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Echocardiography Killip Classification (eKillip Class) as a Predictor of Cardiovascular Rehospitalization and Mortality in Patients with Acute Myocardial Infarction

Ayu Putu Harina Ferdiyanthi*, Ida Bagus Rangga Wibhuti, and I Kadek Susila Surya Darma

Department of Cardiology and Vascular Medicine, Faculty of Medicine Udayana University Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

E-mail: harinadian@gmail.com; rangga.w@gmail.com; kadek.susila@yahoo.co.id

*Corresponding author: Ayu Putu Harina Ferdiyanthi; harinadian@gmail.com

ABSTRACT

Background: Patients with acute myocardial infarction (AMI) are at risk of experiencing cardiovascular events such as rehospitalization and mortality. The eKillip Class is a combined echocardiographic hemodynamic assessment based on the Killip class, which uses stroke volume index (SVI) and diastolic function as indicators of systemic perfusion and pulmonary congestion to assess the prognosis of AMI patients. This study aims to assess the eKillip Class as a predictor of cardiovascular rehospitalization and mortality in AMI patients. ***Method:*** The research design used a prospective cohort. The independent variable is the eKillip class. The outcomes studied were cardiovascular rehospitalization and mortality. A total of 114 samples were obtained using a consecutive sampling technique that met the inclusion and exclusion criteria and were followed for 30 days. ***Results:*** eKillip Class IV was present in 39 patients (34.3%), while 25 (21.9%), 20 (17.5%), and 30 (26.3%) patients were in eKillip Classes I to III, respectively. During 30 days of follow-up, a total of 22 (19.3%) cardiovascular rehospitalizations and 13 (13.2%) cardiovascular mortalities occurred. Multivariate cox regression analysis using the backward stepwise LR method showed that eKillip Class IV is independently associated with cardiovascular rehospitalization and mortality (adjusted HR 3.7; 95%CI 1.6–8.6; p = 0.003; and adjusted HR 3.5; 95%CI 1.2–9.9; p = 0.018, respectively). eKillip Class IV had a significantly lower mean survival time and 30-day survival rate than non-eKillip Class IV in terms of cardiovascular rehospitalization (24.7 days [95%CI 21.9-27.6] and 66.7% vs. 27.9 days [95%CI 26.4-29.4] and 88%; p = 0.001) and cardiovascular mortality (23.7 days [95%CI 19.9-27.3] and 76.9% vs. 27.8 days [95%CI 26.2-29.5] and 92%; p = 0.019). ***Conclusion:*** eKillip Class is an independent predictor of cardiovascular rehospitalization and mortality in AMI patients. Patients with eKillip Class IV had lower survival rates for cardiovascular rehospitalization and mortality compared to patients with non-eKillip Class IV.

Keywords: eKillip class; acute myocardial infarction; cardiovascular rehospitalization; cardiovascular mortality

INTRODUCTION

Acute myocardial infarction has varying degrees of clinical severity in the acute phase, ranging from stable hemodynamic status to cardiogenic shock [1]. Cardiogenic shock and the pre-shock state of acute decompensated heart failure represent a spectrum of hemodynamic deficits in patients with cardiovascular disease. Both conditions describe situations in which cardiac output is insufficient to provide adequate tissue perfusion or may be sufficient but requires compensatory hemodynamic changes. Currently, the incidence of decompensated heart failure with cardiogenic shock resulting from MI is increasing [2, 3].

The prevention of complications from AMI also depends on the ability to identify high-risk individuals. Risk stratification methods can include clinical, laboratory, imaging, invasive, and non-invasive examinations [4]. Non-invasive support such as echocardiography has been proven to provide an overview of the prognosis in patients with AMI. Echocardiography can assess the systolic and diastolic functions of the heart, which are the basis of the patient's hemodynamic condition [5].

Until now, in patients experiencing acute coronary syndrome, especially STEMI, the Killip classification is still the clinical classification method used for real-time risk assessment [6]. The Killip classification has been shown to be a significant predictor of short- and long-term mortality in STEMI, NSTEMI, and UAP patients.

Patients with a higher Killip class had worse coronary angiography, a higher incidence of arrhythmias, and left ventricular dilatation and dysfunction. The Killip classification has been validated to predict mortality in patients treated with thrombolytic agents or primary percutaneous intervention. The study stated that Killip classification was significantly associated with all-cause mortality among all patients with CVD who underwent echocardiography in a tertiary hospital [6].

The Killip classification hierarchy is a combined assessment of the two main functions of the left heart to take blood from the peripheral and pulmonary circulation and circulate it, namely the diastolic and systolic functions. [6]. The Killip classification system was introduced for the clinical assessment of patients with acute myocardial infarction, which groups individuals according to the severity of heart failure due to their myocardial infarction. This system provides effective stratification of long-term and short-term outcomes in patients with acute myocardial infarction, as well as influencing treatment strategies [7].

According to the Killip and Kimball criteria, patients are classified into four classes based on findings on physical examination, including class I (no evidence of heart failure), class II (physical findings consistent with slightly increased filling pressures), class III (presence of pulmonary edema), and class IV (cardiogenic shock) [6]. However, the determination of Killip classification is quite subjective because the main basis is physical examination. Apart from that, the clinical features and predictors of high Killip class on admission and its prognostic impact in patients with STEMI as the first clinical cardiovascular event are still poorly known. [8]. In elderly patients who experience AMI, the symptoms that appear are often shortness of breath. So that clinical presentations that arise need to be followed up with early echocardiography testing. Echocardiographic evaluation is highly specific for the diagnosis of AMI (95% to 97%) but not sensitive (approximately 30%). [9]. Using the same logic of thinking inspired by Killip's classification, echocardiography, which is the main examination of CVD patients in hospitals, should be used to evaluate a combination of systolic and diastolic function [6]. However, echocardiography in terms of assessing hemodynamic, both systolic and diastolic functions, is still separate; there is no combination of these two functions yet [6].

As previously described, hemodynamic evaluation is very useful for AMI, including in stratifying prognosis and determining management [10]. The objective hemodynamic assessment modality that is quite easy to carry out to date is echocardiography [11, 12]. Emergency echocardiography on arrival is indicated for patients with suspected hemodynamic instability, mechanical complications, cardiogenic shock, or cardiac arrest. Routine echocardiography after revascularization is also recommended to assess the function of the left ventricle, right ventricle, valves, etc. in detecting post-infarction complications [11]. Various echocardiographic parameters have been known to be important predictors of morbidity and mortality, such as LVEF and LVEDD. However, until now, there is still no combined hemodynamic data from echocardiography, even though echocardiography is a fairly fast, easy, and non-invasive modality to use in emergency cases and provides an objective assessment. [6]. Including various guidelines regarding AMI, they do not provide recommendations for combined hemodynamic assessment via echocardiography [11–13].

Echocardiography based on the Killip classification can provide a combined hemodynamic assessment, which will be used to objectively assess the patient's hemodynamic. This is because the assessment results are based on parameters that can be measured and standardized. Echocardiographic assessment of the degree of diastolic function is used as an indicator of pulmonary congestion, and stroke volume index (SVI) is used as an indicator of systemic perfusion. Combination hemodynamic classification via echocardiography is based on inspiration from the Killip classification, hereinafter referred to as the Echocardiography Killip Classification (eKillip Class). eKillip class is divided into 4 classifications, including eKillip class I (normal SVI [35 mL/m2] with normal or grade I diastolic function), eKillip class II (normal SVI with grade 2 diastolic dysfunction), eKillip class III (normal SVI with dysfunction diastolic grade 3), and eKillip class IV (SVI decreased [<35 mL/m2] with grade 2 or grade 3 diastolic dysfunction) [6]. It is hoped that the eKillip Class can be useful as a risk stratification modality in predicting rehospitalization and cardiovascular mortality in AMI patients.

Based on the explanation above, researchers intend to examine the eKillip Class, which is an echocardiography examination based on the Killip classification, as a combined hemodynamic parameter in predicting cardiovascular rehospitalization and mortality from cardiovascular disease in AMI patients.

METHODS

This research is an analytical observational study with a prospective cohort design. This research began with an echocardiography Killip Classification (eKillip Class) assessment in acute myocardial infarction (AMI) patients, which were then categorized into four groups according to the eKillip class category. Each group was followed for 30 days after the eKillip Class assessment to see whether one or both of cardiovascular rehospitalization and/or cardiovascular mortality occurred.

This research was conducted from October 2023 to January 2024, located at Integrated Heart Services Installation Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali. An echocardiography examination to assess eKillip Class in AMI patients is carried out in the installation emergency room of Prof. Dr. I.G.N.G. Ngoerah, Denpasar Hospital, Bali. The target population in this study was all patients with acute myocardial infarction who came to the emergency room at the Integrated Heart Services Installation at Prof. Dr. I.G.N.G. Ngoerah Hospital.

