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Comparison Between 6 Minutes Walking Distance (6MWD), Changes in Rate Pressure Product (RPP) and Heart Rate Walking Speed Index (HRWSI) of 6 Minutes Walk Test (6MWT) Pre-Discharge as a Predictor Major Adverse Cardiac Event (MACE) in Patients with Acute Heart Failure

Komang Aditya Yudistira*, AAA Dwi Adelia Yasmin, and Nyoman Wiryawan

Department of Cardiology and Vascular Medicine
Faculty of Medicine Udayana University, Prof. dr. IGNG Ngoerah, Denpasar, Indonesia

E-mail: adityayds@gmail.com; adeliajasmine@gmail.com; dr_wiryawan@yahoo.com

*Corresponding author details: Komang Aditya Yudistira; adityayds@gmail.com

ABSTRACT

Background: Heart failure (HF) is a significant cause of morbidity and mortality worldwide in middle-aged and older adults. A simple 6MWT assay can provide useful information noninvasively for risk stratification and patient prognosis. A potential parameter is incorporating pulse and blood pressure values into RPP and pulse rate with WS into HRWSI. It is easy to assess the risk of rehospitalization and mortality in HF patients and can be compared with conventional predictors and predictors with expensive biomarker examinations. ***Aims:*** To determine the role and comparison of 6MWD, RPP changes and HRWSI in patients with acute heart failure outcomes. ***Methods:*** This study was conducted with a prospective observational cohort design. This study is a collaborative study to determine whether 6MWD, changes in RPP and HRWSI at 6MWT pre-discharge can predict MACE events within 90 days after hospital discharge in patients with AHF. ***Result:*** The AUC value of 6WMD was 0.338, with a cut-off of 251.0 meters. The sensitivity and specificity of 6MWD were 72% and 63.5%. The AUC value of RPP changes was 0.692 with a cut point 3139.5. The sensitivity and specificity of RPP changes for MACE prediction were 90.0% and 48.0%. HRWSI AUC value was 0.721, with a cut-off of 22.66. The sensitivity and specificity of HRWSI was 80.0% and 64.0%. Low 6MWD had a survival of 54.6%, while patients with GJA who had high 6MWD had an 84.6% survival. Low RPP changes had a survival of 92.3%, and patients with high RPP changes had a survival of 58.8%. Low HRWSI had 88.9% survival, and patients with high RPP changes had 52.5% survival. ***Conclusion:*** 6MWD, changes in RPP and HRWSI of 6MWT are potential predictors for MACE within 90 days post hospital discharge in patients with acute heart failure.

Keywords: 6-minutes walk test; 6-minutes walking distance; rate pressure product; heart walking speed index; major adverse cardiac event; acute heart failure

INTRODUCTION

Heart failure (GJ) is a clinical syndrome characterized by a series of symptoms (shortness of breath, orthopnoea, swelling of the lower extremities) and signs (increased jugular venous pressure, pulmonary congestion), which are often caused by structural and/or functional abnormalities of the heart causing decreased cardiac output and/or increased intracardiac pressure. Heart failure is a significant cause of morbidity and mortality in middle-aged to older adults worldwide[1]. Based on data from the 2013 Basic Health Survey, the most common heart disease in adults is heart failure. The prevalence of heart failure in Indonesia was 478,000 people in 2013, which tends to increase yearly. Based on the 2020 Indonesia Health Profile, GJ disease is the biggest burden for the state, spending around 8.3 trillion rupiah in health costs, and the number of cases recorded is 11,592,990 [2].

Based on research by Reyes et al., the percentage of rehospitalization within 30 days in patients with heart failure in Indonesia is 7%, and the mortality within 30 days is 17%. This mortality percentage is among the highest compared to other countries such as Malaysia, the Philippines, Vietnam and the United States[3]. This causes GJ disease to be a frequent cause of morbidity and mortality worldwide. Therefore, the composite end-point in the form of a major adverse cardiac event (MACE) is the primary outcome often studied in prognostic studies in cardiovascular disease populations. MACE is a major cause of increased morbidity and mortality in GJ patients.[4] Patient stratification based on the risk of rehospitalization and mortality is important for optimizing therapeutic strategies for patients and healthcare systems.

Several symptoms related to functional capacity appear in GJ patients, such as decreased aerobic capacity, decreased muscle strength, low physical activity and exercise intolerance, which are related to the prognosis of these patients. Functional capacity is an important component in evaluating GJ patients and is a factor associated with survival in patients with heart failure.

Methods for assessing functional capacity and exercise tolerance in heart failure patients can be assessed by the New York Heart Association (NYHA) functional status classification; the gold standard examination of exercise capacity is the direct cardiorespiratory assessment of peak oxygen consumption (VO2 peak) in a maximal exercise test (cardiopulmonary exercise test; CPET) and assessment of daily activity performance through a submaximal exercise test, namely the 6-minute walk test (6MWT) which is a test is simple and easy to perform and well tolerated by patients. 6MWT is considered an alternative to CPET for risk stratification in GJ patients. Although the CPET test with metabolic gas changes is the gold standard in assessing activity ability, this test is rarely available. Simple checks such as 6MWT are quite easy to do and sensitive to detect changes in quality of life. This examination is carried out independently by a submaximal test, and its intensity can mimic daily activities in patients with mild to moderate heart failure. A decrease in 6-minute walking distance (6MWD) was an independent predictor of increased mortality in patients with left ventricular systolic dysfunction. The assessment includes the holistic response of all systems during exercise and the patient's global capabilities. Study data show a correlation of 6MWD with maximal oxygen consumption and a predictive association with rehospitalization and mortality in heart failure patients. The assessment includes the holistic response of all systems during exercise and the patient's global capabilities. Study data show a correlation of 6MWD with maximal oxygen consumption and a predictive association with rehospitalization and mortality in heart failure patients. The assessment includes the holistic response of all systems during exercise and the patient's global capabilities. Study data show a correlation of 6MWD with maximal oxygen consumption and a predictive association with rehospitalization and mortality in heart failure patients.[5].

