



Six Minute Walking Test as Predictor for Mortality and Rehospitalization within 3 Months in Post Coronary Bypass Surgery Patients

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ABSTRACT

Background: Patients underwent Coronary Artery Bypass Surgery are at risk of developing post-operative complications that affect length of stay, re-hospitalization and increase in mortality rate. Impaired functional capacity is associated with poor outcomes in patients after CABG. The Six Minute Walk Test (6MWT) is generally used to evaluate functional capacity before cardiac rehabilitation and to prescribe the intensity of exercise training. The six minute walk test (6MWT) is a simple test and has been used in heart failure patients to assess exercise tolerance, the effects of therapy and prognosis. This study is to investigate the relationship between the distance of 6MWT with re-hospitalization and mortality rate in post coronary artery bypass surgery patients.

Method: This is a retrospective cohort study conducted at Cardiac Centre of Adam Malik Hospital. Subjects of the study consists of 104 patients underwent coronary bypass surgery between January 2019 until February 2020. 6MWT is performed before the patient discharge. Rates of re-hospitalisation and mortality were observed during 3 months of follow-up. The distance walk during 6MWT was compare to rate of rehospitalization and cardiac mortality.

Result: Total of 104 patients (91 males, mean age 57,4±5,7 years). Six patients died (5,8%) of cardiovascular cause and 18 (17,3%) were rehospitalized. Significant relationship was found between the distance of 6MWT and incidence of mortality and re-hospitalization (p <0.001). Patients with 6MWT <250 meters had a higher risk of re-hospital compared to those with 6MWT >250 meters with RR 16.74 (95% CI: 2.53-110.78) and p = 0.008.

Conclusion: The six minute walk test (6MWT) is a predictor of re-hospitalization in patients post CABG. Patients who walked in shorter distance group <250 meters would increase risk of re-hospitalization rate 16.74 greater than patients with distances >250 meters.

INTISARI

Latar Belakang: Pasien paska Bedah Pintas Arteri Koroner (BPAK) berisiko mengalami komplikasi paska operasi yang dapat mempengaruhi lama rawatan, rehospitalisasi dan peningkatan kematian. Kapasitas fungsional yang terganggu terkait dengan hasil yang buruk pada pasien paska BPAK. Uji Jalan Enam Menit (UJ6M) umumnya digunakan untuk mengevaluasi kapasitas fungsional sebelum rehabilitasi jantung dan untuk meresepkan intensitas Latihan olahraga. UJ6M adalah tes sederhana dan telah digunakan pada pasien gagal jantung untuk menilai toleransi latihan, efek erapi dan prognosis. Penelitian ini bertujuan untuk melihat hubungan antara uji jalan 6 menit dengan rehospitalisasi dan tingkat kematian paska BPAK.

Metode: Penelitian ini adalah studi kohort retrospektif yang dilakukan di Pusat Jantung Rumah Sakit H. Adam Malik. Subjek penelitian terdiri dari 104 pasien yang menjalani operasi BPAK antara Januari 2019 hingga Februari

2020. Uji jalan 6 menit dilakukan sebelum pasien pulang dari rawatan. Tingkat rehospitalisasi dan kematian diamati selama 3 bulan follow up. Jarak berjalan selama UJ6M dibandingkan dengan tingkat rehospitalisasi dan mortalitas jantung.

Hasil: Total 104 pasien (91 laki-laki, rerata usia $57,4 \pm 5,7$ tahun). Enam pasien meninggal (5,8%) karena penyebab kardiovaskular dan 18 (17,3%) pasien mengalami rehospitalisasi. Ditemukan hubungan yang signifikan antara jarak UJ6M dengan kematian dan rehospitalisasi ($p < 0,001$). Kelompok pasien dengan UJ6M < 250 meter memiliki risiko lebih tinggi tingkat rehospitalisasi dibandingkan dengan mereka dengan UJ6M > 250 meter dengan RR 16,74 (IK 95%:2,53-110,78) dan $p = 0,008$.

