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Systemic Immune-Inflammation Index as A Predictor of Mortality and Rehospitalization in Heart Failure Patients

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ABSTRACT

Background: Heart failure (HF) is a disease closely associated with inflammation and the *Systemic Immune inflammation Index* (SII) is a novel inflammatory marker. SII is a combined inflammatory indicator that incorporates three significant immune cells namely neutrophils, lymphocytes and platelets. SII is considered an excellent indicator of local immune response and systemic inflammation. SII is an inexpensive and easily accessible laboratory test in peripheral health facilities.

Research Objective: This study aims to determine whether SII can be used as a predictor of clinical outcomes, which are mortality and rehospitalization in patients with chronic heart failure.

Research Methods: This study is a retrospective cohort study using data of chronic heart failure patients who underwent hospitalization from the HF (Heart Failure) registry of Dr. Sardjito Hospital for the period January 2022 - February 2023. SII was calculated as platelet count × absolute neutrophil count / absolute lymphocyte count.

Results: There were 188 patients who met the inclusion criteria as research subjects from 282 chronic heart failure patients who underwent hospitalization. Subjects had a mean age of 58.80 ± 11.48 years. A total of 67,6% (n=127) of the subjects were male. SII value for mortality based on *receiver operating characteristic* (ROC) *cut-off* was 1459,59 (*area under curve* (AUC) 0.600, sensitivity (Sn) 55,6%, specificity (Sp) 68,8%) and the ROC cut-off for rehospitalization was 0,474. Kaplan-Meier analysis of SII with mortality, subjects with highSII values (>1459.59) had a 50,5% survival rate with a mean survival of 8,5 months and low SII (<1459.59) had a 74% survival rate with a mean survival of 9,9 months. Multivariate regression analysis found SII as an independent predictor of mortality *odds ratio* (OR 3,08, 95% confidence interval (CI) 1,59 – 5,95, p=<0.001) but not significant for rehospitalization.

Conclusion: Systemic Immune-inflammation Index (SII) is an independent predictor of mortality, but not a predictor of rehospitalization in chronic heart failure patients undergoing hospitalization.

INTISARI

Latar Belakang: Gagal jantung atau *heart failure* (HF) adalah penyakit yang terkait erat dengan peradangan dan *Systemic Immune-inflammation Index* (SII) adalah penanda inflamasi baru. SII merupakan indikator inflamasi gabungan dari tiga sel imun yang signifikan yaitu neutrofil, limfosit dan trombosit. SII dianggap sebagai indikator yang sangat baik untuk respon imun lokal dan inflamasi sistemik. SII merupakan pemeriksaan laboratorium yang murah dan mudah dijangkau di fasilitas kesehatan perifer.

Tujuan Penelitian: Penelitian ini bertujuan untuk mengetahui SII dapat digunakan sebagai prediktor terhadap luaran klinis yakni mortalitas dan rehospitalisasi pada pasien gagal jantung kronik.

Metode Penelitian: Penelitian ini merupakan studi kohort retrospektif menggunakan data pasien gagal jantung kronik yang menjalani rawat inap dari registri HF (Heart Failure) RSUP Dr. Sardjito periode

Januari 2022 - Februari 2023. SII dihitung sebagai jumlah trombosit × jumlah neutrofil absolut/jumlah limfosit absolut.
Hasil: Didapatkan 188 pasien yang memenuhi kriteria inklusi sebagai subjek penelitian dari 282 pasien gagal jantung kronik yang menjalani rawat inap. Subjek penelitian memiliki rerata usia 58.80 ± 11.48 tahun. Sebanyak 67,6% (n=127) subjek merupakan laki-laki. Didapatkan nilai SII terhadap mortalitas berdasarkan *cut-off receiver operating characteristic* (ROC) yaitu 1459,59 (*area under curve* (AUC) 0,600, sensitivitas (Sn) 55,6%, spesifisitas (Sp) 68,8%) dan cut-off ROC terhadap rehospitalisasi yaitu 0,474. Dari analisis *Kaplan-Meier* SII dengan mortalitas, subjek dengan nilai SII tinggi (>1459,59) memiliki tingkat ketahanan hidup 50,5% dengan rerata survival 8,5 bulan dan SII rendah (<1459,59) memiliki tingkat ketahanan 74% dengan rerata survival 9,9 bulan. Analisis regresi multivariat didapatkan SII sebagai prediktor independen terhadap mortalitas odds ratio (OR 3,08, interval kepercayaan (IK) 95% 1,59-5,95, p=<0,001) namun tidak signifikan terhadap rehospitalisasi.
Simpulan: Systemic *Immune-inflammation Index* (SII) merupakan prediktor independen terhadap mortalitas, namun tidak sebagai prediktor rehospitalisasi pada pasien gagal jantung kronik yang menjalani rawat inap.