Both pulse and blood pressure values are incorporated as the rate pressure product (RPP), an indirect index of myocardial oxygen consumption that predicts cardiac function, morbidity and mortality in patients with cardiovascular disease. Myocardial oxygen consumption is an important indicator of cardiac load[6]. This simple RPP measurement can provide meaningful information to stratify risk and provide patient prognostic information[7]

Multivariate analysis of clinical variables has helped identify the most significant predictors of survival, and predictive models have been developed and validated, but data gaps remain. Although RPP is strongly associated with important cardiovascular morbidity and mortality indices, its significance in GJ patients has yet to be well defined. Research on RPP as a predictor of mortality and rehospitalization in patients with heart failure still needs to be completed and much debated. A study by Verma et al. showed that changes in RPP – an increase in RPP from baseline until the patient was discharged – are associated with an increase in mortality within 30 days and the incidence of rehospitalization in heart failure patients with decreased ejection fraction or preserved ejection fraction.[7] In another study conducted by Nugiaswari et al., a strong correlation was found with the direction of a negative relationship between increased RPP and 6MWD in patients with chronic heart failure, where the less the RPP increased during the six-minute walk test, the further the 6MWD on the six-minute walk test. In patients with chronic heart failure and vice versa. Increased RPP was shown to be independently associated with decreased 6MWD on the six-minute walk test in heart failure patients[8]

A simple 6MWT assay can provide useful information noninvasively for risk stratification and patient prognosis. Pulse rate, WS and systolic blood pressure can be potential predictors and prognostic information in patients with GJ. A potential parameter is incorporating pulse and blood pressure values into RPP and pulse rate with WS into HRWSI. Assessing the risk of rehospitalization and mortality in GJ patients is easy and can be compared with conventional predictors and predictors with expensive biomarker examinations. Based on this background, evaluation and assessment of 6MWD, HRWSI and changes in RPP at 6MWT pre-discharge can be an additional examination that can be performed and is useful as a guide in the therapy and evaluation of patients with heart failure.

METHODS

This study was conducted with a prospective observational cohort design. This study is a collaborative study to determine whether 6MWD, changes in RPP and HRWSI at 6MWT pre-discharge can predict MACE events within 90 days after hospital discharge in patients with ARF.

The research took place at Prof. dr. I GNG Ngoerah, Denpasar, Hospital Bali. The 6MWT test examination was carried out on the 3rd floor of the Integrated Heart Services Building at Prof. Hospital. dr. I GNG Ngoerah. Inclusion criteria: 1. Patients with AHF who are ≥18 years old and willing to participate by signing a consent form after explanation; 2. Patients with recurrent or de novo AHF or acute decompensated heart failure (ADHF); 3. Patients with HFpEF, HFmrEF or HFrEF. Exclusion criteria: 1. Musculoskeletal disorders, cognitive impairments, chronic lung disease, visual impairments that impede movement; 2. Impaired walking for other reasons; 3. Unable to complete the six-minute walk test; 4. The sampling technique used in this study was non-probability sampling, namely using consecutive sampling; 5. Seventy samples with GJA were selected who were hospitalized at Prof. Hospital. dr. I GNG Ngoerah. All samples were given medical therapy according to the guidelines for the management of CHF based on the European Society of Cardiology[9]

After undergoing treatment and being eligible to be discharged, the sample was delivered to the cardiac intensive care room for a 6MWT examination (assessment of 6MWD, HRWSI and calculation of RPP). Patients are calculated HRWSI values with formulas[10,11]

$$\text{HRWSI} = \frac{\text{laju nadi}}{\text{Kececepatan Jalan } \left(\frac{\text{meter}}{\text{menit}}\right) \times\ 10}$$

Patients were divided into normal or decreased RPP groups. RPP changes are calculated using a formula[12]
Changes in RPP

$$= \left(\text{TDS}_{\text{peak 6MWT}} \times \text{HR}_{\text{peak 6MWT}}\right) - \left(\text{TDS}_{\text{baseline}} \times \text{HR}_{\text{baseline}}\right)$$

TDS: systolic blood pressure
HR: Rate pulse

Patients are then followed up every 4 weeks using text messages or telephone to evaluate the outcome of MACE events (rehospitalization or death from cardiovascular disease). Data on the causes of rehospitalization were traced based on medical record data at the hospital where the patient was undergoing treatment or based on the medical summary at the time of discharge. Suppose the patient dies during treatment at the hospital. In that case, data on the cause of death is traced based on medical record data at the hospital where the patient is undergoing treatment or through proof of a death certificate issued by the hospital/doctor.

If the patient dies at home, deaths from cardiovascular disease are identified through in-depth interviews with family members with first-degree relatives (parents, siblings or children) regarding the chronology of sample deaths and evidenced by a death certificate issued by the civil registry office.