Kesimpulan: Uji jalan enam menit (UJ6M) adalah prediktor kematian dan rehospitalisasi pada pasien paska BPAK. Pasien yang berjalan dalam kelompok jarak pendek kurang dari 250 meter akan meningkatkan risiko tingkat rehospitalisasi 16,74 kali lebih besar dari pasien dengan jarak lebih dari 250 meter.

Introduction

Coronary artery disease (CAD) is one of the diseases that causes the highest incidence of death in cardiovascular disease in the world and is also the second leading cause of death in Indonesia after stroke, which is 12.9%.^{1,2} Based on the increasing number of deaths due to CAD, it is necessary to carry out optimal management. One of them is by performing a revascularization surgery called Coronary Artery Bypass Graft (CABG) surgery. Coronary artery bypass surgery is indicated to improve symptoms, prolong life, and improve quality of life.^{3,4}

Besides has a positive impact on the condition of CAD patients, patients who undergo CABG surgery are also at risk of experiencing postoperative complications that can affect outcomes including length of stay and increased postoperative mortality.⁵ One study reported that 58% of post-cardiac surgery patients had complications such as the pulmonary system (31%), cardiovascular system (15.8%), and nervous system (13.9%).⁶ Patients who undergo CABG surgery are not only at risk of complications but also experiencing physical and psychological problems such as pain, decreased heart muscle strength, anxiety, stress, depression which can affect the patient's quality of life.

Immediately after the cardiac surgery procedure, a patient will be prescribed an individual rehabilitation program. The comprehensive benefits of a cardiac rehabilitation program are increasing activity tolerance, increasing muscle strength, reducing symptoms, reducing morbidity and reducing mortality. At the start of a cardiovascular rehabilitation program, the Six Minute Walk Test (6MWT) is generally used both to evaluate pre-rehabilitation functional capacity and to prescribe exercise intensity.⁷ Exercise testing is a key component of the initial assessment performed when a patient is enrolled in a cardiac rehabilitation program, and evaluation of changes in functional capacity has become a common clinical

outcome in cardiac rehabilitation programs after cardiac surgery.⁸

The 6MWT evaluates the global and integrated response of all systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. The 6MWT assesses the level of functional capacity submaximal. Since most activities of daily life are performed at a submaximal level of activity, the 6MWT may better reflect levels of functional exercise for daily physical activity.⁹

One study showed that the 6MWT at the start of cardiac rehabilitation in patients after cardiac surgery could identify a 44% mortality rate in the group of patients who could not perform the 6MWT before discharge.¹⁰ Another study also showed patients undergoing cardiovascular rehabilitation programs after open heart valve surgery, the 6MWT proved to be an independent prognostic tool. They observed that an inability to walk more than 215 m identified patients with a higher risk of cardiovascular death or hospitalization.¹¹ based on a study involving 882 post-CABG patients alone, found that the 6MWT after surgery predicted 5-year survival in elderly patients (≥ 65 years).¹²

The aim of this study was to investigate the relationship between the distance of 6 minute walk test before discharge with re-hospitalization and mortality rate in post coronary artery bypass surgery patients and the ability of 6MWT in predicting the incidence of death and rehospitalization within 3 months of follow-up after CABG surgery.

Methods

This study is a retrospective cohort observational study at Haji Adam Malik Hospital Medan (RSHAM) with permission from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara-RSHAM.

The Data of subjects was collected from medical records. The population of this study were post-CABG patients between January 2019 and February 2020 who underwent a 6MWT examination before discharge to undergo phase II cardiac rehabilitation at Haji Adam Malik Hospital (RSHAM) Medan and followed for 3 months. This study aims to test the ability of 6MWT before discharge as a predictor of death and rehospitalization within 3 months of post hospitalization of patients after CABG surgery. Rehospitalization and death were defined as re-admission of subjects due to medical conditions such as worsening heart failure, arrhythmias, stroke, myocardial infarction and re-vascularization at Adam Malik Hospital. The inclusion criteria were post CABG patients at RSHAM Medan who were able to do the 6MWT examination before discharge and undergoing phase II cardiac rehabilitation. Exclusion criteria were suffering from congenital heart disease or heart valve abnormalities, grade I obesity (Body Mass Index <30 kg / m²), suffering from COPD, bronchial asthma, musculoskeletal and neurological disorders, patients who could not be contacted or patients who did not have complete medical records.