INTRODUCTION

In developed countries, the age-specific incidence of heart failure may be decreasing, possibly due to a better cardiovascular disease management, but as people get older, the overall incidence increases. According to 2018 Basic Health Research data, the prevalence of heart failure in Indonesia is estimated at 1.5%[1]. This disease contributes to higher healthcare costs, decreased functional capacity, and significantly affects quality of life. It is very essential to diagnose and treat this disease effectively to prevent re-hospitalization, reduce morbidity and mortality, and improve patient outcomes[2].

Between 2000 and 2010, the mortality rates at one and five years after being diagnosed for all types of HF patients in the Olmsted County cohort were 20% and 53%. According to the Centers for Disease Control and Prevention (CDC) in December 2015, heart failure was the cause of 96.9 deaths per 100,000 people in 2014, up from 89.5 deaths in 2009 and 103.1 deaths per 100,000 people in 2000. The estimated death rate following heart failure hospitalization is 10% in 30 days, 22% in 1 year, and 42% in 5 years. In individuals with stage D heart failure, this percentage can rise to more than 50%[3].

Inflammation contributes to the pathogenesis and progression of heart failure through a variety of mechanistic pathways, including effectors such as proinflammatory cytokines, components of the innate and humoral immune responses, and inflammatory mediators generated by the spleen, adipose tissue, and gastrointestinal tract. The proinflammatory cytokines IL-1 and TNF-α induce systolic and diastolic dysfunction, as well as adverse cardiac remodeling[4]. Circulating immune cells and their subtypes have an important indicative effect on the prognosis of cardiovascular diseases. Neutrophils, lymphocytes, and platelets are all escalating indicating that there is a relative increase in platelets and neutrophils or a relative decrease in lymphocytes. Neutrophils are the main component of white blood cell, making up 60-70% of total white blood cells and playing an important role in the nonspecific immune system. In the inflammatory response, neutrophils react swiftly with powerful chemotaxis and phagocytosis, contributing to the development of a various cardiovascular diseases, including heart failure[5].

Systemic Immune-inflammation Index (SII) is an index which includes three important immune cells - neutrophils, lymphocytes, and platelets. It serves as an accurate indicator of both local immune response and systemic inflammation. Compared with the total number of individual immune cells, the Systemic Immune Inflammation Index (SII) provides a more accurate indication of the body's inflammatory conditions, and it is more consistent across time. At this point, there have been studies that show a strong link between SII and negative outcomes in several cardiovascular conditions such as coronary artery disease, aortic stenosis, infective endocarditis, and others[6]. SII is an easy examination of standard blood tests and can be easily performed in peripheral health facilities.

Therefore, SII can be used as a biomarker. However, research demonstrating a correlation between SII and clinical outcomes in heart failure patients, including mortality and rehospitalization, has not been widely studied. This research will investigate the relationship between SII and clinical outcomes in chronic heart failure patients

METHODS

Design and Subjects

This research was an analytical observational study with a retrospective cohort research design. This research was conducted at RSUP Dr. Sardjito. Data of heart failure patients was taken from secondary data from the heart failure registry at RSUP Dr. Sardjito from January 1, 2022 to February 28, 2023. The inclusion criteria in this study were (1) patients hospitalized through the emergency department (IGD) from January 1,2022 to February 28, 2023, (2) patients diagnosed as chronic heart failure (3) Patients registered in the Heart Failure registry at RSUP Dr.

Sardjito, (4) had a routine blood test in the emergency room during admission, and 5) Age > 18 years.