Inclusion criteria are patients aged 18 and over who had their first MI incident in the period October to December 2023 at the integrated installation at Prof. Dr. I.G.N.G. Ngoerah. Exclusion criteria include: 1) Incomplete stroke volume index (SVI) assessment; 2) AMI patients who find it difficult to assess left ventricular diastolic function, such as patients with mitral valve stenosis or significant mitral valve regurgitation, aortic valve stenosis or significant aortic valve regurgitation, mitral or aortic valve prosthesis, use of a pacemaker, presence of shunts as in congenital heart disease, or during echocardiography examination there were arrhythmias such as atrial fibrillation or atrial flutter, supraventricular tachycardia, and/or ventricular tachycardia; 3) AMI patients who have received revascularization therapy before echocardiography is performed; 4) AMI patients who have received hemodynamic therapy before echocardiography is performed; 5) Patients with other hemodynamic disorders or high output states such as sepsis; 6) Patients who are not willing to participate or are not willing to sign the consent form after explaining informed consent. The sampling technique used in this research is non-probability sampling, namely by using consecutive sampling.

All the data collected in each group was then analyzed using the SPSS version 26 program, which includes descriptive analysis, comparative proportion analysis using the Kaplan-Meier test, and a Cox-regression test. The confidence level in this research is 95%. Ho is rejected, and H1 is accepted if the p value is <0.05.

RESULTS

The results of the descriptive analysis of the research population based on the eKillip Class are shown in Tables 1 and 2. The results of the descriptive analysis of the research population are divided into 2 tables, namely sociodemographic characteristics and echocardiographic characteristics of the eKillip Class.

The influence of control variables on independent variables with numerical scale data (variables age, BMI, SV, SVI, CO, EF, LAVI, LVVI, ePCWP, E/e' average, and E/A ratio) was tested for normality using the Kolmogorov-Smirnov test. Variables that have a normal distribution are continued to test significance using the One Way Anova test, while variables that are not normally distributed or are not homogeneous in the One Way Anova test are continued to test significance using the Kruskal Wallis test. A variable is said to be significant if the p value is <0.05.

The influence of control variables on independent variables with categorical scale data (gender, smoking, hypertension, DM, dyslipidemia, hyperuricemia, incidence of MI, PCI, and degree of diastolic function) was tested for significance using the Chi Square test. A variable is said to be significant if the p value is <0.05.

Based on the results of the significance test as shown in Table 1 and Table 2, variables that were significant to the eKillip Class were obtained, including the variables PCI, SV, SVI, CO, LAVI, ePCWP, EF, degree of diastolic function, E/e' average, as well as cardiovascular rehospitalization and cardiovascular mortality, with a p value <0.05.

TABLE 1: Sociodemographic Characteristics of Research Subjects Based on eKillip Class.

Variable	Total	eKillip Class				*p*
		I	II	III	IV	
Number of subjects	**114**	**25 (21.9)**	**20 (17.5)**	**30 (26.3)**	**39 (34.3)**	
Age, mean±SD (years)	58±10.4	57±8.7	58±10.4	58±11.2	58±11.1	
young adults, n (%)	4 (3.5)	0 (0)	0 (0)	1 (3,3)	3 (7.7)	0.975$^{\sigma}$
old adults, n (%)	65 (57)	17 (68)	12 (60)	15 (50)	21 (53.8)	0.900#
elderly, n (%)	45 (39.5)	8 (32)	8 (40)	14 (46.7)	15 (38.5)	
Gender						
Man, n (%)	93 (81.6)	21 (84)	17 (85)	27 (90)	28 (81.6)	0.232#
Woman, n (%)	21 (18.4)	4 (16)	3 (15)	3 (10)	11 (18.4)	
Smoke						
Yes, n (%)	60 (52.6)	11 (44)	8 (40)	18 (60)	23 (59)	0.130#
No, n (%)	54 (47.4)	14 (56)	12 (60)	12 (40)	16 (41)	
BMI, median (kg/m2)	24.7 (16.6-41.6)	24.8 (18.4-32.8)	25.3 (18.7-39.2)	24.2 (18.1-36.8)	24.0 (16.6-41.6)	
Normal, n (%)	56 (49.1)	13 (52)	8 (40)	14 (46.7)	21 (53.8)	0.968$^{\rho}$
Low, n (%)	4 (3.5)	1 (4)	0 (0)	2 (6.7)	1 (2.6)12 (30.8)	0.755$^{\#}$
excess, n (%)	39 (34.2)	8 (32)	9 (45)	10 (33.3)	5 (12.8)	
Obesity, n (%)	15 (13.2)	3 (12)	3 (15)	4 (13.3)		
Hypertension						
Yes, n (%)	65 (57)	15 (60)	11 (55)	14 (46.7)	25 (64.1)	0.784#
No, n (%)	49 (43)	10 (40)	9 (45)	16 (53.3)	14 (35.9)	
Diabetes mellitus						
Yes, n (%)	42(36.8)	8 (32)17 (68)	6 (30) 14 (70)	7 (23.3)	21 (53.8)	0.080#
No, n (%)	72 (63.2)			23 (76.7)	18 (46.2)	
Hyperuricemia						
Yes, n (%)	31 (28.2)	5 (20)	8 (42.1)	7 (24.1)	11 (29.7)	0.712#
No, n (%)	79 (71.8)	20 (80)	11 (57.9)	22 (75.9)	26 (70.3)	
Dyslipidemia						
Yes, n (%)	106 (96.4)	24 (96)	17 (89.5)	29 (100)	36 (97.3)	0.420#
No, n (%)	4 (3.6)	1 (4)	2 (10.5)	0 (0)	1 (2.7)	
AMI						
STEMI, n (%)	88 (77.2)	18 (72)	15 (75)	21 (70)	34 (38.6)	0.180#
NSTEMI, n (%)	26 (22.8)	7 (28)	5 (25)	9 (30)	5 (19.2)	
PCI						
Yes, n (%)	80 (70.2)	21 (84)	16 (80)	19 (63.3)	24 (61.5)	0.030#*
No, n (%)	34 (29.8)	4 (16)	4 (20)	11 (36.7)	15 (38.5)	

$^{\sigma}$One Way Anova Test
$^{\rho}$Kruskal-Wallis test
$^{\#}$Linear-by-Linear Association Test
* Statistically significant

TABLE 2: Echocardiographic Characteristics of Research Subjects Based on eKillip Class.

Variable	Total	eKillip Class				*p*
		I	II	III	IV	
SV, mean±SD (mL)	54.4±18.7	72.5±13.6	62.0±13.1	51.7±19.1	40.9±11.3	<0.001$^{\sigma}$*
Low, n (%)	43 (37.7)	0 (0)	3 (15)	15 (50)	25 (64.1)	<0.001#*
Normal, n (%)	71 (62.3)	25 (100)	17 (85)	15 (50)	14 (35.9)	
SVI, mean±SD (mL/m2)	30.8±10.3	40.6±7.5	35.9±8.3	29.2±9.8	23.3±5.9	<0.001$^{\sigma}$*
Low, n (%)	66 (57.9)	0 (0)	4 (20)	25 (83.3)	37 (94.9)	<0.001#*
Normal, n (%)	48 (42.1)	25 (100)	16 (80)	5 (16.7)	2 (5.1)	
CO, median (L/min)	4.1 (1.6-11.1)	5.9 (3.6-8.1)	4.9 (2.5-6.5)	3.7 (2.3-11.1)	3.5 (1.6-8.1)	<0.001$^{\rho}$*
Low, n (%)	53 (46.5)	2 (8)	5 (25)	18 (60)	28 (71.8)	<0.001#*
Normal, n (%)	61 (53.5)	23 (92)	15 (75)	12 (40)	11 (28.3)	
LAVI, median (mL/m2)	26.7 (6.5-63.9)	22.4 (6.5-38.9)	32.9 (13-56.4)	23.3 (12.7-51.4)	38.7 (11.8-63.9)	<0.001$^{\rho}$*
Height, n (%)	39 (34.2)	1 (4)	10 (50)	4 (13.3)	24 (61.5)	<0.001#*
Normal, n (%)	75 (65.8)	24 (96)	10 (50)	26 (86.7)	15 (38.5)	
LVVI, median (mL/m2)	52.0 (17.3-259.7)	51.3 (27.4-108.2)	65.8 (34.8-259.7)	47.7 (19.7-135)	48.9 (17.3-164)	0.058$^{\rho}$
Height, n (%)	27 (23.7)	4 (16)	9 (45)	4 (13.3)	10 (25.6)	0.984#
Normal, n (%)	87 (76.3)	21 (84)	11 (55)	26 (86.7)	29 (74.4)	
ePCWP, median (mmHg)	20.3 (8.5-46.8)	14.8 (8.5-38.4)	23.3 (13.2-32.3)	19.4 (8.8-35.7)	23.9 (12.4-46.8)	<0.001$^{\rho}$*
Height, n (%)	92 (80.7)	12 (48)	19 (95)	25 (83.3)	36 (92.3)	<0.001#*
Normal, n (%)	22 (19.3)	13 (52)	1 (5)	5 (16.7)	3 (7.7)	
EF, mean±SD (%)	43.3±10.7	48.8±10.5	43.9±12.8	42.1±8.9	40.3±10.1	0.018$^{\sigma}$*
Normal, n (%)	32 (28.1)	11 (44)	7 (35)	6 (20)	8 (20.5)	0.007#*
Mildly reduced, n (%)	42 (36.8)	10 (40)	6 (30)	13 (43.3)11 (36.7)	13 (33.3)	
Reduced, n (%)	40 (35.1)	4 (16)	7 (35)		18 (46.2)	
Degree of diastolic function						
Normal, n (%)	14 (12.3)	9 (36)	0 (0)	5 (16.7)	0 (0)	<0.001#*
Decreased grade I, n (%)	35 (30.7)	16 (64)	0 (0)	18 (60)	1 (2.6)	
Decreased grade II, n (%)	45 (39.5)	0 (0)	17 (85)	0 (0)	28 (71.7)	
Decreased grade III, n (%)	14 (12.3)	0 (0)	0 (0)	5 (16.7)	9(23.1)1 (2.6)	
Indeterminate, n (%)	6 (5.2)	0 (0)	3 (15)	2 (6.6)		
E/e' average, median	14.8 (5.3-36.2)	10.4 (5.3-29.5)	17.3 (9.1-34.5)	14.1 (5.6-27.2)	17.7 (8.4-36.2)	<0.001$^{\rho}$*
Height, n (%)	71 (62.3)	3 (12)	18 (90)	16 (53.3)	34 (87.2)	<0.001#*
Normal, n (%)	43 (37.7)	22 (88)	2 (10)	14 (46.7)	5 (12.8)	
E/A Ratio, median	1.1 (0.4-4.3)	0.9 (0.5-1.6)	1.1 (0.5-1.5)	1.1 (0.5-3.1)	1.3 (0.4-4.3)	0.063$^{\rho}$
Normal, n (%)	74 (64.9)	19 (76)	16 (80)	20 (66.7)	19 (48.7)	0.002#*
Low, n (%)	26 (22.8)	6 (24)	4 (20)	4 (13.3)	12 (30.8)	
High, n (%)	14 (12.3)	0 (0)	0 (0)	6 (20)	8 (20.5)	

