cm, mean±SB	1.86 ± 0.43	1.91 ± 0.41	0.679	1.78±0.41	1.96±0.42	0.099
EF, %, mean±SB	35.43±12.38	35.93±14.47		36.66±12.71	34.93 ±13.98	
≤40%, n(%)	22 (71.0)	21 (67.7)	0.783	18 (66.7)	25 (71.4)	0.687
>40%, n(%)	9 (29.0)	10 (32.3)		9 (33.3)	10 (28.6)	
Laboratory						
WBC, 103/µL, mean±SB	12.70±6.20	11.86 ± 5.02	0.561	12.44±6.40	12.16 ± 5.01	0.849
RBC, 106/µL, mean±SB	4.55 ± 0.89	4.51 ± 0.89	0.889	4.10±0.814	4.86±0.79	0.001
HGB, g/dL, mean±SB	12.20±2.49	13.48 ± 2.14	0.035*	10.7±1.45	14.42±1.66	0.001*
Anemia, n(%)	16 (51.6)	7 (22.6)	0.018*	20 (74.1)	3 (8.6)	0,000*
Not anemic, n(%)	15 (48.4)	24 (77.4)		7 (25.9)	32 (91.4)	
HCT, mean±SB	0.37±0.06	0.39±.06	0.208	0.34±0.51	0.42±0.53	0.001*
SC, mg/dL, mean±SB	1.45 ± 0.54	1.78 ± 0.98	0.114	1.74 ± 0.76	1.52 ± 0.83	0.280
SC ≥ 2.5 mg/dL	4 (12.9)	6 (19.4)	0.490	6 (22.2)	4 (11.4)	0.252
SC < 2.5 mg/dL	27 (87.1)	25 (80.6)		21 (77.8)	31 (88.6)	
Sodium, mmol/L, mean±SB	138.58±4.53	138.38±4.25	0.863	138.66±4.57	138.34±4.25	0.775
Sodium disorders, n(%)	10 (32.3)	9 (29)	0.783	8 (29.6)	11 (31.4)	0.879
Normal sodium	21 (67.7)	22 (71)		19 (70.4)	24 (68.6)	
Potassium, mmol/L, mean±SB	4.02 ± 0.81	4.26 ± 0.64	0.214	4.16±0.84	4.13±0.66	0.859
Potassium disorders, n(%)	11 (35.5)	6 (19.4)	0.155	9 (33.3)	8 (22.9)	0.359
Normal potassium, n(%)	20 (64.5)	25 (80.6)		18 (66.7)	27 (77.1)	
Chloride, mmol/L, mean±SB	104.60±5.32	104.92 ± 4.61	0.796	105.30±5.63	104.34±4.36	0.455
GDS, mg/dL, mean±SB	150.9±37.99	149.8±82.5	0.973	150.0±48.05	150.6 ± 74.3	0.973

Numerical data are displayed as mean ± standard deviation (SB). Numerical data analysis was carried out using the independent student t-test. Categorical data are displayed in frequencies (n) and column percentages (%) and analyzed using the Chi-square test.

* = There is a statistical difference between the two groups (p<0.05).

Initial presentation of systolic blood pressure (SBP) ≤100 mmHg and diastolic (DBP) <60 mmHg is more likely to experience MACE. Both stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) tended to be lower in the MACE group. The obese and smoking groups were more likely to experience MACE.

The use of mechanical ventilation during hospitalization tends to have MACE, shorter length of stay, and lower hemoglobin levels. The ERAP was higher in the MACE group (13.75±2.73 vs 9.47±3.95 cm; p<0.001). Both groups with and without MACE had clinically high ECPWP (22.51 ± 6.25 vs. 26.06 ± 10.07 mmHg; p = 0.109).

TABLE 3: Sample Characteristics Based on Major Cardiovascular Events.