Data collection

This research relies on secondary data from data from the heart failure registry at RSUP Dr. Sardjito from January 1, 2022 to February 28, 2023. Heart failure patients admitted at RSUP Dr. Sardjito, who completed the research inclusion and exclusion criteria, was included as research subject. The event's outcome, especially mortality and rehospitalization, was monitored over a 12-month period. There were 188 patients who met the inclusion criteria as research subjects from 282 chronic heart failure patients who underwent hospitalization.

Statistical Analysis

Statistical analysis was performed using SPSS version 23. Data distribution was determined using the Kolmogorov Smirnov normality test. The research population will be divided into two groups based on high and low SII scores. ROC analysis will be used to determine the SII cut-off value. Comparative tests between two categorical variables were analyzed using chi square comparative analysis. A p-value of less than 0.05 indicates statistical significance. Comparative tests between two numerical variables are analyzed using t-test comparative analysis if the data is normally distributed, or by Mann-Whitney comparative analysis if the data is not normally distributed. The results of the bivariate test with a p value <0.25 will then be entered into a multivariate analysis using logistic regression to determine the independent variables on the outcome.

RESULTS

There were 188 patients who met the inclusion criteria as research subjects from 282 chronic heart failure patients who underwent hospitalization. A total of 94 subjects were excluded in accordance with the exclusion criteria, resulting in a total of 188 subjects of chronic heart failure patients who were hospitalized as research subjects. The excluded subjects consisted of 13 patients with a diagnosis of sepsis, 9 patients with malignancy, 17 patients with a diagnosis of stage V chronic renal failure undergoing routine hemodialysis, 1 patient with severe thrombocytopenia, 1 patient with autoimmune disease, 4 patients with the use of ventilator breathing apparatus, 9 patients with heart failure due to acute coronary syndrome (SCS) and 30 patients could not be contacted.

Subjects of this study had a mean age of 58.80 ± 11.48 years with an age of 60 years and over as many as 94 patients (50%) and subjects with an age of less than 60 years as many as 94 patients (50%). Gender of the study subjects was dominated by men as many as 127 patients (67.6%) with the remaining 61 (32.4%) women. Systolic blood pressure of the study subjects had a range of 64 mmHg to 240 mmHg with a median value of 124 mmHg. Diastolic blood pressure of the research subjects had a range of 40 mmHg to 140 mmHg with a median value of 73 mmHg. Heart rate of the study subjects had a mean value of 96 times per minute with a range of 40 to 170 times per minute.

The median platelet count was 248.5 thousand/mcL with a range of 55 -678 thousand/mcL. The median leukocyte value was 9.1 thousand/mcL with a range of 4.3 - 27.9 thousand/mcL. The median value of neutrophils was 6.53 thousand/mcL with a range of 2.33 - 26.87 thousand/mcL. The mean value of lymphocytes was 1.4 thousand/mcL with a range of 0.24-7.8 thousand/mcL. The median SII value was 1038.13 (59.27 - 22279.71). The median blood glucose (GDS) was 132.5 (56.1-542). The mean BUN value was 22.75 (7.83 - 115). The mean value of creatinine was 1.35 (0.53-7.54). The median left ventricular ejection fraction was 30% (14-87) %. Of 188 patients, 131 subjects had left ventricular ejection fraction <40% (71.2%) while patients with ejection fraction ≥40% were 53 subjects (28.8%). A history of DM was present in 79 subjects (42%). Hyperglycemia was present in 25.5% of subjects. A total of 63.3% of all subjects had a history of hypertension. A history of ischemic heart disease (IHD) was present in 75% of subjects, and a history of smoking was present in 51.1% of subjects. A total of 13 subjects (6.9%) were diagnosed as COPD. A total of 100 research subjects (53.2%) were diagnosed with infection during hospitalization either lung infection or urinary tract infection. A total of 80 subjects (42.6%) were diagnosed with acute renal failure. A total of 80 subjects (42.6%) were obese.