$^{\sigma}$One Way Anova Test
$^{\rho}$Kruskal-Wallis test
#Linear-by-Linear Association Test
* Statistically significant

Distribution analysis results for rehospitalization cardiovascular based on the sociodemographic and echocardiographic characteristics of each research subject can be seen in Table 3 and Table 4.

In addition to the independent variable eKillip Class, the influence of the control variable on the dependent variable cardiovascular rehospitalization with categorical scale data (gender, smoking, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, PCI, and degree of diastolic function) was tested for significance using the Chi Square test. It is said to be significant if the p value is <0.05.

The influence of control variables on the dependent variable of cardiovascular rehospitalization with numerical scale data (variables age, BMI, SV, SVI, CO, EF, LAVI, LVVI, ePCWP, E/e' average, and E/A ratio) was tested for normality with the Kolmogorov-Smirnov test. Variables that have a normal distribution are continued to be tested for significance using the Independent Sample T Test, while variables that are not normally distributed are continued to be tested for significance using the Mann-Whitney test. It is said to be significant if the p value is <0.05.

Based on the results of the significance test as shown in Table 3 and Table 4, variables were found that were significant for cardiovascular rehospitalization, including the eKillip Class variable, gender, hyperuricemia, LVVI, and degree of diastolic function, with $p < 0.05$. Variables with $p < 0.25$ and theoretically related to the outcome will then be entered into a multivariate analysis to see whether there is an independent relationship with the outcome. However, variables that represent hemodynamic or are the main assessment component of the eKillip Class itself, even though they have a significant p value, are not included in the multivariate analysis of cardiovascular rehospitalization outcomes. The variables that will be controlled through multivariate analysis are gender, smoking, hyperuricemia, hypertension, diabetes mellitus, PCI, and LVVI.

TABLE 3: Distribution of Cardiovascular Rehospitalization Based on Sociodemographic Characteristics of Research Subjects.

Variable	**Cardiovascular Rehospitalization**		***p***
	Yes	**No**	
Number of subjects	**22 (19.3)**	**92 (80.7)**	
Age, mean±SD (years)	57±11.6	58±10.2	
young adults, n (%)	1 (25)	3 (75)	0.651µ
old adults, n (%)	14 (21.5)	51 (78.5)	0.410#
elderly, n (%)	7 (15.6)	38 (84.4)	
Gender			
Man, n (%)	14 (15.1)	79 (84.9)	$0.028^{\wedge*\varphi}$
Woman, n (%)	8 (38.1)	13 (61.9)	
Smoke			
Yes, n (%)	9 (15)	51 (85)	$0.220^{\Omega\varphi}$
No, n (%)	13 (24.1)	41 (75.9)	
BMI, median (kg/m2)	24.6 (16.6-37.5)	24.7 (18.1-41.6)	
Normal, n (%)	10 (17.9)	46 (82.1)	
Low, n (%)	1 (25)	3 (75)	0.954¶
excess, n (%)	6 (15.4)	33 (84.6)	0.447#
Obesity, n (%)	5 (33.3)	10 (66.7)	
Hypertension			
Yes, n (%)	15 (23.1)	50 (76.9)	$0.239^{\Omega\varphi}$
No, n (%)	7 (14.3)	42 (85.7)	
Diabetes mellitus			
Yes, n (%)	11 (26.2)	31 (73.8)	$0.154^{\Omega\varphi}$
No, n (%)	11 (15.3)	61 (84.7)	
Hyperuricemia			
Yes, n (%)	10 (32.3)	21 (67.7)	$0.044^{\Omega*\varphi}$
No, n (%)	12 (15.2)	67 (84.8)	
Dyslipidemia			
Yes, n (%)	21 (19.8)	85 (80.2)	1,000^
No, n (%)	1 (25)	3 (75)	
AMI			
STEMI, n (%)	15 (17)	73 (83)	0.262^{Ω}
NSTEMI, n (%)	7 (26.9)	19 (73.1)	
PCI			
Yes, n (%)	13 (16.2)9 (26.5)	67 (83.8)	$0.206^{\Omega\varphi}$
No, n (%)		25 (73.5)	

µIndependent T Test
¶Mann Witney Test
#Linear-by-Linear Association Test
^ Fisher's Exact Test
ΩPearson Chi-Square Test
* Statistically significant
φEnter the multivariate test

TABLE 4: Distribution of Cardiovascular Rehospitalization
Based on Echocardiographic Characteristics of Research Subjects.

Variable	Cardiovascular Rehospitalization		p
	Yes	No	
eKillip Class			
I, n (%)	1 (4)	24 (96)	
II, n (%)	3 (15)	17 (85)25 (83.3)	0.004#*φ
III, n (%)	5 (16.7)	26 (66.7)	
IV, n (%)	13 (33.3)		
SV, mean±SD (mL)	49.9±23.7	55.5±17.3	0.215μ
Low, n (%)	11 (25.6)11 (15.5)	32 (74.4)	0.186Ω
Normal, n (%)		60 (84.5)	
SVI, mean±SD (mL/m2)	28.4±12.1	31.4±9.8	0.210μ
Low, n (%)	16 (24.2)	50 (75.8)	0.117Ω
Normal, n (%)	6 (12.5)	42 (87.5)	
CO, median (L/min)	3.8 (1.6-11.1)	4.1 (1.7-8.1)	0.628¶
Low, n (%)	12 (22.6)	41 (77.4)	0.399Ω
Normal, n (%)	10 (16.4)	51 (83.6)	
LAVI, median (mL/m2)	33.9 (11.8-63.9)	24.4 (6.5-60.6)	0.029¶*
Height, n (%)	11 (28.2)	28 (71.8)	0.082Ω
Normal, n (%)	11 (14.7)	64 (85.3)	
LVVI, median (mL/m2)	69.0 (26.4-164)	48.1 (17.3-259.7)	0.001¶*φ
Height, n (%)	11 (40.7)	16 (59.3)	0.001Ω*φ
Normal, n (%)	11 (12.6)	76 (87.4)	
ePCWP, median (mmHg)	22.2 (12.4-45.3)	20.2 (8.5-46.8)	0.272¶
Height, n (%)	19 (20.7)	73 (79.3)	0.560^
Normal, n (%)	3 (13.6)	19 (86.4)	
EF, mean±SD (%)	40.7±11.3	43.9±10.6	
Normal, n (%)	6 (18.8)	26 (81.2)	0.212μ
Mildly reduced, n (%)	5 (11.9)	37 (88.1)	0.302#
Reduced, n (%)	11 (27.5)	29 (72.5)	
Degree of diastolic function	2 (14.3)	12 (85.7)	
Normal, n (%)	2 (5.7)	33 (94.3)	
Decreased grade I, n (%)	11 (24.4)	34 (75.6)	
Decreased grade II, n (%)	6 (42.9)	8 (57.1)	0.033#*
Decreased grade III, n (%)	1 (16.7)	5 (83.3)	
Indeterminate, n (%)			
E/e' average, median	16.4 (8.4-35)	14.7 (5.3-36.2)	0.272¶
Height, n (%)	16 (22.5)	55 (77.5)	0.260Ω
Normal, n (%)	6 (14)	37 (86)	
E/A Ratio, median	1.2 (0.5-4.3)	1.1 (0.4-3.3)	
Normal, n (%)	11 (14.9)	63 (85.1)	0.451¶
Low, n (%)	6 (23.1)	20 (76.9)	0.061#
High, n (%)	5 (35.7)	9 (64.3)	

μIndependent T Test
¶Mann Witney Test
#Linear-by-Linear Association Test
^ Fisher's Exact Test
ΩPearson Chi-Square Test
* Statistically significant
φEnter the multivariate test

Distribution analysis results in mortality cardiovascular based on the sociodemographic and echocardiographic characteristics of each research subject can be seen in Tables 5 and 6.