If the patient has MACE, the time interval between the patient being discharged from the hospital (when the patient was first included in the study) and the subsequent event of hospitalization or death is recorded in days.

All data collected in each group was then analyzed using the SPSS program. Data analysis was carried out with descriptive analysis, normality test with Kolmogorov-Smirnov test, and homogeneity test with Levene's test. Receiver Operating Characteristic (ROC) curve analysis to obtain the best cut-off point to state 6MWD, HRWSI and 6MWT pre-discharge RPP values as risk factors for MACE events. In this analysis, 6MWD, HRWSI and RPP changes at 6MWT will be categorical variables, while MACE events will be reference variables. This analysis will form a ROC curve consisting of the X and Y axes. The X axis is 1-specificity, and the Y axis is sensitivity. The best cut-off point is 6MWD; changes in RPP and HRWSI at a certain 6MWT produce the highest accuracy as a predictor of MACE events. Survival Analysis with the Kaplan-Meier Curve was used to assess the outcome of MACE events based on 6MWD, HRWSI and changes in RPP values at 6MWT pre-discharge. A multivariate test with logistic regression was performed to identify risk factors that were independently associated with predictors of MACE. Cox regression analysis carried out the interaction between 6MWD values and changes in RPP and HRWSI at 6MWT on MACE.

The level of confidence in this study is 95%. Ho is rejected if the value of $p < 0.05$.

RESULTS

This study obtained 70 subjects with CHF patients hospitalized at Prof. dr. I GNG Ngoerah. The characteristics of the study subjects can be seen in Table 1. Subjects were 56.28 ± 14.53 years old, dominated by male sex (62.9%), not obese (91.4%), suffered from hypertension (55 .7%), did not suffer from DM (68.6%), did not smoke (60%), did not suffer from kidney failure (92.9%), did not suffer from stroke (95.7%), did not suffer from dyslipidaemia (71.4 %), no history of infection (72.9%) and all adherent to treatment.

The characteristics of the research subjects based on the diagnosis (Table 2) show the majority. The cause of AHF in this study was the result of coronary heart disease (CHD), which was 37.1% of the study subjects. Classification of heart failure, according to the ejection fraction of 62.9% of study subjects, was categorized as heart failure with reduced ejection fraction (HFrEF). 52.9% of the study subjects had their first episode of hospitalization due to cardiovascular disease. The incidence of cardiogenic Shock during hospitalization in the study subjects occurred 17.1%, and the average length of stay in the study subjects was 6.2 ± 2.9 days. Characteristics of Laboratory Examination Results and Echocardiography of Study Subjects are presented in Table 3.

MACE events occurred in 25.7% of subjects, with MACE events in rehospitalization due to cardiovascular events 27.1% and MACE events resulting in cardiovascular deaths of 10.0% (Table 4).

TABLE 1: Characteristics of research subjects.

Characteristics	N=70
Age (years), n (%)	
≥60 years	40 (57.1)
60 years	30 (42.9)
Gender, n (%)	
Man	44 (62.9)
Woman	26 (37.1)
Obesity, n (%)	
Yes	6 (8,6)
No	64 (91.4)
Hypertension, n (%)	
Yes	39 (55.7)
No	31 (44.3)
Diabetes Mellitus, n (%)	
Yes	22 (31.4)
No	48 (68.6)
Smoking, n (%)	
Yes	28 (40.0)
No	42 (60.0)
Kidney Failure, n (%)	
Yes	5 (7,1)
No	65 (92.9)
Strokes, n (%)	
Yes	3 (4,3)
No	67 (95.7)

Characteristics	N=70
Strokes, n (%)	
Yes	19 (27.1)
No	51 (72.9)
Infection, n (%)	
Yes	19 (27.1)
No	51 (72.9)
Treatment Adherence, n (%)	
Yes	70 (100.0)
No	0 (0,0)
Dyslipidaemia, n (%)	
Yes	20 (28.6)
No	50 (71.4)

TABLE 1: Diagnostic characteristics of research subjects.

Characteristics	N=70
Causes of GJA, n (%)	
CHD	26 (37.1)
HHD	10 (14,3)
Acute myocardial infarction	22 (31.4)
RHD	2 (2,9)
VHDACHD	2 (2,9)
PPCM	2 (2,9)
SLE CM	3 (4,3)
Chemotherapy-induced CM	1(1,4)
DCM	1(1,4)
GJ category by ejection fraction, n (%)	
HFpEF	17 (24,3)
HFmrEF	9(12,9)
HFrEF	44 (62.9)
Hospitalization Status	
New	37 (52.9)
Rehospitalization	33 (47.1)
Cardiogenic Shock Incidence, n (%)	
Yes	12 (17,1)
No	58(82.9)
Length of stay (days), mean ± SD	**6.2 ± 2.9**

TABLE 2: Characteristics of Laboratory Examination Results and Echocardiography of Study Subjects.