The use of β-blocker therapy was found in 88 subjects (46.8%). Subjects who received renin angiotensin aldosterone (RAAS) inhibitor therapy, namely Angiotensin-converting enzyme inhibitor or ACE-I, Angiotensin II receptor blocker or ARB and angiotensin receptor/neprilysin inhibitor or ARNI were 125 (66.5%). A total of 66% of subjects received loop-diuretic therapy. Antiplatelet therapy, namely aspilet was found in 78 (41.5%) subjects and P2Y12 inhibitors 53 (28.2%). A total of 63 study subjects (33.5%) died within 12 months post-hospitalization. A total of 69 study subjects (36.7%) experienced rehospitalization within 12 months (Table 1).

The results of the receiver operating characteristic (ROC) curve analysis of SII on mortality obtained area under the ROC curve (AUC)=0.600. This means that SII is significant in predicting mortality, but with weak discrimination quality. The limit value obtained by the Youden Index method, namely the farthest distance of sensitivity with 1-specificity to mortality, obtained an SII value of 1459.59 with a sensitivity of 55.6% and a specificity of 68.8% (Figure 1)

Table 1. Baseline Characteristics

Variabel		n (188)	%	Mean ± SD atau Median (min-max)
Demographic Parameters				
Age, years				58,80 ± 11,48
Age	≥60 years	94	50%	
	<60 years	94	50%	
Gender	Male	127	67,6%	
	Female	61	32,4%	
Body Mass Index (BMI)				24,29 (15,56 – 48,44)
Clinical Parameters				
Systolic BP , mmHg				124 (64-240)
Diastolic BP, mmHg				77,5 (40-140)
Heart Rate, bpm				96 (40-170)
Parameter Laboratorium				
Platelets (10^3/mcL)				248,5 (55 - 678)
Leukocytes(10^3/mcL)				9,1 (4,3 – 27,9)
Neutrophils (10^3/mcL)				6,53 (2,33 – 26,87)
Lymphocytes (10^3/mcL)				1,4 (0,24 – 7,8)
SII				1038,13 (59,27-22279,71)
GDS (mg/dL)				132,5 (56,1-542)
BUN (mg/dL)				22,75 (7,83-115)
Kreatinin (mg/dL)				1,35 (0,53-7,54)
Echocardiographic Parameter				
LVEF (Simpsons), %				30 (14-87)
LVEF	<40%	131	71,2%	
	≥40%	53	28,8%	
Comorbidities				
Diabetes Mellitus	Yes	79	42%	
	No	109	58%	
Hypertension	Yes	119	63,3%	
	No	69	36,7%	
Smoking history	Yes	96	51,1%	
	No	92	48,9%	
IHD	Yes	141	75%	
	No	47	25%	
Complicating Factors				
Infections	Yes	100	53,2%	
	No	88	46,8%	
Hyperglycemia	Yes	48	25,5%	
	No	140	74,5%	
COPD	Yes	13	6,9%	
	No	175	93,1%	
Obesity (BMI ≥ 25 kg/m2)	Yes	80	42,6%	
	No	108	57,4%	
Acute Kidney Injury	Yes	80	42,6%	
	No	108	57,4%	
Therapy				
β- blocker	Yes	88	46,8%	
	No	100	53,2%	
ACE-I/ARB/ARNI	Yes	125	66,5%	
	No	63	33,5%	
Loop-Diuretic	Yes	124	66%	

	No	64	34%
Aspilet	Yes	78	41,5%
	No	110	58,5%
P2Y$_{12}$ *inhibitor*	Yes	53	28,2%
	No	135	71,8%
Dependent Variabel			
Mortality	Yes	63	33,5%
	No	125	66,5%
Rehospitalization	Yes	69	36,7%
	No	119	63,3%

Table descriptions BP : blood pressure, n: number (jumlah), SD: standard deviation, LVEF: Left ventricular ejection fraction, DM : diabetes mellitus, COPD : chronic obstructive pulmonary disease, IHD : Ischaemic heart disease, , SII : systemic immune inflammation index,, BUN : blood urea nitrogen, ACE-I : Angiotensin-converting enzyme inhibitor, ARB : Angiotensin II receptor blocker, ARNI : angiotensin receptor/neprilysin inhibitor