TABLE 5: Distribution of Cardiovascular Mortality Based on Sociodemographic Characteristics of Research Subjects.

Variable	Cardiovascular Mortality		*p*
	Yes	No	
Number of subjects	**15 (13.2)**	**99 (86.8)**	
Age, mean±SD (years)	62±11.1	57±10.2	
young adults, n (%)	0 (0)	4 (100)	0.049¶*
old adults, n (%)	4 (6.2)	61 (93.8)	0.005#*φ
elderly, n (%)	11 (24.4)	34 (75.6)	
Gender			
Man, n (%)	14 (15.1)	79 (84.9)	0.298^
Woman, n (%)	1 (4.8)	20 (95.2)	
Smoke			
Yes, n (%)	5 (8.3)	55 (91.7)	0.108Ω φ
No, n (%)	10 (18.5)	44 (81.5)	
BMI, median (kg/m2)			
Normal, n (%)	9 (16.1)	47 (83.9)	
Low, n (%)	1 (25)	3 (75)	0.263#
excess, n (%)	4 (10.3)	35 (89.7)	
Obesity, n (%)	1 (6.7)	14 (93.3)	
Hypertension			
Yes, n (%)	7 (10.8)	58 (89.2)	0.385Ω
No, n (%)	8 (16.3)	41 (83.7)	
Diabetes mellitus			
Yes, n (%)	9 (21.4)	33 (78.6)	0.046Ω*φ
No, n (%)	6 (8.3)	66 (91.7)	
Hyperuricemia			
Yes, n (%)	4 (12.9)	27 (87.1)	1,000^
No, n (%)	9 (11.4)	70 (88.6)	
Dyslipidemia			
Yes, n (%)	13 (12.3)	93 (87.8)	1,000^
No, n (%)	0 (0)	4 (100)	
AMI			
STEMI, n (%)	10 (11.4)	78 (88.6)	0.327^
NSTEMI, n (%)	5 (19.2)	21 (80.8)	
PCI			
Yes, n (%)	7 (8.8)	73 (91.3)	0.065^φ
No, n (%)	8 (23.5)	26 (76.5)	

µ Independent T Test
¶ Mann Witney Test
#Linear-by-Linear Association Test
^ Fisher's Exact Test
ΩPearson Chi-Square Test
* Statistically significant
φEnter the multivariate test

TABLE 6: Distribution of Cardiovascular Mortality Based on Echocardiographic Characteristics of Research Subjects.

Variable	Cardiovascular Mortality		*p*
	Yes	No	
eKillip Class			
II, n (%)	1 (5)	25 (100)	0.004#*φ
III, n (%)	5 (16.7)	19 (95)25 (83.3)	
IV, n (%)	9 (23.1)	30 (76.9)	
SV, mean±SD (mL)	47.9±14.9	55.4±19.1	
Low, n (%)	7 (16.3)	36 (83.7)	0.151µ 0.443Ω
Normal, n (%)	8 (11.3)	63 (88.7)	
SVI, mean±SD (mL/m2)	27.7±8.9	31.3±10.4	
Low, n (%)	10 (15.2)	56 (84.8)	0.207µ 0.460Ω
Normal, n (%)	5 (10.4)	43 (89.6)	
CO, median (L/min)	4.2 (1.7-8.1)	4.1 (1.6-11.1)	
Low, n (%)	6 (11.3)	47 (88.7)	0.980¶ 0.589Ω
Normal, n (%)	9 (14.8)	52 (85.2)	

Variable	Cardiovascular Mortality		*p*
	Yes	**No**	
LAVI, median (mL/m2)	23.9 (12-52.8)	26.7 (6.5-63.9)	0.927¶
Height, n (%)	5 (12.8)	34 (87.2)	0.939$^{\Omega}$
Normal, n (%)	10 (13.3)	65 (86.7)	
LVVI, median (mL/m2)	53 (26.2-87)	51.3 (17.3-259.7)	0.438¶
Height, n (%)	5 (18.5)	22 (81.5)	0.343^
Normal, n (%)	10 (11.5)	77 (88.5)	
ePCWP, median (mmHg)	27.2 (15.5-46.8)	19.8 (8.5-45.3)	0.002¶*
Height, n (%)	15 (16.3)	77 (83.7)	0.072^
Normal, n (%)	0 (0)	22 (100)	
EF, mean±SD (%)	38.1±11.1	44.1±10.5	
Normal, n (%)	4 (12.5)	28 (87.5)	0.045µ*
Mildly reduced, n (%)	3 (7.1)	39 (92.9)	0.304#
Reduced, n (%)	8 (20)	32 (80)	
Degree of diastolic function			
Normal, n (%)	1 (7.1)	13 (92.9)	
Decreased grade I, n (%)	1 (2.9)	34 (97.1)	
Decreased grade II, n (%)	6 (13.3)	39 (86.7)	0.007#*
Decreased grade III, n (%)	6 (42.9)	8 (57.1)	
Indeterminate, n (%)	1 (16.7)	5 (83.3)	
E/e' average, median	20.4 (10.9-36.2)	14.3 (5.3-35)	0.002¶*
Height, n (%)	13 (18.3)	58 (81.7)	0.037$^{\Omega}$*
Normal, n (%)	2 (4.7)	41 (95.3)	
E/A Ratio, median	1.8 (0.8-3.3)	1.1 (0.4-4.3)	
Normal, n (%)	8 (10.8)	66 (89.2)	0.001¶*
Low, n (%)	0 (0)	26 (100)	0.007#*
High, n (%)	7 (50)	7 (50)	

µ Independent T Test
¶ Mann Witney Test
#Linear-by-Linear Association Test
^ Fisher's Exact Test
$^{\Omega}$Pearson Chi-Square Test
* Statistically significant
φEnter the multivariate test

As with cardiovascular rehospitalization, apart from the independent variable eKillip Class, the influence of the control variable on the dependent variable cardiovascular mortality with categorical scale data (gender, smoking, hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, PCI, and degree of diastolic function) was tested for significance using the Chi Square test. It is said to be significant if the p value is <0.05.

Meanwhile, the influence of the control variables on the dependent variable cardiovascular mortality with numerical scale data (variables age, BMI, SV, SVI, CO, EF, LAVI, LVVI, ePCWP, E/e' average, and E/A ratio) was tested for normality using the Kolmogorov-Smirnov. Variables that have a normal distribution are continued to be tested for significance using the Independent Sample T Test, while variables that are not normally distributed are continued to be tested for significance using the Mann-Whitney test. It is said to be significant if the p value is <0.05.

Based on the results of the significance test as shown in Table 5 and Table 6, variables that were significant for cardiovascular mortality were obtained, including: eKillip Class variables, age, diabetes mellitus, degree of diastolic function, E/e' average, and E/A ratio,with p < 0.05.

For variables with p < 0.25 that are theoretically related to the outcome, they will then be entered into a multivariate analysis to see whether there is an independent relationship with the outcome. However, as is the case with cardiovascular rehospitalization outcomes, variables that assess hemodynamics or are the main assessment component of the eKillip Class itself, even though they have a significant p value, are not included in the multivariate analysis of cardiovascular mortality outcomes. So, the variables that are then controlled through multivariate analysis are age, smoking, diabetes mellitus, and PCI.

Of the 114 AMI cases who underwent the eKillip Class assessment when they first arrived at the emergency room at the integrated heart service installation at Prof. Hospital. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, it is known that there are 39 patients in the eKillip Class IV category and 75 patients in the non-eKillip Class IV (eKillip Class I-III). Among the patients who underwent cardiovascular rehospitalization, there were 13 patients in the eKillip Class IV category and 9 patients in the non-eKillip Class IV category. An overview of the Kaplan Meier survival estimates for cardiovascular rehospitalization events based on eKillip Class value categories is shown in Figure 1.

Based on Table 7, the 30 day survival rate for cardiovascular rehospitalization in eKillip Class IV patients was 66.7% and the mean survival time was 24.7 days (95% CI = 21.9–27.6), while the 30 day survival rate in patients with non-eKillip Class IV was 88% and the mean survival time was 27.9 days (95% CI = 26.4–29.4). After the log rank test was carried out, it was found that there was a significant difference in the cardiovascular rehospitalization survival rate of eKillip Class IV and non-eKillip Class IV patients, with a value of p = 0.001.