Parameter	
Laboratory, mean ± SD	
WBC	11.92 ±5.045
HB	12.29 ± 2.195
HCT	41.85 ± 36.03
PLT	275.46 ± 123.246
BUN pre-discharge	21.86 ± 14.45
SC pre-discharge	1.28 ± 0.75
Na	137.28 ± 4.20
K	5.18 ± 11.93
cl	102, 18 ± 6.07
NT proBNP	1014.0 ± 1180.09
6MWT	
METs, mean ± SD	
Walking speed(meters/minute), mean ± SD	3.32 ± 0.71
6MWD (meters), mean ± SD	44.51 ± 11.68
HRWSI, mean ± SD	265.04 ± 69.61
RPP change, median (IQR	23.16 ± 8.63
Echocardiography, mean ± SD	5191 (2258-7575)
EF (%)	39.80 ± 16.20

TABLE 3: Characteristics of MACE Events.

MACE events, n (%)	
Yes	20 (28.6)
No	50 (71.4)
MACE rehospitalization, n (%)	19 (27.1)
MACE cardiovascular death, n (%)	7 (10.0)

The ROC curve was analyzed and described to obtain the 6MWD cut-off, RPP changes, and HRWSI for MACE events. The cut-off values obtained can be seen in Table 5. The AUC value of 6WMD was 0.338, with a cut-off point of 251.0, having a sensitivity of 72% and a specificity of 63.5%.

The AUC value of RPP changes was 0.692, with a cut point of 3139.5, having a sensitivity of 90.0% and a specificity of 48.0%. HRWSI AUC value is 0.721 with a cut point of 22.66, which has a sensitivity of 80.0% and a specificity of 64.0%.

TABLE 4: ROC Analysis Results.

Variable	AUC	P value	Cut value	Sensitivity	specificity
6MWD	0.338	0.035	251	72%	63.5%
Changes in RPP	0.692	0.014	3139,5	90.0%	48.0%
HRWSI	0.721	0.004	22.66	80.0%	64.0%

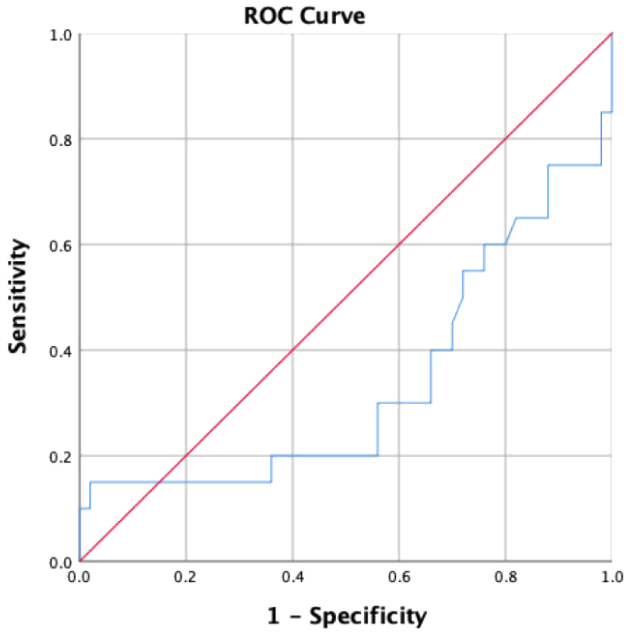

FIGURE 1: ROC Curve 6 Minutes Walking Distance.

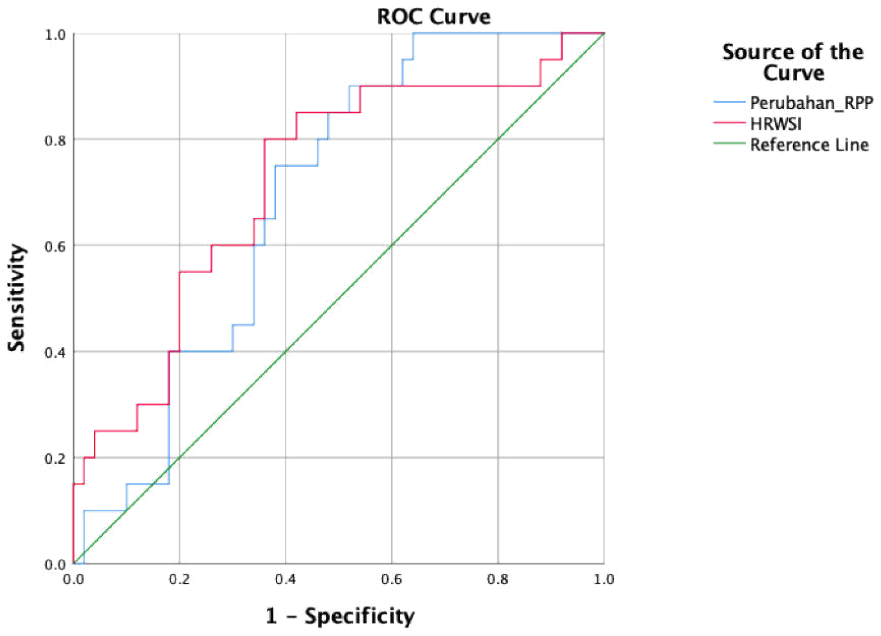

FIGURE 2: ROC curve for changes in RPP and HRWSI.

Follow-up was carried out for 90 days. Throughout the study period, 20 (28.6%) MACE events were found, which in this survival analysis were events that were assessed as the outcome. Another 50 subjects completed the observation period without any MACE events and were censored due to the end of the study period.

The survival analysis results based on the Kaplan-Meier curve showed that patients with low 6MWD had a survival of 54.6%, while patients with high 6MWD had a survival of 84.6%.