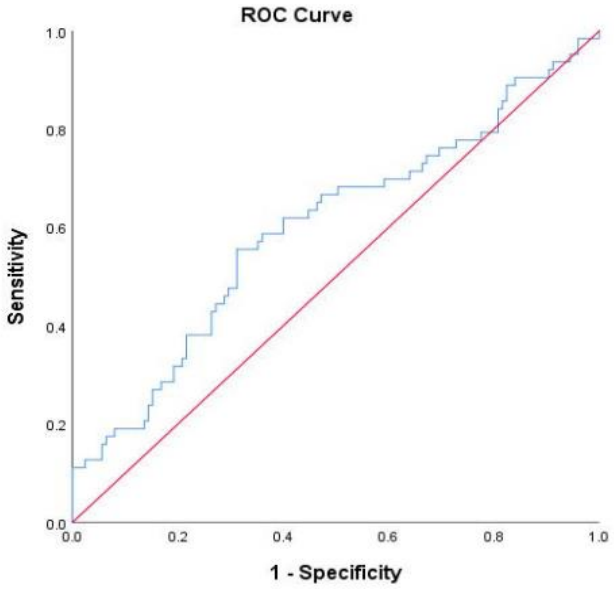

Figure 1. ROC analysis of mortalities

Bivariate analysis was performed using independent variables with nominal forms including SII, diabetes mellitus (DM), hyperglycemia, IHD, hypertension, smoking history, infection, COPD, acute renal failure, obesity and heart failure therapy. Numerical data in the form of age was converted into nominal variables with cut off values taken based on previous studies and SII values were converted into nominal variables according to the ROC curve cut off. Age data used a cut off value of 60 years into age groups <60 years and ≥60 years. Based on bivariate analysis, the relationship between the independent variable, SII, and mortality rate was found in patients with SII >1459.59 who experienced mortality within 12 months, 35 subjects (47.3%) compared to those who did not experience mortality, 39 subjects (52.7%). In patients with SII <1459.59 there were 28 subjects (24.6%) who experienced mortality with 86 subjects (75.4%) who did not experience mortality. The difference was significant with a p value = 0.001. The relationship between SII and mortality has a relative risk (RR) of 1.93 (IK 1.29-2.88). There were no other significant variables for mortality (Table 2)

Table 2. Bivariate analysis of mortalities

		Mortalitas				P	RR	IK 95%
		Yes		No				
		n	%	n	%			
SII	>1459,59	35	47,3%	39	52,7%	0,001*	1,93	1,29-2,88
	<1459,59	28	24,6%	86	75,4%			
Usia	≥60 years	37	39,4%	57	60,6%	0,089	1,42	0,94-2,15
	<60years	26	27,7%	68	72,3%			
LVEF	<40%	43	32,8%	88	67,2%	0,922	1,02	0,64-1,64
	≥40%	17	32,1%	36	67,9%			
Diabetes	Yes	27	34,2%	52	65,8%	0,869	1,04	0,69-1,55
Melitus	No	36	33,0%	73	67,0%			
Hyperglicemia	Yes	8	23,5%	26	76,5%	0,173	0,65	0,34-1,25
	No	55	35,7%	99	64,3%			
Hypertension	Yes	36	30,3%	83	69,7%	0,214	0,77	0,52-1,16
	No	27	39,1%	42	60,9%			
Smoking	Yes	33	34,4%	63	65,6%	0,798	1,05	0,70-1,58
history	No	30	32,6%	62	67,4%			
Infection	Yes	34	34,0%	66	66,0%	0,880	1,03	0,69-1,55
	No	29	33,0%	59	67,0%			
IHD	Yes	49	34,8%	92	65,2%	0,532	1,17	0,71-1,91
	No	14	29,8%	33	70,2%			
COPD	Yes	7	53,8%	6	46,2%	0,131$	1,68	0,97-2,91
	No	56	32,0%	119	68,0%			
AKI	Yes	30	37,5%	50	62,5%	0,319	1,23	0,82-1,83
	No	33	30,6%	75	69,4%			
Obesity	Yes	24	38,1%	56	44,8%	0,380	0,83	0,55-1,26
	No	39	61,9%	69	55,2%			
β- blocker	Yes	32	36,4%	56	63,6%	0,437	1,27	0,69-2,33
	No	31	31,0%	69	69,0%			
ACE-I/	Yes	43	34,4%	82	65,6%	0,716	1,12	0,59-2,15
ARB/ARNI	No	20	31,7%	43	68,3%			
Loop-Diuretic	Yes	46	37,1%	78	62,9%	0,147	1,39	0,87-2,22
	No	17	26,6%	47	73,4%			
Aspilet	Yes	30	38,5%	48	61,5%	0,226	1,28	0,85-1,93
	No	33	30,0%	77	70,0%			
$P2Y_{12}$ *inhibitor*	Yes	21	39,6%	32	60,4%	0,266	1,274	0,84-1,93
	No	42	31,1%	93	68,9%			