Variable	Major Cardiovascular Events		p-value
	Yes (N=28)	No (N=34)	
Age, years, mean±SB	56.32±9.01	58.73±13.92	0.432
≥70 years, n(%)	3 (25)	9 (75)	0.118
<70 years, n(%)	25 (50)	25 (50)	
Gender			
Male, n(%)	22 (52.4)	20 (47.6)	0.098
Female, n(%)	6 (30.0)	14 (70.0)	
Acute Heart Failure			
De novo, n(%)	11 (48)	13 (52)	0.712
Decompensation, n(%)	16 (43.2)	21 (58.6)	
Comorbidity			
Hypertension, n(%)	15 (40.5)	22 (37)	0.374
Diabetes mellitus, n(%)	14 (51.9)	13 (48.1)	0.352
COPD, n(%)	4 (40)	6 (60)	0.720
Coronary heart disease, n(%)	12 (57.1)	9 (42.9)	0.175
Kidney disorders, n(%)	13 (39.4)	20 (60.6)	0.330
Infection/Sepsis, n(%)	13 (41.9)	18 (58.1)	0.610
Body mass index, kg/m2, mean±SB	27.24 ± 5.54	25.88±5.9	0.359
Obesity, n(%)	18 (51.4)	17 (48.6)	0.259
Smoking, n(%)	21 (51.2)	20 (48.8)	0.180
Initial inpatient systolic blood pressure, mmHg, mean±SB	109.96±31.28	124.11±29.41	0.072
≤100 mmHg, n(%)	10 (55.6)	8 (44.4)	0.293
>100 mmHg, n(%)	18 (40.9)	26 (59.1)	
Initial inpatient diastolic blood pressure, mmHg, mean±SB	71.82±16.78	79.23 ± 15.95	0.08
< 60 mmHg, n(%)	9 (56.3)	7 (43.8)	0.301
≥ 60 mmHg, n(%)	19 (41.3)	27 (58.7)	
Initial heart rate of hospitalization, times/minute, mean ± SB	92.75±23.45	91.91±19.11	0.877
>100 x/minute, n(%)	20 (43.5)	26 (56.5)	0.652
≤100 x/minute, n(%)	8 (50)	8 (50)	
Initial inpatient respiratory rate, times/minute, mean ± SB	22.32±4.50	22.97±4.46	0.573
Initial inpatient peripheral oxygen saturation, %, mean±SB	97.28±2.29	96.67±3.09	0.391
Therapy before hospitalization			
RAAS blockers, n(%)	22 (43.1)	29 (56.9)	0.490
Diuretics, n(%)	26 (44.1)	33 (55.9)	0.443
Beta-blockers n(%)	21 (47.7)	23 (52.3)	0.526
MRA, n(%)	23 (44.2)	29 (55.8)	0.737
CCB, n(%)	2 (33.3)	4 (66.7)	0.540
Oxygen supplementation, n(%)	13 (44.8)	16 (55.2)	0.961
Mechanical ventilation during treatment, n(%)	8 (100)	0 (0)	0.001*
Length of stay, days, mean±SB	2.85±1.00	5.20 ± 2.77	<0.001*
Echocardiography			
ERAP, mean±SB	13.75 ± 2.73	9.47±3.95	0.001*
EPCWP, mmHg, mean±SB	22.51±6.25	26.06 ± 10.07	0.109
SV, ml, mean±SB	48.50±15.8	51.79±18.9	0.467
CO, liters/minute, mean±SB	4.39 ± 1.42	4.73 ± 2.07	0.457

Variable	Major Cardiovascular Events		p-value
	Yes (N=28)	No (N=34)	
SVR, dyne/sec/cm5, mean±SB	1440.64 ± 682.80	1690.88 ± 626.22	0.138
TAPSE, cm, mean±SB	1.88 ± 0.48	1.89 ± 0.37	0.892
EF, %, mean±SB	37.67±11.04	34.04 ± 14.97	
≤40%, n(%)	19 (44.2)	24 (55.8)	0.291
>40%, n(%)	9 (47.4)	10 (52.6)	0.816
Laboratory			
WBC, 103/µL, mean±SB	13.13±6.36	11.59±4.90	0.288
RBC, 106/µL, mean±SB	4.52 ± 0.89	4.54 ± 0.89	0.918
HGB, g/dL, mean±SB	11.69 ± 2.16	13.78±2.17	0.001*
Anemia, n(%)	17 (37.9)	6 (26.1)	<0.001*
Not anemic, n(%)	11 (28.2)	28 (71.8)	
HCT, mean±SB	0.36±0.05	0.40±0.06	0.06
SC, mg/dL, mean±SB	1.75±0.60	1.51 ± 0.93	0.253
S.C≥2.5 mg/dL, n(%)	6 (60)	4 (40)	0.303
SC < 2.5 mg/dL, n(%)	22 (42.3)	30 (57.7)	
Sodium, mmol/L, mean±SB	138.50±4.71	138.47±4.12	0.979
Sodium disorders (hypo/hypernatremia), n(%)	19 (44.2)	24 (55.8)	0.816
Normal sodium, n(%)	9 (47.4)	10 (52.6)	
Potassium, mmol/L, mean±SB	4.05 ± 0.83	4.21 ± 0.66	0.413
Potassium disorders (hypo/hyperkalemia), n(%)	17 (37.8)	28 (62.2)	0.057
Normal potassium, n(%)	11 (64.7)	6 (35.5)	
Chloride, mmol/L, mean±SB	104.63±5.11	104.87±4.86	0.854
GDS, mg/dL, mean±SB	157.75±39.56	144.32 ± 78.41	0.414