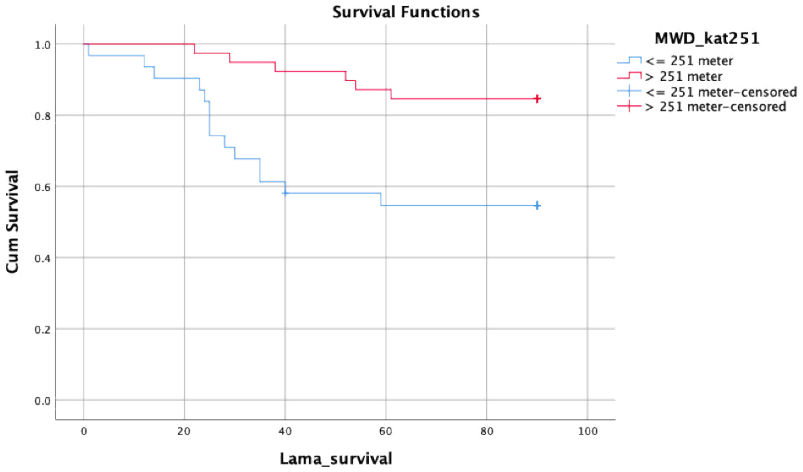

FIGURE 3: Kaplan-Meier 6MWD survival curve as a predictor of MACE events.

The survival analysis results based on the Kaplan-Meier curve (Figure 3) showed that patients with low RPP changes had a survival of 92.3%, while patients with high RPP had a survival of 58.8% (Figure 4).

In addition, the survival analysis based on the Kaplan-Meier curve showed that patients with low HRWSI had an 88.9% survival, while patients with high RPP changes had a survival of 52.5% (Figure 5).

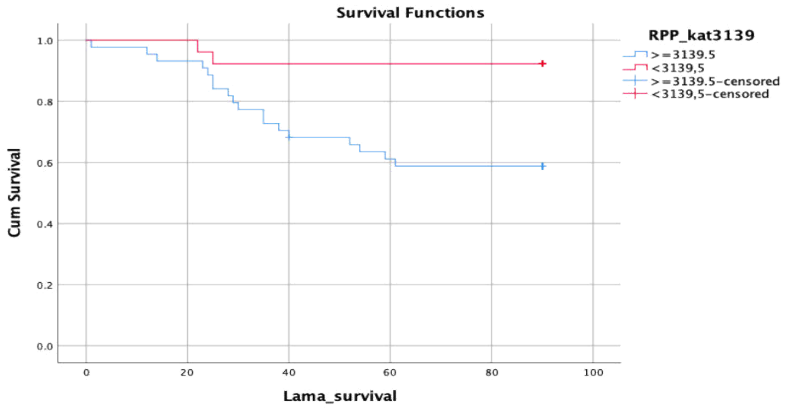

FIGURE 4: Kaplan-Meier survival curve for changes in RPP as a predictor of MACE events.

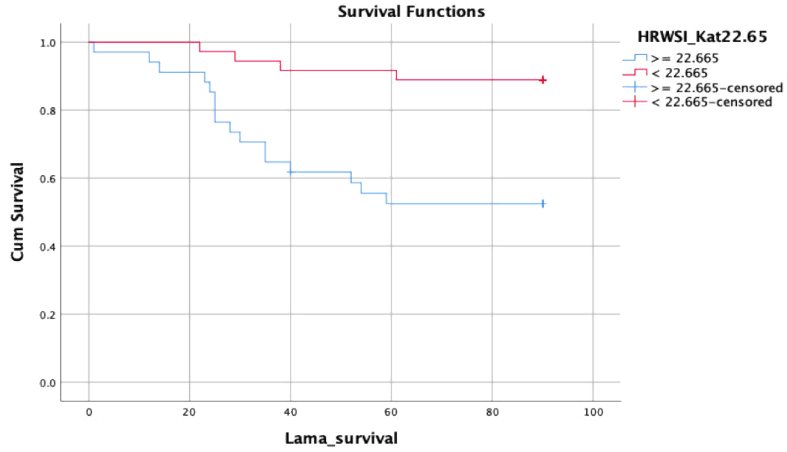

FIGURE 5: Kaplan-Meier HRWSI survival curve as a predictor of MACE events.

Based on the multivariate Cox regression analysis in Table 6, the variables that influence the incidence of MACE in ARF patients are diabetes mellitus (HR=3.259 [95% CI 1.342-7.917]; p=0.009) and 6MWD < 251 meters (HR= 5.675 [95% CI 3.611-50.839]; p=0.000).

Based on the multivariate Cox regression analysis in Table 7, the variables that influence the incidence of MACE in patients with ARF are diabetes mellitus (HR=2.586 [95% CI 1.008 – 6.634]; p=0.048) and change in RPP > 3139.5 (HR=10.007 [95% CI 2.078 – 48.199]; p=0.004).

Based on the multivariate Cox regression analysis in Table 8, the variables that influence the incidence of MACE in ARF patients are diabetes mellitus (HR=4.515 [95%CI 1.706 – 11.950]; p=0.046) and HRWSI > 22.665 (HR=13.549 [95%CI 3.611 –50.839]; p= <0.001). The multivariate Cox regression analysis of the three variables found that HRWSI had the best performance for predicting the incidence of MACE in patients with ARF.