Multivariate analysis was performed with logistic regression test with backward stepwise method to determine independent predictors that significantly affect the incidence of mortality and rehospitalization in chronic heart failure patients. Variables that had p<0.25 in the bivariate test were continued in the multivariate analysis. From the results of multivariate analysis of mortality, the significant parameters were SII value (OR 3.08, 95% CI 1.59-5.95, p < 0.001) and hypertension (OR 0.46, IK 0.23-0.91, p = 0.025) (Table 3)

Table 3. Multivariate analysis of mortalities

			IK 95%	
	p	OR	Min	Maks
SII	<0,001*	3,08	1,59	5,95
Age	0,383	1,34	0,69	2,61
Hypertension	0,025	0,46	0,23	0,91
Hyperglicemia	0,193	0,54	0,22	1,35
COPD	0,143	2,47	0,74	7,94
Loop-Diuretic	0,163	1,66	0,81	3,39
Aspilet	0,582	1,21	0,60	2,46

Bivariate analysis on rehospitalizations, variables of age ≥60 years, diabetes mellitus, hypertension, smoking history, infection, IHD, COPD, acute renal failure, obesity and heart failure therapy did not have a significant difference in the incidence of rehospitalization in patients with chronic heart failure. If using a difference of p<0.25 as the basis for multivariate analysis, the variables that were analyzed were infection (p=0.235), acute renal failure (p=0.140) and P2Y12 inhibitors (p=0.129) (Table 4)

Table 4. Bivariate analysis of rehospitalizations

		Rehospitalizations				p	RR	IK 95%
		Yes		No				
		n	%	n	%			
SII	>576,57	28	28,9%	69	71,1%	0,436	1,35	0,62-2,92
	<576,57	6	21,4%	22	78,6%			
Age	≥60 year	13	22,8%	44	77,2%	0,312	0,74	0,41-1,34
	<60 year	21	30,9%	47	69,1%			
LVEF	<40%	50	38,2%	81	61,8%	0,437	1,19	0,76-1,86
	≥40%	17	32,1%	36	67,9%			
Diabetes Melitus	Yes	14	26,9%	38	73,1%	0,953	0,98	0,55-1,76
	No	20	27,4%	53	72,6%			
Hyperglicemia	Yes	9	34,6%	17	65,4%	0,322	1,25	0,81-1,94
	No	25	25,3%	74	74,7%			
Hypertension	Yes	22	26,5%	61	73,5%	0,340	1,37	0,73 -2,56
	No	12	28,6%	30	71,4%			
Smoking history	Yes	18	28.6%	45	71,4%	0,728	1,11	0,62-1,97
	No	16	25,8%	46	74,2%			
Infection	Yes	15	22,7%	51	77,3%	0,235	0,71	0,39-1,26
	No	19	32,2%	40	67,8%			
IHD	Yes	55	39,0%	86	61,0%	0,256	1,31	0,80-2,12
	No	14	29,8%	33	70,2%			
COPD	Yes	1	16,7%	5	83,3%	1,000$	0,60	0,09-3,68
	No	33	27,7%	86	72,3%			
AKI	Yes	10	20,0%	40	80,0%	0,140	0,63	0,33-1,19
	No	24	32,0%	51	68,0%			
Obesity	Yes	28	40,6%	52	43,7%	0,677	0,92	0,62-1,35
	No	41	59,4%	67	56,3%			
β- blocker	Yes	15	26,8%	41	73,2%	0,925	0,97	0,54-1,73
	No	19	27,5%	50	72,5%			
ACE-I/	Yes	22	26,8%	60	73,2%	0,898	0,96	0,52-1,75
ARB/ARNI	No	12	27,9%	31	72,1%			
Loop-Diuretic	Yes	22	28,2%	56	71,8%	0,745	1,10	0,64-2,01
	No	12	25,5%	35	74,5%			
Aspilet	Yes	14	29,2%	34	70,8%	0,696	1,12	0,62-2,00
	No	20	26,0%	57	74,0%			
$P2Y_{12}$ *inhibitor*	Yes	12	37,5%	20	62,5%	0,129	1,58	0,89-2,82
	No	22	23,7%	71	76,3%			