Numerical data are displayed as mean ± standard deviation (SB). Numerical data analysis was carried out using the independent student t-test. Categorical data were displayed in frequency (n) and percentage (%) and analyzed using the Chi-square test.
* = There is a statistical difference between the two groups (p<0.05)

The AHF patients with an ERAP/EPCWP ratio ≥ 0.535 have a significantly 6 times higher risk of experiencing MACE during hospitalization (CI 95% 2.35 - 15.27; p<0.001).

The AHF patients with an EPVS ratio ≥ 4.895 had a significantly 2.73 times higher risk of experiencing MACE during hospitalization (95% CI 1.48 - 5.05; p<0.001).

TABLE 4: Table of Distribution of ERAP/EPCWP and EPVS Ratios Based on Major Cardiovascular Events and Results of Independent Cox Regression Analysis.

Variable	Major Cardiovascular Events		RR (95% CI)	Adjusted HR (95% CI)	p-value
	Yes (N=28)	No (N=34)			
ERAP/EPCWP					
≥ 0.535, n(%)	24 (77.4)	7 (22.6)	6.00 (2.35 - 15.27)	8,89 (2.93 – 26.97)	<0.001*
< 0.535, n(%)	4 (12.9)	27 (87.1)			
EPVS					
≥ 4,895, n(%)	19 (70.4)	8 (29.6)	2.73 (1.48 – 5.05)	5.04 (1.89 -13.44)	<0.001*
< 4.895, n(%)	9 (25.7)	26 (74.3)			

* = There is a statistical difference between the two groups (p<0.05).

Based on Kaplan-Meier curve analysis, the proportion of cumulative survival on the fifth day in the ERAP/EPCWP ≥ 0.535 was lower compared with the ERAP/EPCWP < 0.535 (19.6 vs 86.5%; p<0.001). The fifth-day cumulative survival proportion was lower in the EPVS ≥ 4,895 (29.6% vs. 71.7%; p<0.001). After adjusting with confounding variables (age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary heart disease, obesity, smoke, EF ≤ 40%, creatinine ≥ 2.5 mg/dL, sodium disorders, potassium disorders, systolic blood pressure < 100 mmHg, diastolic blood pressure < 60 mmHg, heart rate≥100 times/minute, peripheral oxygen saturation, anemia, and mechanical ventilation during hospitalization), the ERAP/EPCWP ratio ≥ 0.535 was a significant predictor of MACE in AHF patients during hospitalization (adjusted HR 8.899; 95% CI 2.936-26.972; p<0.001). In the final Cox regression model, MACE also significantly influenced by anemia (adjusted HR 2.604; 95% CI 1.18-5.73; p=0.017).