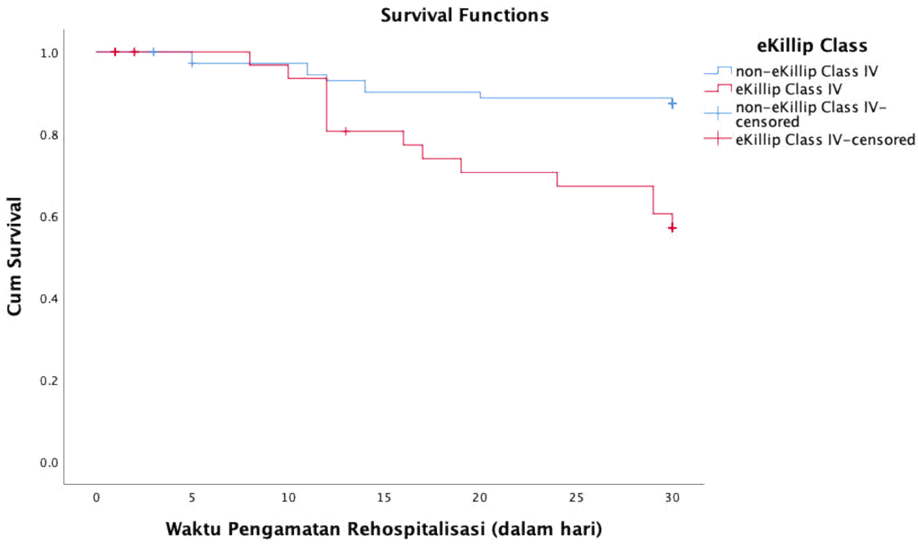

FIGURE 1: Kaplan Meier Survival Estimation Curve for the Occurrence of Cardiovascular Rehospitalization based on eKillip Class.

TABLE 7: Mean Survival Time and 30 Days Survival Rate for Cardiovascular Rehospitalization Based on eKillip Class.

Variable	***Mean Time Survival*(day)**	**IK (95%)**	***30 Days Survival Rate*(%)**	***p***
eKillip Class IV	24.7	21.9-27.6	66.7	0.001*
non-eKillip Class IV	27.9	26.4-29.4	88.0	

* Statistically significant.

Of the 114 AMI cases that underwent the eKillip Class assessment when they first arrived at the emergency room at the integrated heart service installation at Prof. Hospital. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, it is known that there are 39 patients in the eKillip Class IV category and 75 patients in the non-eKillip Class IV category.

Among the patients who experienced cardiovascular mortality, there were 9 patients in the eKillip Class IV category and 6 patients in the non-eKillip Class IV category. An overview of the Kaplan Meier survival estimates for cardiovascular mortality events based on eKillip Class value categories is shown in Figure 2 below.

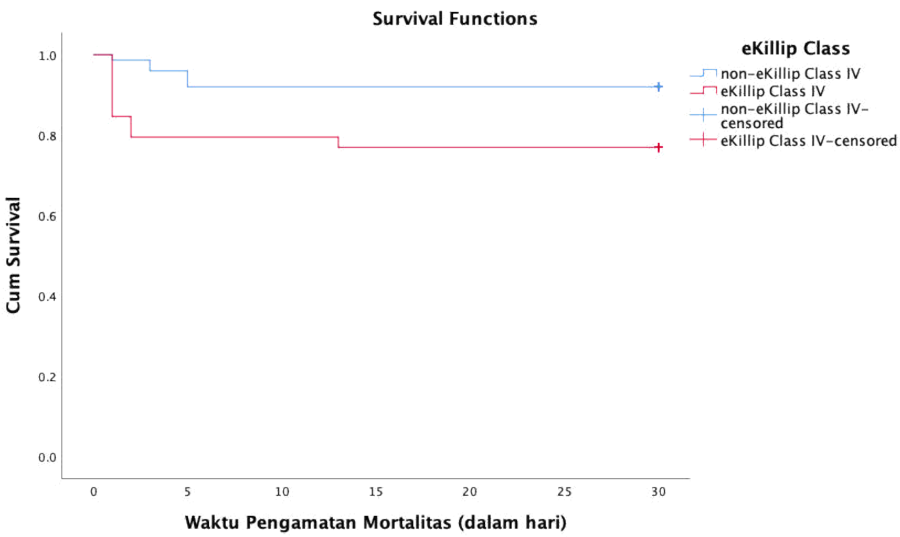

FIGURE 2: Kaplan Meier Survival Estimation Curve for the Occurrence of Cardiovascular Mortality based on eKillip Class Category.

Based on Table 8, the 30 day survival rate for cardiovascular mortality in eKillip Class IV patients was 76.9% and the mean survival time was 23.7 days (95% CI = 19.9–27.3), while the 30 day survival rate of patients with non-eKillip Class IV is 92% and the mean survival time is 27.8 days (95% CI =26.2-29.5). After the log rank test was carried out, it was found that there was a significant difference in the survival rate of cardiovascular mortality in eKillip Class IV and non-eKillip Class IV, with a value of p = 0.019.

TABLE 8: Mean Survival Time and 30 Days Survival Rate for Cardiovascular Mortality Based on eKillip Class.

Variable	*Mean Time Survival*(day)	IK (95%)	*30 Days Survival Rate*(%)	*p*
eKillip Class IV	23.7	19.9-27.3	76.9	0.019*
non-eKillip Class IV	27.8	26.2-29.5	92.0	

* Statistically significant.

In this study, eKillip Class was used as the independent variable, cardiovascular rehospitalization as the dependent variable, and other factors such as gender, smoking, hyperuricemia, hypertension, diabetes mellitus, PCI, and LVVI according to the selection results from previous bivariate analysis as confounding variables. The multivariate analysis used to independently determine the effect of the eKillip class on the incidence of cardiovascular rehospitalization was Cox regression.

In this analysis, eKillip Class is further divided into 2 categories, namely eKillip Class IV and non-eKillip Class IV. The effect of eKillip Class IV in AMI patients on the incidence of cardiovascular rehospitalization was significant compared with patients with non-eKillip Class IV (unadjusted HR 3.8; 95% CI 1.6–8.9; p = 0.002), as shown in Table 9.

This shows that the risk of cardiovascular rehospitalization within 30 days in AMI patients with eKillip Class IV was almost four times higher than in AMI patients with non-eKillip Class IV.

Based on Table 9, multivariate analysis shows that eKillip Class IV is proven to be an independent predictor of cardiovascular rehospitalization events in AMI patients within 30 days (adjusted HR 3.7; 95% CI 1.6–8.6; p = 0.003). This means that cardiovascular rehospitalization in AMI patients within 30 days with eKillip Class IV after controlling for confounding factors is almost four times higher than in patients with non-eKillip Class IV. However, not only eKillip Class IV, but there are other variables that have also been proven to remain independently associated with the incidence of cardiovascular rehospitalization, namely high LVVI (adjusted HR 4.2; 95% CI 1.8–9.7; p = 0.001).

TABLE 9: Multivariate Cox Regression eKillip High Class analysis of cardiovascular rehospitalization using the Backward LR (7 step) method.

Variable	*Unadjusted*HR	IK 95%	*p*	*Adjusted*HR	IK 95%	*p*
eKillip Class IV	3.8	1.6-8.9	0.002*	3.7	1.6-8.6	0.003*
JK (female)	2.5	1.1-6.0	0.037*	1.3	0.4-4.1	0.666
Smoke	0.5	0.2-1.2	0.135	0.6	0.2-1.6	0.347
Hyperuricemia	2,4	1.0-5.6	0.041*	1.4	0.5-3.9	0.494
Hypertension	1.6	0.6-3.9	0.314	1.5	0.6-3.9	0.367
Diabetes mellitus	2.1	0.9-4.9	0.073	1.9	0.8-4.6	0.135
PCI	2.1	0.9-4.9	0.082	1.9	0.8-4.7	0.124
LVVI (high)	4.1	1.7-9.4	0.001*	4.2	1.8-9.7	0.001*

* Statistically significant.

In this study, eKillip Class was used as the independent variable, cardiovascular mortality as the dependent variable, and other factors such as age, smoking, diabetes mellitus, and PCI, according to the selection results from the previous bivariate analysis, as confounding variables. The multivariate analysis used to determine the influence of the eKillip class on the incidence of cardiovascular mortality independently was Cox regression.

TABLE 10: Cox Regression eKillip Class IV analysis as a predictor of cardiovascular mortality using the Backward LR (4 step) method.

Variable	*Unadjusted*HR	IK 95%	*p*	*Adjusted*HR	IK 95%	*p*
eKillip Class IV	3,2	1.1-8.9	0.028*	3.5	1.2-9.9	0.018*
Age (elderly)	4.6	1.4-14.3	0.009*	4.9	1.6-15.6	0.006*
Smoke	0.4	0.1-1.3	0.133	0.7	0.2-2.1	0.481
Diabetes mellitus	2.7	0.9-7.6	0.060	1.6	0.5-4.9	0.435
PCI (no)	2.9	1.1-8.2	0.036*	2.1	0.7-5.8	0.171

* Statistically significant.

As with cardiovascular rehospitalization, in this multivariate analysis, eKillip Class is further divided into 2 categories, namely eKillip Class IV and non-eKillip Class IV. The effect of eKillip Class IV in AMI patients on the incidence of cardiovascular mortality was significant compared to patients with non-eKillip Class IV (unadjusted HR 3.2; 95% CI 1.1–8.9; p = 0.028), as shown in Table 10. This shows that the risk of cardiovascular mortality within 30 days in AMI patients with eKillip Class IV was three times higher than in AMI patients with non-eKillip Class IV.

Based on Table 10, multivariate analysis also shows that eKillip Class IV is proven to be an independent predictor of cardiovascular mortality in AMI patients within 30 days (adjusted HR 3.5; 95% CI 1.2–9.9; p = 0.018). This means that cardiovascular mortality in AMI patients within 30 days with eKillip Class IV after controlling for confounding factors is 3.5 times higher than in patients with non-eKillip Class IV. However, not only eKillip Class IV, there are other variables that have also been proven to remain independently associated with cardiovascular mortality, namely elderly age (adjusted HR 4.9; 95% CI 1.6-15.6; p = 0.006).