From the results of multivariate analysis of rehospitalization, no significant parameters were found (p>0.05). The variables analyzed were infection (OR 0.67, 95% CI 0.29-1.50, p=0.332), acute renal failure (OR 0.50, 95% CI 0.21-1.20, p=0.126), and P2Y12 inhibitor (OR 2.04, 95% CI 0.84-4.94, p=0.113) (Table 5)

Table 5. Multivariate analysis of rehospitalizations

			IK 95%	
	p	OR	Min	Maks
Infection	0,332	0,67	0,29	1,50
AKI	0,126	0,50	0,21	1,20
$P2Y_{12}$ *inhibitor*	0,113	2,04	0,84	4,94

Based on the graph in Figure 2, it can be concluded that patients with high SII (>1459.59) had a survival rate of 50.5% with a mean survival of 8.5 months and patients with low SII (<1459.59) had a survival rate of 74.0% with a mean survival of 9.9 months. The difference was significant based on the log rank test with p=0.002. There was a significant deviation in survival at month 2.

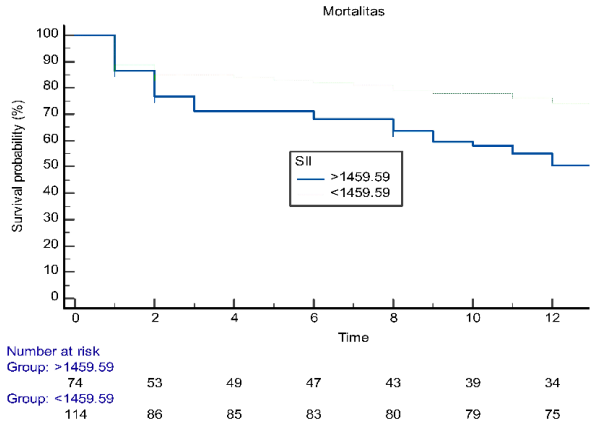

Figure 2. Kaplan-Meier analysis of SII with mortality

DISCUSSION

Based on demographic data, the subjects in this study had a mean age of 58.8 ± 11.48 years with 94 patients aged 60 years and over (50%) and subjects aged under 60 years were 94 patients (50%). This is similar to the research of Mumpuni et al. (2020) obtained a median age value of 59 years (19-91). Research by Wang et al. (2023) obtained mean age of 60.0 ± 16.63. From research by Zhu et al. (2024) mean age 62.46 ± 14.22 years. As opposed to the research subjects of Tang et al. (2021) with a median age of 74 years (64 -83). However, the prevalence of HF in those aged 65-70 years old increased by 4.3% in 2012 and is estimated to increase by 8.5% in 2030 (Zhu *et al.*, 2024)

The gender of the research subjects was dominated by male with 127 patients (67.6%) the remaining 61 (32.4%) female subjects. This is similar to research by Mumpuni et al. (2020) with male (68.2%) and female (31.8%). Males dominated females by 68.7%

The average leukocyte count was 9.10 thousand/mcL, with a range of 4.30–27.9 thousand/mcL. Mean neutrophil count was 6.53 thousand/mcL, with a range of 2.33 to 26.87 thousand/mcL. Median lymphocyte count was 1.40 thousand/mcL, with a range of 0.24 to 7.8 thousand/mcL. Median platelet count was 248.5, with a range of 55 to 678 thousand/mcL. In heart failure patients, neutrophils can be activated and release high amounts of pro-inflammatory cytokines and oxidative stress substances, which can contribute to the development of cardiovascular disease and the progression of heart failure. On the contrary, lymphocytes are considered as important cell type that regulates immune responses. Decreased lymphocyte count in HF patients is considered one of the worst predictors of systemic inflammation and heart failure prognosis (Strassheim et al., 2019).