The EPVS ≥ 4.895 is a significant independent predictor of MACE in AHF patients during hospitalization (adjusted HR 5.046; 95% CI 1.893-13.449; p<0.001). In the final model of Cox regression, there are other variables that also significantly influenced MACE: age ≥70 years old (adjusted HR 4.582; 95% CI 1.185-17.724; p=0.027) and coronary artery disease (adjusted HR 2.968; 95% CI 1.022-8.621; p=0.045)

DISCUSSION

In the ESCAPE study, RAP/PCWP at interquartile 3 (0.62-1.21) was associated with an increased risk of death and hospitalization in advanced heart failure patients within 6 months (HR 1.16; 95% CI 1-1.4; p<0.05)[6]. Another study found that RAP/PCWP at interquartile 4 (≥0.75) had increased risk of all caused mortality compared with interquartile 1 even after justifying age, gender, mean arterial pressure (MAP), RAP, cardiac index (CI), pulmonary vascular resistance (PVR), and estimated glomerular filtration rate (EGFR), the RAP/PCWP ratio was still associated with mortality (adjusted HR 2.4; 95% CI 1.4-39; p<0.05)[16]. This present study had a lower cut-off because of using ROC and divided into 2 groups. Based on the mean RAP and PCWP, heart failure patients in the Grodin et al. and ESCAPE study were more congestive, and the MACE group in that study had higher ERAP/EPCWP value [26]. There was a significant difference in ERAP based on ERAP/EPCWP and EPVS, but not EPCWP. This may indicate that the increase of ERAP/EPCWP was largely influenced by the increase of ERAP.

A multicenter study showed that pre-hospital EPVS >5.5 had worse outcomes in patients with decompensated AHF (adjusted OR 4.2; 95% CI 1.10 – 19.67; AUC = 0.85 (0.82-0.89))[17]. The EPVS ≥5.28 was associated with worse outcomes (adjusted OR 1.06; 95% CI 1.03–1.09; p<0.001; AUC 0.667 (0.653–0.681))[18]. This study found the cut-off of EPVS at 4.895 (95% CI 0.656-0.89; p<0.001; AUC 0.773, sensitivity 74.1% and specificity 78.4%). The differences might be caused by higher mean hemoglobin and hematocrit from the previous studies [17].

The RAP/PCWP ratio was associated with a low right ventricular stroke work index (SWI) (RAP/PCWP ≥ 0.75 with a median SWI of 3.5 (2.7-7.3) gm/m2 per beat; p<0.0001)[16]. The ESCAPE study also found similar results (RAP/PCWP ≥ 0.62 with median SWI 5.5 (4-7.6) gm/m2 per beat; p<0.0001)[6]. In the ESCAPE study, it was found that a RAP/PCWP ratio ≥ 0.62 was associated with a lower CI (median 1.8 (1.5-2.2) liters/minute/m2, p=0.049) and higher PVR (median 3.6 (2-4.7) woods units, p=0.003). These findings strengthen the theory regarding the interdependence of the right and left sides of the heart. A small SWI value will cause a decrease in left ventricular preload, which will further reduce cardiac output if it was compensated inappropriately. An increase in left ventricular filling pressure can also cause a backward effect so that there is an increase in pulmonary vascular resistance and pressure in the right ventricular space[19].

High RAP/PCWP values are associated with decreased kidney function, as indicated by serum creatinine, blood urea nitrogen (BUN), and creatinine clearance (p≤0.005)[6]. The decrease in kidney function can be caused by decreased cardiac index, which causes systemic and renal hypoperfusion. The AHF patients tend to have increased central venous pressure, which can be transmitted to the glomerular efferent arteriole and reduced the glomerular filtration pressure gradient. Transmission of pressure to the renal vein also causes an increase in renal interstitial pressure, which led to renal parenchymal hypoxia [20].

Higher ERAP/EPCWP was associated with using a mechanical ventilator during hospitalization (p=0.023). It was associated with MACE (p=0.001). However, after controlling for other variables, using a ventilator during hospitalization did not significantly increase the risk of MACE (adjusted HR 2,224; 95% CI 0.935-5.292; p=0.071). Higher ERAP/EPCWP was associated with the incidence of decompensated pulmonary hypertension and associated with acute respiratory failure. In conditions of increased PVR, intubation and mechanical ventilation posed challenges from sedative agents, lung recruitment, and applied positive pressure. These may decrease the venous return and right ventricular afterload [21].

In this study, the ERAP/EPCWP ratio had higher adjusted hazard ratio than EPVS. The ERAP/EPCWP described hemodynamic congestion, which can occur several days or weeks before the clinical congestion [22]. High EPVS values are only associated with heavier plasma volumes (NYHA III and IV) [17]. Higher ERAP/EPCWP might be able to determine MACE more thoroughly before clinical congestion appears and at the early phase of AHF with less plasma volume.