DISCUSSION

Acute myocardial infarction (AMI) remains a burden of disease worldwide, being one of the main causes of death. AMI complications are also a cause of morbidity and mortality. As science develops, especially in the cardiovascular field, understanding regarding the management of acute myocardial infarction is also growing.

Major cardiovascular events are a form of AMI complication that is related to the patient's survival and quality of life, including cardiovascular rehospitalization and mortality. The high morbidity and mortality due to AMI complications has encouraged efforts to develop a risk stratification system for AMI patients.

Several AMI stratification systems have been widely applied in daily practice, one of which is the Killip classification. The Killip classification is still a clinical classification method regarding the patient's hemodynamic condition and is used for real-time risk assessment [6]. The Killip classification system was introduced for the clinical assessment of patients with acute myocardial infarction, which groups individuals according to the severity of heart failure resulting from their myocardial infarction as well as being significantly associated with all-cause mortality among all patients with cardiovascular disease. This system provides effective stratification of long-term and short-term outcomes in patients with acute myocardial infarction, as well as influencing treatment strategies [7].

However, as a hemodynamic assessment, determining the Killip classification is quite subjective because the main basis is a physical examination [8]. The objective hemodynamic assessment modality that is quite easy to carry out to date is echocardiography [11, 12].

Echocardiography based on the Killip classification can provide a combined hemodynamic assessment, which will be used to objectively assess the patient's hemodynamics. As explained in the previous chapter, the combined hemodynamic classification using echocardiography based on inspiration from the Killip classification is called the Echocardiography Killip Classification (eKillip Class). The eKillip classification is defined based on diastolic function and SVI. eKillip Class is divided into 4 classifications, including eKillip class I (normal SVI [≥35 mL/m2] with normal diastolic function or grade I diastolic dysfunction), eKillip class II (normal SVI with grade 2 or indeterminate diastolic dysfunction), eKillip class III (normal SVI with grade 3 diastolic dysfunction or decreased SVI with normal diastolic dysfunction or grade I diastolic dysfunction or indeterminate), and eKillip class IV (decreased SVI [<35 mL/m2] with grade 2 or 3 diastolic dysfunction) [6].

This study evaluates the eKillip Class as a predictor of KKM, especially cardiovascular rehospitalization and mortality in AMI patients. An important finding from this study is that a high eKillip class is a predictor of KKM in patients with AMI. It is hoped that the results of this research will be able to provide additional information to support the "clinical judgment" of a heart and blood vessel specialist in carrying out risk stratification and management considerations for AMI patients.

This study involved 114 patients with acute myocardial infarction who were treated in the emergency room and treatment room at the Integrated Heart Services Installation at Prof. Dr. I.G.N.G. Ngoerah Hospital by fulfilling the predetermined inclusion and exclusion criteria. Of this number, 39 patients (34.2%) fell into the eKillip Class IV category, while the eKillip Class I to III categories consisted of 25 (21.9%), 20 (17.5%), and 30 (26.3%) patients, respectively. Overall, the non-eKillip Class IV category (eKillip Class I to III) included 75 patients (65.8%). This finding is quite different from the previous journal, which also discussed eKillip Class; in that journal, patients with eKillip Class IV were only 7% of the total sample [6]. This is due to the different types of populations; in the previous journal, all patients underwent echocardiography without looking at the underlying disease, whereas this study specifically uses patients with acute myocardial infarction, which essentially causes hemodynamic changes ranging from mild to threatening [14]. So many AMI patients fall into the higher category, such as eKillip Class III and IV.

A similar study on combined hemodynamic assessment via echocardiography conducted in 2017 by Abbas et al. said that dividing heart failure patients based solely on ejection fraction (EF) might oversimplify the patient's hemodynamic condition, so a heart failure hemodynamic model was created based on the correlation between SVI (< or ≥35 mL/m2) and left atrial pressure (E:E′ ≥ or <15). The classification is divided into 4 groups, including group A (normal flow and normal filling pressure), group B (normal flow and high filling pressure), group C (low flow and low filling pressure), and group D (low flow and high filling pressure). It was found that patients with HFrEF mostly had a group D hemodynamic classification profile, whereas patients with HFpEF had varying hemodynamic classification profiles [15].

This non-invasive combined hemodynamic classification via echocardiography is a fairly easy but powerful model as an adaptation of the Killip classification model. There is also an invasive combined hemodynamic classification model, which is also an adaptation of the Killip classification model, namely the Diamond Forrester classification, which is assessed using pulmonary capillary wedge pressure (PCWP) and cardiac index (CI), with limits of 18 mmHg and 2.2 L/m2, respectively. In the Diamond Forrester classification, patients are classified into 4 groups: low PCWP group (< 18 mmHg) with normal CI (> 2.2 L/m2), high PCWP group (> 18 mmHg) with normal CI (> 2.2 L/m2), PCWP group low (< 18 mmHg) with low CI (< 2.2 L/m2), and high PCWP group (> 18 mmHg) with low CI (< 2.2 L/m2). The mortality rate in this group is in the range of 3% to 51% [16].

Research by Donato Mele et al. in 2020 also showed that patients with more severe heart failure had a higher percentage of those in the low combined echocardiography profile category. In his study, in a subsample of 200 heart failure patients, left ventricular SVI, left ventricular filling pressure estimation (LV filling pressure estimation), tricuspid annular plane systolic excursion (TAPSE), and systolic pulmonary artery pressure (sPAP) were combined to determine four hemodynamic profiles: normal flow-normal pressure, normal flow-high pressure, low flow without RV dysfunction, and low flow with RV dysfunction profile. [17]

Based on the characteristics of the research subjects, apart from cardiovascular rehospitalization and mortality, which are the main outcomes of this study, there are other variables that are also significant to the eKillip Class, namely PCI. Patients who do not undergo PCI tend to have a higher percentage in the high eKillip Class category. PCI is a revascularization procedure to open blockages in blocked coronary arteries, which can restore blood supply to the ischemic myocardium in an effort to limit ongoing damage, reduce ventricular irritability, and improve short- and long-term outcomes in patients with ACS [18]. Restoration of myocardial blood flow leads to improved metabolic function, so revascularization is essential in management. Decreased myocardial blood flow causes mitochondrial dysfunction and sarcoplasmic reticulum dysregulation, resulting in decreased adenosine triphosphate production and impaired ion pumps, which can lead to ischemia, ultimately compromising hemodynamics. The longer the ischemia occurs, the more severe the complications that lead to hemodynamic disorders [19]. These theories support the description of the characteristics of research subjects, where significantly more patients who did not undergo PCI were in the high eKillip Class category.

Similar things regarding the relationship between revascularization and hemodynamic improvements in AMI patients were also found in research by Fortuni et al. in 2019. From a total of 2387 samples, there were 1254 AMI samples that underwent revascularization and showed significant hemodynamic improvements compared to those that did not undergo revascularization [20].

In this study, the average age of all participants was 58 ± 10.4 years, with 93 people (81.6%) male and 21 people (18.4%) female. Based on the eKillip Class category, there is no significant age difference. Likewise, gender does not differ significantly between each eKillip class. Research by Ramteke et al. in 2023 also obtained similar data, where of the total AMI sample, the average age was 58.2 ± 10.7 years, with 82.1% male [21]. Based on data from a nationwide prospective registry, Junxing Lv et al. found that patients aged ≤ 45 years accounted for 8.5% of the total acute myocardial infarction patients in China. Young patients with AMI tend to be more male. In addition, it was also said that young patients were more likely to experience myocardial infarction related to the left anterior descending artery (LAD) and be treated with PCI than older patients. Nevertheless, treatment outcomes were significantly better in younger patients than in older patients [22]. Although the number of female patients with acute myocardial infarction is lower, a French study analyzed data from 74,389 patients hospitalized for acute myocardial infarction and found that female patients had a higher in-hospital mortality rate (14.8% compared with 6.1%; $p < 0.0001$) [23]. Another study with a similar population variation found that women with AMI in France were on average older (75 years compared with 63 years; $p < 0.001$). Female gender independently increased in-hospital mortality by nearly 7% in STEMI cases but was associated with reduced mortality in NSTEMI cases [24]. However, there are also studies that do not show any differences in hospital mortality related to gender. In a nationwide cohort study of AMI patients in Poland, female gender did not increase in-hospital mortality with an OR of 0.97 [25].

In terms of body weight, which is assessed based on body mass index (BMI), there are no significant differences between each eKillip class. However, the majority of samples in this study were classified as normal (49.1%). This research is supported by research conducted by Patlolla et al., where of a total of 6,089,979 acute myocardial infarction patients, it was found that 5,094,721 (83.7%) were classified as having a having a normal BMI, the remaining 38,070 (0.6%) were below-weight, and 957,188 (15.7%) were overweight or obese. In this study, most of the acute myocardial infarction patients who were overweight or obese were younger and more likely to be women compared to the normal BMI group [26]. Being overweight and obese increases the incidence of AMI, which is in accordance with its pathophysiology, including through the mechanisms of inflammation and atherosclerosis, so it is important to control body weight as a preventative measure. [27].