TABLE 5: Results of multivariate Cox Regression analysis 6 minutes walking distance (6MWD), changes in rate pressure product (RPP) and heart rate walking speed index (HRWSI) as predictors of a major adverse cardiac event (MACE).

Step	Variable	HR	95% CI		p-value
			Lower limit	Upper limit	
Step1	6MWD (<251)	0,7,321	2,062	25,985	0.002
	Age (> 60 years)	1.517	0.547	4,207	0.423
	Male gender)	2,027	0.431	4,661	9,521
	Obesity (yes)	0.564	0.155	2,054	0.385
	Hypertension (yes)	0.798	0.261	2,437	0.692
	DM (yes)	3.175	1,179	8,549	0.022
	smoking (yes)	0.654	0.199	2,149	0.484
	Kidney Failure (yes)	2,433	0.344	17,189	0.373
	HFrEF (yes)	0.327	0.087	1.228	0.098
	strokes (yes)	2,312	0.159	33,568	0.129
	infection (yes)	0.949	0.247	3,641	0.939
	Dyslipidemia (yes)	1,457	0.358	5,925	0.599
	Cardiogenic Shock (yes)	0.661	0.159	2,758	0.570
Step 11	DM (yes)	3,259	1,342	7,917	0.009
	HFrEF	0.389	0.139	1,084	0.071
	6MWD (<251 meters)	5,675	2025	15,905	0.001

TABLE6 7: Results of multivariate Cox Regression analysis of changes in rate pressure product (RPP) as a predictor of a major adverse cardiac event (MACE).

Step	Variable	HR	95% CI		p-value
			Lower limit	Upper limit	
Step1	Changes in RPP (>3139.5)	18,228	2,917	113,897	0.002
	Age (>60 years)	2,220	0.779	6,330	0.136
	Male gender)	2,170	0.469	10,048	0.322
	Obesity (yes)	0.223	0.052	0.951	0.043
	Hypertension (yes)	0.918	0.287	2,940	0.886
	DM (yes)	2,807	0.952	8,273	0.061
	smoking (yes)	0.478	0.144	1,580	0.226
	Kidney Failure (yes)	1.213	0.202	7,306	0.833
	HFrEF (yes)	0.298	0.075	1,191	0.27
	strokes (yes)	2,342	0.158	34,797	0.536
	infection (yes)	1,608	0.385	6,718	0.515
	Dyslipidemia (yes)	0.820	0.207	3,256	0.778
	Cardiogenic Shock (yes)	0.362	0.071	1,853	0.223
Step9	Age (> 60 years)	2,567	0.971	6,788	0.057
	DM (yes)	2,586	1.008	6,634	0.048
	HFrEF	0.373	0.124	1,121	0.079
	RPP (>3139.5)	10.007	2,078	48,199	0.004

TABLE 7: Results of multivariate Cox Regression analysis heart rate walking speed index (HRWSI) as a predictor of a major adverse cardiac event (MACE).

Step	Variable	HR	95% CI		p-value
			Lower limit	Upper limit	
Step1	HRWSI (>22,665)	22,472	4,637	108,895	<0.001
	Age (>60 years)	2,590	0.839	7,998	0.098
	Male gender)	1.428	0.325	6,270	0.637
	Obesity (yes)	0.343	0.084	1,401	0.136
	Hypertension (yes)	1,429	0.434	4,705	0.557
	DM (yes)	4,256	1,430	12,665	0.009
	smoking (yes)	0.547	0.156	1,922	0.347
	Kidney Failure (yes)	1.146	0.172	7,638	0.888
	HFrEF (yes)	0.188	0.046	0.776	0.210
	strokes (yes)	5,478	0.344	87,251	0.229
	infection (yes)	1,332	0.350	5,062	0.674
	Dyslipidemia (yes)	1.009	0.225	4,529	0.991
	Cardiogenic Shock (yes)	0.763	0.181	3,221	0.712
Step10	Age (> 60 years)	2,709	1.018	7,213	0.046
	DM (yes)	4,515	1,706	11,950	0.002
	HFrEF	0.278	0.095	0.812	0.190
	HRWSI (>22,665)	13,549	3,611	50,839	<0.001

DISCUSSION

The subjects in this study were predominantly >60 years old. These results are from a study in the United States with a median age of 74 years of CHF patients (Parikh et al., 2019). In a study conducted in a hospital in the Czech Republic, the median age of AHF patients was 74 years.[13] In a study conducted at Prof. Hospital. Dr. RD Kandou Manado, patients with GJA are dominated by patients aged 60 years and over.[14] With age, structural and functional degeneration occurs in the heart, contributing to an increased susceptibility to heart failure in older people.[15]

Subjects in this study were dominated by male sex (62.9%). These results are from a study by Donsu et al. (2020), which stated that there were more male patients with CHF (58%) than women (42%).[14] These results also follow the research by Dokupil et al. (2022), with only 34% women, and Parikh et al., with 48% women.[13] Male sex is a risk factor for AKI because men have larger hearts and blood vessels than women, and cholesterol tends to accumulate and form plaque in the main arteries. In women, there is the hormone estrogen, which triggers the production of collagen in cardiac fibroblasts. In addition, risk factors for AHF, such as smoking, are also more common in men.[16]

As many as 8.6% of patients with CHF in this study were obese or had a BMI above 30 kg/m2. Obesity-related factors are estimated to account for 11% of cases of heart failure in men and 14% in women. Obesity can cause heart failure by inducing hemodynamic and myocardial changes that lead to cardiac dysfunction or increasing the predisposition to other heart failure risk factors.[17]