The ERAP/ECPWP ratio also had the potential for hemodynamic monitoring, early predictors of decreased renal function, and even the need for RRT. In the setting of AHF, monitoring urine output, renal function, and hemodynamics is essential to achieve optimal therapy [23]. Using jugular venous pressure (JVP) to evaluate congestion may lead to overestimated fluid status and PCWP. It might lead to hypotension and decreased cardiac index [24]

In the PARADISE registry study, EPVS >5.12 was associated with a high risk of mortality during hospitalization (adjusted OR 1.47; 95% CI 1.04 – 2.09; p=0.029)[25]. In the ASCEND-HF study, EPVS with Duarte's formula at initial admission was associated with cardiovascular mortality and rehospitalization at 30 days (adjusted OR 1.07; 95% CI 1.00 – 1.15; p=0.05)[12]. The EPVS >5.5 ml/g had a poor outcome in patients with decompensated AHF (adjusted OR 4.2; 95% CI 1.10 – 19.67; p<0.05; AUC = 0.85; 95% CI 0.82-0.89)[17]. EPVS score ≥5.28 was associated with worse outcomes (adjusted OR 1.06; 95% CI 1.03–1.09; p<0.001; AUC 0.667 (0.653–0.681))[18].

Higher EPVS values were associated with higher BUN, serum creatinine, use of norepinephrine, and RRT ($p<0.05$)[18]. In AHF, an increased EPVS was accompanied by excessive renin-angiotensin system activation. Excessive neurohormonal activation will cause water and sodium retention, worsening hemodynamic congestion, and extravascular edema [26]. High EPVS is associated with a higher mean heart rate, which also increases myocardial oxygen consumption, progressive dilatation of the left ventricle, remodeling, heart wall stress, and leading to ischemia [27].

The EPVS is associated with an increased risk of acute renal failure (12.32 vs. 3.52%; $p<0.001$) and RRT (5.96% vs. 0.60%; $p<0.001$)[18]. Congestion in the splanchnic veins will initiate the sympathetic nervous system, baroreceptors, and hepatorenal reflexes, causing increased efferent activity of the kidneys and cardiopulmonary region. Subsequently, renal vasoconstriction will occur, followed by the release of renin, causing water and sodium reabsorption, reduced renal blood flow due to increased renal venous pressure and ultimately decreased in renal function [28,29].

Anemia in this study was an independent predictor of MACE in AHF (adjusted HR 2.604; 95% CI 1.183-5.731; $p=0.017$). Anemia increased the short-term risk of all-cause mortality (OR 1.91; 95% CI 1.31–2.79; $p<0.01$)[30]. Anemia can occur in 55% of chronic heart failure patients and 80% of AHF patients. Anemia contributes to poor outcomes in AHF through multiple mechanisms. Patients with anemia experienced the reduction of oxygen delivery to metabolic tissues. A reduced number of circulating red blood cells results in a decrease of blood viscosity, leading to a reduction in systemic peripheral vascular resistance. At the same time, low level of hemoglobin will be activated nitric oxide-mediated vasodilation, leading to hypotension. The heart is chronically overworked, ultimately leading to ventricular hypertrophy and myocardial remodeling. Renin-angiotensin system (RAAS) inhibitors increase the risk of anemia. This was related to disturbance of erythropoietin synthesis by RAAS inhibitors [1] .

This study had limitations. First, noninvasive EPCWP parameters using the Nagueh formula are less reliable in cases of moderate and severe mitral valve disease, atrial fibrillation, and congenital heart disease. This study also excluded AHF patients who had these comorbidities. Second, the given treatment was wholly based on the doctor's expertise in charge, and there might be treatment differences during hospitalization. Third, this study did not analyze other confounding variables, such as NT-Pro BNP and troponin, which are already known to be associated with MACE.

CONCLUSION

A high ERAP/EPCWP (≥0.535) and high EPVS (≥4.895) were significant independent predictors of major cardiovascular events during hospitalization in AHF patients.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

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ETHICS IN RESEARCH

This research received approval from the research ethics committee of Prof. Dr. IGNG Ngoerah Hospital/Faculty of Medicine, Udayana University.

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