From the research, it was found that 131 (71.2%) subjects had ejection fraction (EF) <40% or HFrEF and 53 (28.8%) subjects had EF ≥40%. This is in accordance with the ESC Long-Term registry findings in outpatient situations, which found 60% HFrEF, 24% HFmrEF, and 16% HFpEF. Platz et al. (2018) studied a total of 1668 inpatients with heart failure, 1152 with HFrEF and 516 with HFpEF.

Mean SII value was 1038.13 (59.27-22279.71). SII value was divided into 3 quartiles where the first quartile was SII <966, the second quartile was SII range 966-2327 and the third quartile was SII >2327 (Yuan et al., 2022). Research by Wang et al. (2023) The SII value is divided into <1228 and >1228. Tang et al. (2021) found that the mean value was 174.76 (92.24-344.55). SII value was higher in the non-survivor group, where the mean SII value in the survivor group was 163.11 (88.62-309.02) and in the non-survivor group 213.97 (105.80-430.34) with significant results p<0.001.

Bivariate test of SII according to ROC cut-off obtained RR 1.93 (IK 95% 1.29 - 2.88, p = 0.001). SII is a predictor of mortality in patients with chronic heart failure who undergo hospitalization at Dr. Sardjito Hospital, but is not significant in predicting the incidence of rehospitalization for 1 year. Patients with severe chronic heart failure have higher mortality rates, more severe symptoms and poorer quality of life (Bekelman et al., 2009). So it is important to use effective laboratory indicators to predict the risk of death in heart failure patients.

Recently, Bozkurt et al. (2010) found that inflammatory factors can be biomarkers of heart failure and some inflammatory factors are involved in the pathogenesis of heart failure. The increase and activation of inflammation-related cytokines is not only a reflection of inflammatory activation in vivo, but has also been identified to be associated with poor prognosis in heart failure. SII, calculated based on platelet count and NLR, is considered a clinical marker that reflects the inflammatory and immune status of patients simultaneously. As a new biomarker, SII can systematically and comprehensively reflect the inflammatory status in vivo and one of the advantages of SII is that it is easily accessible in peripheral health facilities (Yndestad et al., 2007).

The results of multivariate analysis of SII values have an OR of 3.08 (IK95% 1.59 - 5.95, p = <0.001), indicating that high SII values have a 3.08 times risk of mortality. Hypertension was found to be a significant protective factor against mortality (OR 0.46 IK95% 0.23-0.91, p=0.025). Other variables such as age, hyperglycemia, COPD, loop-diuretic

and aspilet were not significant. So that SII is an independent factor as a predictor of mortality in chronic heart failure patients who undergo hospitalization in this population. This is in accordance with the research of Yuan et al. (2022) showed that the SII value can be used as a predictor of prognosis in critically ill heart failure patients. Patients with higher SII values on admission had a longer hospitalization period and a higher risk of mortality. Yuan et al. (2022) found that at the same follow-up time, the mortality risk of heart failure patients increased as the SII value at admission increased, including mortality at 30 days, 60 days, 180 days, and 365 days after admission. This suggests that at the time of admission, SII is useful in predicting mortality risk, despite different follow-up times. Performed Cox proportional hazard regression analysis, a higher SII value at the time of admission was an independent predictor of mortality, regardless of whether the confounding variables were adjusted for or not. Therefore, we can conclude that SII is robust in predicting the prognosis of patients with heart failure. The studies of Yuan et al. (2022) and Tang et al. (2021) showed that the risk of all-cause mortality increased with increasing SII values.

CONCLUSION

The Systemic Immune Inflammation Index is an independent predictor of mortality, but not as a predictor of rehospitalization in patients with chronic heart failure undergoing hospitalization

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The Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada gave their approval to this study protocol under the ethical clearance number KE/FK/0568/EC/2024.

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