Nonetheless, there appears to be an "obesity paradox" among patients after MI such that higher BMI is associated with lower mortality, an effect that is not modified by patient characteristics and is similar across age groups, gender, and diabetes subgroups [28, 29]. When BMI was evaluated as a continuous variable, the hazard curve decreased with increasing BMI and then increased above a BMI of 40. Compared with patients with a BMI of 18.5, patients with a higher BMI had a 20% to 68% lower 1-year mortality [28].

Analysis of several classic AMI comorbidities in this study showed that hypertension was the most common comorbid disease (57%), followed by diabetes mellitus (36.7%) and high LDL levels. Comorbidities are common and have a major negative impact on the prognosis of patients with acute myocardial infarction. Research by Junxing Lv et al. in 2021 stated that patients with AMI tend to have a medical history of hyperlipidemia [22]. In a study conducted by Yadegarfar et al., 412,809 acute myocardial infarction patients had at least one comorbidity, including hypertension (302,388 [48.7%]), diabetes (122,228 [19.4%]), chronic obstructive pulmonary disease (COPD), 89,221 [14.9%]), cerebrovascular disease (51,883 [8.6%]), chronic heart failure (33,813 [5.6%]), chronic renal failure (31,029 [5.0%]), and peripheral blood vessels (27,627 [4.6%]) [30]. Naderi et al.'s research in 2014 showed that hypertension, diabetes mellitus, liver disease, chronic lung disease, chronic kidney failure, obesity, hyperlipidemia, smoking, and anemia were not associated with a higher risk of AMI after acute myocardial infarction. Although diabetes mellitus and smoking are known risk factors for AMI and have been considered in the stroke scoring systems in ABCD2 and ESSEN, However, the current study suggests that these factors are not independent risk factors for AMI in patients treated for acute myocardial infarction [31]. In this study, smoking also did not show a significant difference in AMI patients with or without KKM outcomes. While diabetes mellitus in this study showed a significant difference compared to no diabetes mellitus in major cardiovascular events, it was not an independent risk factor for major cardiovascular events in patients with AMI.

In this study, the heart failure phenotype was identified based on the ejection fraction (EF) of left ventricular function. The results of the analysis showed that 35.1% of the sample fell into the HFrEF category, which is characterized by poor EF (<40%). A total of 28.1% of the sample was classified as HFpEF, which is characterized by normal EF (≥ 50%) with signs and symptoms of heart failure. Meanwhile, the remaining 36.8% are included in HFmrEF, namely mild low EF (40%–49%). In research conducted by Abbas et al., it was shown that in HFrEF, there was a tendency to increase levels of type B natriuretic peptide with a decrease in stroke volume index (SVI) and an increase in the degree of diastole seen from the E/e' ratio (P = 0.05), which was rare. in HFpEF. In his study, it was shown that in HFrEF, the majority of patients had low SVI and high filling pressure compared to patients with HFpEF, whose distribution was more heterogeneous (P<0.001). In addition, the study also showed no difference in major cardiovascular events between the two groups, with increased rehospitalization in HFpEF patients [15]. Apart from EF, there are several echocardiographic characteristics of research subjects that are significant to the eKillip Class, such as stroke volume, CO, LAVI, PCWP, degree of diastolic function, and E/e average. Stroke volume, CO, LAVI, degree of diastolic function, and E/e average are constituent components of the eKillip Class itself, where the more abnormal the value, the higher the eKillip Class category [6].

Pulmonary capillary wedge pressure (PCWP) is an integrated measurement of the compliance of the left side of the heart and pulmonary circulation. PCWP measurement can be useful in some diagnostic situations, where it can be measured via echocardiography or catheterization. PCWP can increase in conditions of increased left ventricular filling pressure due to disorders of the left ventricle, such as cases of MI [32]. In other similar combined hemodynamic studies, PCWP was used as part of a combined hemodynamic measurement along with cardiac index (CI), called the Diamond Forrester classification, as previously described. Patients in the high PCWP group with a low CI had the highest mortality percentage [16].

In this study, during a follow-up period with a median of 30 days, 19.3% of the sample experienced cardiovascular rehospitalization and 13.2% experienced cardiovascular mortality. These two major cardiovascular events showed a significant relationship with the eKillip Class, which will be discussed more specifically in the next sub-chapter.

In this study, based on the analysis of research results and the distribution of cardiovascular rehospitalization based on the characteristics of the research subjects, apart from eKillip Class, it was found that gender and LVVI were also significantly related to the incidence of cardiovascular rehospitalization. These variables, along with other confounding variables such as diabetes mellitus and hyperuricemia, were controlled to determine the independence of the eKillip Class on cardiovascular rehospitalization.

An eKillip Class IV was analyzed as a predictor of cardiovascular rehospitalization events in patients with acute myocardial infarction (AMI). The results showed that among patients who underwent cardiovascular rehospitalization, there was a significant difference in survival rate between patients with eKillip Class IV and non-eKillip Class IV. The 30-day cardiovascular rehospitalization survival rate in patients with eKillip Class IV is lower than in patients with non-eKillip Class IV, with a shorter average survival time.

Furthermore, the risk of 30-day outcomes in AMI patients with eKillip Class IV compared to non-eKillip Class IV patients was also evaluated, which showed that patients with eKillip Class IV had a higher risk of cardiovascular rehospitalization events in the 30-day period after AMI compared with patients with non-eKillip Class IV. An eKillip Class IV, even after controlling for confounding factors. These findings indicate that eKillip Class IV is an independent predictor of cardiovascular rehospitalization events in AMI patients.

An eKillip Class IV is a combination of low SVI and high diastolic pressure. In theory, this is equivalent to cardiogenic shock and significant cardiovascular dysfunction, which is the most severe condition of acute heart failure. Cardiogenic shock is caused by a severe reduction in myocardial performance, resulting in reduced cardiac output, end organ hypoperfusion, and hypoxia [33, 34]. Vahdatpour et al. from the AHA article also stated that the main cause of cardiogenic shock in AMI is a decrease in myocardial contractility, which results in reduced cardiac output, hypotension, systemic vasoconstriction, and cardiac ischemia, where the characteristic features are peripheral vasoconstriction and damage to vital end organs, which is caused by ineffective stroke volume and insufficient circulation compensation. Compensatory peripheral vasoconstriction may initially improve coronary and peripheral perfusion, but it contributes to increased cardiac afterload that overloads the damaged myocardium. So oxygenated blood flow is reduced to peripheral tissues and, ultimately, to the heart [34]. Myocardial diastolic function is also impaired in cardiogenic shock, where myocardial ischemia causes decreased compliance and increased left ventricular filling pressure. In addition, the compensatory increase in left ventricular volume to meet stroke volume ultimately increases filling pressure. Clinically, this condition will cause pulmonary edema and hypoxia [34, 35].

Patients with AMI, both STEMI and NSTEMI, are the conditions that contribute to the highest incidence of cardiogenic shock, up to 81%. However, this does not mean that patients with AMI will develop cardiogenic shock; in prevalence, the percentage of AMI patients experiencing cardiogenic shock complications is around 5% to 10%. The incidence of rehospitalization within 30 days after AMI is said to reach 18.6% with a median of 10 days, where patients with STEMI are slightly lower than those with NSTEMI, with the most frequent conditions according to the course of the disease being heart failure and recurrent AMI. Apart from that, female gender, low socioeconomic status, and the use of mechanical circulatory assistance are also mentioned as predictors of rehospitalization in AMI patients [34, 36, 37]. Research by Arnold et al. also said that in hierarchical and multivariable models, the strongest predictors of rehospitalization for AMI were female gender with HR 1.67 and in-hospital PCI with HR 1.85 [38].

In general, rehospitalization after acute myocardial infarction is not only expensive but can also impact the patient's quality of life. A study conducted by Arnold et al. estimated the rates of rehospitalization due to AMI and revascularization after acute myocardial infarction to be 6.8% and 4.1%, respectively [38]. Based on research from Kwok CS et al in 2017 which evaluated rehospitalization within 30 days after AMI, of the total post-AMI patients, 9% of patients experienced rehospitalization, of which around 17.1% of patients experienced AMI recurrence, 11.6% of patients experienced stable angina, and 9.8% experienced failure of heart [39]. In another similar study by Kim LK et al. (2018), of all STEMI patients who were hospitalized based on data from the Nationwide Readmissions Database (NRD) from 2010 to 2014, within 7 days and 30 days after hospitalization, 43.9% and 12.3% of patients experienced rehospitalization. either in the form of recurrent AMI or acute heart failure. Post-AMI rehospitalization also poses a huge economic burden to the country's health system, with rehospitalization within 30 days said to result in a 50% increase in cumulative inpatient costs. Moreover, AMI patients with cardiogenic shock will have a higher level of burden [40].

Thus, risk stratification of AMI patients is very important as a basis for making management decisions; namely, the eKillip Class assessment can be a useful tool to identify patients at high risk and guide more intensive clinical management.

Apart from eKillip Class IV, another variable in this study that was also proven to be independently associated with the incidence of cardiovascular rehospitalization was high LVVI. The left ventricular volume index (LVVI), in this case the left ventricular end diastolic volume index (LVEDVI), is an echocardiography examination to assess the size and volume of the left ventricle. According to the 2015 ASE/EACVI heart chamber quantification guidelines and standards, the normal range for left ventricular volume based on BSA is 54±10 mL/m2 (2-SD range: 34-74 mL/m2) in men and 45±10 mL/m2 (2-SD range: 29-61 mL/m2) in women [41]. The results of this research analysis are related to the process of ventricular remodeling after myocardial infarction, which is a common cause of heart failure [42].