As many as 55.7% of AHF patients suffered from hypertension in this study. Various studies have recognized hypertension as the most common cause of acute heart failure. Hypertension is the most common cause of heart failure in Nigeria, with a proportion of 61% and 75.7% in other studies.[18,19] In a study in the United States, as many as 83.6% of patients with CHF suffered from heart failure.[20]

This is because hypertension increases the workload on the heart, which induces structural and functional changes in the myocardium. These changes include left ventricular hypertrophy, which can progress to heart failure.[21]

As many as 31.4% of patients in the study suffered from DM. These results align with a retrospective study by Mando et al. (2021), which reported that patients with elevated HbA1c had a higher risk of experiencing MACE events than patients with low HbA1c.[22] A meta-analysis of 53 prospective cohort studies found that DM patients were associated with an increased risk of cardiovascular events, coronary heart disease, stroke, and all-cause death compared with normoglycemia. The higher incidence of MACE in DM patients is thought to be caused by increased coagulability and increased expression of glycoprotein IIB/IA and vWF receptors, which are responsible for platelet activation.[23]

As many as 40% of patients in this study smoked. In a study in the United States, 17.1% of acute heart failure patients smoked.[20] Smoking is reported to increase the risk of MACE by 1.9 times compared to patients who do not smoke. Smoking can increase the risk of MACE because the free radicals in cigarettes can increase cholesterol levels and plaque in the arteries and damage endothelial cells.[24]

All patients in this study adhered to treatment, assessed by the number of appropriate medication pills at the time of control and assessed adherence to medication using the MMAS-8 questionnaire. Compliance with taking medication is an important component of heart failure self-management, which functions to maintain stable heart performance. Poor medication adherence is one of the most preventable precipitating factors for exacerbations of acute heart failure.[25]

MACE events within 90 days occurred in 25.7% of AHF patients in this study. In a prospective study at a hospital in Switzerland, MACE events occurred in 15.2% of patients at 30 days and 20.6% at 365 days.[26]

In a study in Finland, the incidence of MACE within 3 years after coronary heart disease occurred in 48.4% of patients. Differences in the incidence of MACE in other studies can be caused by differences in patient cardiovascular risk factors, delays in treating cardiovascular events, and different follow-up times.[27]

6-minute walking distance(6MWD) is the farthest distance a patient can walk 30 meters in an uncrowded corridor for 6 minutes. 6MWD examination can reflect the level of functional activity for daily activities.[27]

This study shows that patients with AHF with reduced 6MWD have lower MACE survival than patients with normal 6MWD. This implies that patients with decreased functional capacity in daily activities have a higher probability of experiencing MACE events.

The results of a study by Ingle et al. (2007) stated that a decrease in 6MWD is an independent predictor of increased mortality in patients with heart failure with left ventricular systolic dysfunction. However, it is still less strong when compared to the N-terminal pro-brain natriuretic peptide (NT pro-BNP) as a single predictor. The 6MWD examination is reliable and more applicable because it is cheaper and more affordable than the pro-BNP NT examination. Another study by Lee et al. (2014) also found that in patients with CHF, decreased 6MWD was a predictor of all-cause mortality (HR 0.97). Other independent predictors were increased age, increased NYHA classification, increased NTpro-BNP, decreased blood pressure diastolic, decreased sodium and increased urea. [28]

Another study found that shorter 6MWD had a higher one-year and three-year mortality risk on multivariate analysis. Patients with 6MWD ≤468 m had a mortality hazard ratio of up to 3.22 at one year and 2.18 at three years. Multivariate analysis also showed a higher risk of hospitalization and mortality from cardiovascular disease in patients with 6MWD ≤468 m, having a mortality hazard ratio of up to 2.77 in one year and 1.71 in three years.[29]. In another study, the cut-off point of 6MWD for 1-year mortality was 325m with a sensitivity of 0.75 and a specificity of 0.54.[28] The cut-off value of 6MWD in this study is 251 meters.

The findings of this study are similar to the results of other studies but differ in terms of the finding of the cut point for 6MWD with other studies, possibly because the 6MWD examination can be influenced by several parameters such as older age, female, low body mass index, anaemia, increased pulse rate when rest and diabetes leading to decreased 6MWD in patients with heart failure. Depression in patients with heart failure is related to symptoms of fatigue and feeling unwell and functional capacity and must be assessed independently as a confounding factor in 6MWD.[30]

Rate Pressure Product (RPP) is an indirect index that assesses myocardial oxygen consumption, which can predict cardiac function. RPP is calculated by multiplying heart rate and systolic blood pressure. The normal range of RPP values at rest starts from 12,000 and can increase to 22,000 under stressful conditions.[31] RPP is directly proportional to the work done by the heart and can be considered an indirect indicator of myocardial oxygen uptake, as well as an index for evaluating the response of the coronary circulation to metabolic demands in patients with heart disease.

This study shows that patients with CHF patients with high RPP changes have lower survival than patients with CHF patients with low RPP changes.

These results are consistent with a study by Verma et al. (2018), which stated that changes in RPP were associated with 30-day mortality and repeated hospitalizations (hazard ratio 1.17 per 5 bpm HR, hazard ratio 1.20 per 10 mmHg SBP, and hazard ratio 1.02 per 100 bpm *mmHg RP) in patients with HFpEF and acute heart failure.[7]. These results are also consistent with the study of Patel et al. (2014), who reported that heart failure patients with low systemic blood pressure had a higher 30-day risk of death than those without hypotensive episodes. [32]

The Registry Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) found that changes in systolic blood pressure either increased or decreased and systolic blood pressure <120 mmHg were associated with increased all-cause mortality.[33] In addition to systolic blood pressure, pulse rate or pulse rate is associated with death from cardiovascular causes. A post-hoc analysis on TOPCAT found that temporal changes in heart rate were an independent predictor of cardiovascular death, sudden cardiac arrest and repeated hospitalizations where an increase in heart rate was associated with a higher risk. [34]. This is in line with the research of Lam et al. (2017) [35].

This research is different from the study conducted by Karaye et al. (2015), where RPP is not associated with hospital mortality but is strongly associated with interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), and NT-BNP, which are risk factors for MACE events. [36].

The findings in this study and previous studies support the hypothesis that RPP calculated from pulse rate and systolic blood pressure is associated with mortality and hospitalization outcomes in patients with heart failure. Changes in RPP can predict MACE events because an increase in pulse rate and blood pressure indicates an increase in myocardial consumption.[31]

This study shows that HRWSI can predict MACE events within 90 days post-hospital discharge in patients with acute heart failure. These results agree with the study by McDermott et al., who reported patients with poor HRWSI increased total mortality by 1.86 times and cardiovascular mortality by 2.55 times compared to good HRWSI.[37] The heart rate walking speed index (HRWSI) is the ratio between the pulse rate and walking speed (meters per minute) multiplied by 10 to describe the pulse rate every 10 meters. HRWSI evaluation aims to reduce the effect of physiological adaptation to 6MWT.[38].

A heart rate walking speed index indicates high HR and low WS. A study by Sun et al. (2021) stated that a high heart rate increases the risk of MACE 1.39 times compared to patients with a normal heart rate after controlling for the variables age, sex, initial blood pressure, drinking alcohol, smoking, hyperlipidemia, diabetes, heart disease coronary disease, cerebrovascular disease and use of antihypertensive drugs.[39] In the study of Grazzi et al., patients with low WS (2.1 ± 0.4 km/h) had a 57% mortality risk at 3 years.[40] Hanada et al.'s study. also supports the finding that a low WS (<0.98 m/s) in GJ patients has a worse prognosis compared to a higher WS [11]. Another study showed individuals with low WS (≤ 1.50 m/s in males and ≤1.[10,41]

Research by Grove et al. (2019) shows that HRWSI has increased in patients with high cardiovascular risk compared to patients with low cardiovascular risk. HRWSI has decreased significantly after Cardiac Rehabilitation (CR).

This indicates that HRWSI can be a reliable monitoring method to assess cardiovascular improvement. If, on a repeat test after a cardiovascular rehabilitation program, the HRWSI calculation results decrease, this indicates an increase in aerobic fitness or a corresponding decrease in cardiovascular pressure (cardiovascular strain) at a certain walking speed [42]

From this study, HRWSI was the best predictor in predicting MACE events compared to 6MWD and RPP. This is because the 6MWD measurement results are very dependent on several factors. 6MWD results will decrease if the patient is short height, old age, overweight, female gender, low motivation, musculoskeletal disorders such as arthritis, ankle, knee or hip injuries, muscle wasting and use of shorter corridors causing many turns during the test. At the same time, the factors that cause 6MWD results to increase in patients are high height, male gender, and high motivation[43] [43]. The authors could not control several factors that became confounding in this study: height, patient motivation and gender.

Changes in RPP consider heart rate and blood pressure changes to estimate myocardial oxygen uptake. Myocardial oxygen uptake is most accurately measured by catheterization but can be estimated through RPP at the peak of exercise, called the RPP reserve or double product reserve[44]. This may be a limitation of the RPP changes assessed in this study due to the evaluation used not the maximal practice test but the submaximal test with 6MWT. HRWSI is a better predictor than changes in RPP and 6MWD because HRWSI is a reflection of effort in the form of changes in the pulse rate used by patients to walk every 10 meters so that the examination results and information obtained are more objective compared to 6MWD to reduce the learning effect or familiarization with tests.[10,11,40]. The weakness of this study is that follow-up was carried out in a short time, namely only 90 days. A longer follow-up can be performed to assess the patient's long-term MACE events. In addition, the results of this study cannot be generalized to populations with the HFpEF phenotype due to the small proportion of the sample with the HFpEF phenotype, cognitive impairment, history of chronic lung disease, and musculoskeletal disorders.

CONCLUSION

1. 6MWD pre-discharge can predict MACE events within 90 days post-hospital discharge in patients with acute heart failure.
2. Changes in RPP at 6MWT pre-discharge can predict MACE events within 90 days post-hospital discharge in patients with acute heart failure.
3. HRWSI at 6MWT pre-discharge can predict MACE events within 90 days post-hospital discharge in patients with acute heart failure.
4. HRWSI at 6MWT pre-discharge is better than 6MWD, and changes in RPP in predicting MACE events within 90 days post-hospital discharge in patients with acute heart failure.

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 has received approval from the research ethics committee of Prof. Dr. IGNG Ngoerah Hospital/ University of Udayana with No.1257/UN14.2.2.VII.14/LT/2023

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