Left ventricular remodeling due to acute myocardial infarction is a type of pathological remodeling process [20, 43]. Adverse remodeling of the left ventricle is a maladaptive process caused by cardiac injury characterized by morphological changes in LV shape and structure, with subsequent changes to cardiac function [42]. Adverse remodeling after myocardial infarction is defined as a complex interaction between cellular and extracellular components of the myocardium, where neurohormonal and epigenetic regulation causes changes in cardiac architecture (cardiac architectonics) and geometry that affect both atrial and ventricular [44]. Even with revascularization, injuries caused by myocardial ischemia can still cause adverse left ventricular remodeling, which can then progress to heart failure [45]. Another previous study by Kazato Ito et al. in 2021 also showed the same thing, where left ventricular dilation was an independent predictor of cardiovascular events [46].

This study also investigated eKillip Class IV as a predictor of cardiovascular mortality in AMI patients. The findings showed a significant difference in survival rates between patients with eKillip Class IV and non-eKillip Class IV. Patients with eKillip Class IV had a lower survival rate within 30 days of acute myocardial infarction, indicating a worse prognosis.

The results showed that among patients who experienced cardiovascular mortality, there was a significant difference in survival rate between patients with eKillip Class IV and non-eKillip Class IV. The survival rate for cardiovascular mortality within 30 days in patients with eKillip Class IV is lower than in patients with non-eKillip Class IV, with a shorter average survival time.

Based on risk analysis, the risk of cardiovascular mortality events within 30 days in AMI patients with eKillip Class IV compared to non-eKillip Class IV patients was also evaluated, which showed that patients with eKillip Class IV had a higher risk of cardiovascular mortality events in the 30-day period after AMI. compared to patients with non-eKillip Class IV, even after controlling for confounding factors. These findings indicate that eKillip Class IV is an independent predictor of cardiovascular mortality in AMI patients.

After an acute myocardial infarction, myocardial ischemia, cell necrosis, microvascular dysfunction, and regional wall motion abnormalities occur that affect the rate of active relaxation. In addition, interstitial edema, fibrocellular infiltration, and scar tissue formation will directly influence left ventricular (LV) stiffness. Therefore, abnormalities in LV filling are common in this condition. LV pressure load will cause myocyte stretching, increased wall stress, poor subendocardial perfusion, and reduced energy production. This is then related to neurohormonal activation and ventricular remodeling. Although the remodeling process will initially restore ejection volume and systemic hemodynamics, continued dilatation will have detrimental effects on long-term LV function and survival. Ventricular remodeling and hyperactivity of the renin-angiotensin-aldosterone system likely contribute to excess mortality in these patients [47]. AMI also plays a role in systemic inflammation that causes pathological vasodilation, releasing nitric oxide synthase and peroxynitrite, which have cardiotoxic inotropic effects. Interleukins and tumor necrosis factor alpha (TNF-a) are additional systemic inflammatory mediators that cause vasodilation and contribute to death in AMI patients with cardiogenic shock [34].

At normal physiological pressure, the right ventricular stroke volume and the left ventricular stroke volume are the same. Right ventricular failure (RVF) occurs when ventricular diastolic and/or systolic pressures are not sufficiently compensated by normal myocardial adaptive processes to produce an appropriate stroke volume.

Inadequate blood flow in the compromised right ventricle (RV) causes end-organ perfusion deficits along with increased venous pressure. The RV is less adaptive to afterload pressure and more tolerant of volume overload than the left ventricle (LV), which explains the inability of the right ventricle to tolerate very high increases in pulmonary artery pressure. When RVF results in RV dilatation, the interventricular septum migrates into the left ventricular chamber, impairing LV diastolic filling and further exacerbating systemic hypoperfusion, thereby increasing the risk of mortality [34].

Research by Kim LK et al. (2018) of all hospitalized STEMI patients based on data from the Nationwide Readmissions Database (NRD) from 2010 to 2014, The incidence of mortality in patients with AMI occurs at approximately 8.7% (95% CI, 8.6–8.8), 4.6% (95% CI, 4.5–4.7), 5.4% (95% CI, 5.2–5.7), and 25.1% (95% CI, 24.9–25.3) for overall patients, patients with PCI, patients with CABG, and patients without revascularization, respectively, with a p value < 0.001 [40]. Canto et al. (2012) analyzed data from the National Registry of Myocardial Infarction from 1994 to 2006 on 1,143,513 registered patients, finding that the in-hospital mortality rate was 14.6% in women and 10.3% in men [48]. In a study by Naderi et al. (2014), it was discovered that in a large number of patients treated for acute myocardial infarction between 2006 and 2008 in the United States, the rate of major cardiovascular events in hospitals was found to be relatively low, namely 2%. Although this figure is lower, Naderi et al. found that major cardiovascular events were associated with 3.4 times higher cardiovascular mortality compared with patients without cardiovascular events, which is equivalent to a 3-fold increase in mortality according to other studies [31].

Research by Donato Mele et al. in 2020 regarding combined hemodynamic echocardiography and mortality showed that the group of patients with a poor combined hemodynamic echocardiography profile (low flow with RV dysfunction) was associated with a worse heart failure profile and had a significantly lower survival rate. lower than the better combined hemodynamic echocardiographic profile. In addition, patients with a poor combined hemodynamic echocardiographic profile can independently predict mortality [17].

In research conducted by Milwidsky et al., it was found that eKillip Class was significantly correlated with major cardiovascular events, with eKillip Class II having a hazard ratio of 2.73, eKillip Class III 3.19, and eKillip Class IV 4.79 against eKillip Class I. Multivariate analysis showed that a high eKillip class remained independently associated with mortality [6].

Hemodynamic assessment in AMI patients is very important for risk stratification and as a basis for determining management. Hemodynamic assessment, in this case represented by the eKillip Class, can be a useful tool in identifying AMI patients at high risk of cardiovascular mortality.

Apart from eKillip Class IV, there were other variables in this study that were also proven to be independently related to the incidence of cardiovascular mortality, namely elderly age. The term 'elderly' is applied to individuals aged 60 years and older, who represent the fastest-growing segment of the population worldwide. The percentage of elderly people in developing countries tends to be small, although the numbers are often large. In 1990, there were more than 280 million people aged 60 years and over in developing regions of the world [49].

Age is often associated with abnormalities in the body's organs, including the cardiovascular system. The physiological changes of aging are closely related to the pathophysiology of cardiovascular disease, and comorbid conditions often complicate clinical management. As a result of complex molecular and cellular aging processes over decades, cardiovascular physiology in older adults is characterized by: (1) endothelial dysfunction; (2) increased arterial stiffness; (3) increased left ventricular stiffness; (4) altered function and coupling of the left ventricle and arterial stiffness; (5) weakening of the baroreflex and autonomic reflexes; and (6) degenerative changes in the conduction system [50].

Cardiovascular aging is a complex process of adaptive structural and functional changes over time. With increasing age, the elasticity and compliance of the arteries begin to thicken and decrease, resulting in an increase in pulse wave velocity, systolic blood pressure, and left ventricular afterload. In response to these arterial changes, the myocardium remodels to maintain systolic function and diastolic filling. This adaptive mechanism is not always pathological but increases susceptibility to myocardial ischemia and heart failure (Singam et al., 2019). Thus, advanced age is an important risk factor for cardiovascular disease and is a strong independent predictor of cardiovascular morbidity, mortality, and disability [50].

The results of this study are in line with research by Salari et al. in 2023, which showed that of a total of 2,982,6717 AMI patients, patients aged >60 years experienced a significantly higher percentage of mortality, namely 9.5%, compared to patients aged <60 years, namely 3.8% [51]. Another study by Rodgers et al. in 2019 also said the same thing: cardiovascular incidents increased with age [52]. Including old research from 2011 by Carro and Kaski, it also showed that the incidence of cardiovascular mortality was significantly higher in elderly patients with AMI [53].

Like most research, this study also has limitations, namely that it did not examine other residual confounding factors such as family history, mechanical complications, Dressler syndrome, malignant arrhythmias, valvular heart disease, peripheral vascular disease, stroke, and psychosocial disorders, which are listed in the framework of thinking and concepts. Research based on a literature review, which in theory can also influence eKillip Class and/or major cardiovascular events, both cardiovascular rehospitalization and mortality. This is because the data is not yet available, so it cannot be measured to be taken into account in the analysis.

CONCLUSION

This study, with a prospective cohort design, has evaluated the Echocardiography Killip Classification (eKillip Class) as a predictor of major cardiovascular events, especially cardiovascular rehospitalization and mortality, in acute myocardial infarction (AMI) patients within 30 days.

Based on the results of the research analysis, it can be concluded that eKillip Class can be an independent predictor of cardiovascular rehospitalization and mortality events in patients with acute myocardial infarction. Patients with eKillip Class IV had a worse prognosis and higher risk for cardiovascular rehospitalization and mortality events compared with patients with non-eKillip Class IV.

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 the Prof. Dr. I.G.N.G. Ngoerah Hospital/Faculty of Medicine, Udayana University

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