Study Procedure

Categorical variables are presented by the number or frequency (n) and percentage (%). Numerical variables are presented with a measure of the concentration of the mean (mean) and a measure of the spread of standard deviations for normally distributed data. Meanwhile, data with abnormal distribution are presented in median form. The numerical variable normality test for all study subjects with a sample size of n <50 used the Kolmogorov test. Bivariate analysis for comparison of the characteristics of patients who experienced death and rehospitalization would be tested with the Chi Square test or Fisher's or Kolmogorov Smirnov's test for categorical variables. Meanwhile, for the numerical variables used the independent T test or Mann Whitney. Bivariate analysis with cox regression analysis was used to assess the relationship of each independent variable with mortality and rehospitalization. All numerical data is converted into categorical data with the best cut-off point obtained from the Receiver Operating Characteristic (ROC) curve or cut-off obtained from the literature. Test results will be displayed in odds ratios (OR) and 95% confidence intervals (CI). Variables having a p value <0.25 will be included in the multivariate analysis.

Multivariate analysis of categorical independent variables with categorical dependent variables was tested by logistic regression with the backward stepwise method. The variables found to have a significance value of p <0.05 in the multivariate analysis were presented in the form of Relative Risk (RR) with a 95% confidence interval. The variable is considered significant if the p value <0.05.

Result

Baseline Characteristics

The total number of subjects in this study were 104 post-CABG patients who met the inclusion and exclusion criteria. The mean age of the research subjects was 57.4

years with 91 people (87.5%) of whom were male. Cardiovascular risk factors were found with a history of hypertension 60 people (57.7%) had diabetes mellitus 42 people (40.4%), dyslipidemia as many as 63 people (60.6%), had a family history of coronary heart disease 7 people (6, 7%) and 83 people (79.8%) were smokers.

Table 1.
Baseline Subject Characteristics

Variable	n=104
Age (year)	57.4 ± 5.7
BMI	25,4 ± 2,23
Sex	
Female	13 (12.5%)
Male	91 (87.5%)
Risk Factor	
Smoker	83 (79.8%)
Hypertension	60 (57.7%)
Diabetes Mellitus	42 (40.4%)
Dyslipidemia	63 (60.6%)
Family History	7 (6.7%)
Echocardiography examination	
IVSD	11.0 ± 2.5
IVSS	13.5 ± 2.7
LVPWD	11.4 ± 2.5
LVPWS	14.1 ± 2.7
LVEDD	49.8 ± 7.5
LVEDS	34.5 ± 7.7
LVEF	52.3 ± 11.1
TAPSE	20.5 ± 2.6
Medical Therapy	
ASA	99 (95.2%)
Clopidogrel	35 (33.7%)
ACE-Inhibitor	35 (33.7%)
ARB	57 (54.8%)
Beta Blocker	99 (95.2%)
Nitrate	38 (36.5%)
Furosemide	46 (44.2%)
MRA	11 (10.6%)
6MWT, distance (m)	311,4 ± 96,2
METs	5,47 ± 1.62
Mortality	6 (5.8%)
Rehospitalization	18 (17.3%)
Heart failure	17 (16.3%)
Arrhythmia	2 (1.9%)
Cardiogenic Shock	4 (3.8%)
Stroke	2 (1.9%)
Myocardial Reinfarction	0 (0%)

Bivariate Analysis between 6MWT with Incidence of Death and Rehospitalization for 3 Months

There was a significant difference in cardiovascular risk factors for hypertension (p = 0.003) and diabetes mellitus (p = 0.012) between the two patient groups. From the bivariate analysis between patient characteristics with the incidence of death and rehospitalization, there was a difference in age (p = 0.005). For the medical therapy, there were significant differences based on the use of diuretics (p = 0.035). Based on echocardiography examination, there were differences in the LVEDD parameters (p <0.001) and Ejection Fraction (p <0.001). Meanwhile, for the 6-minute walk test, there was a significant difference in the distance that the patient could travel (p = 0.01) and the METS value obtained (p = 0.01).

Table 2.
Bivariate Analysis 6MWT with Incidence of Death and Rehospitalization

Variable	Mortality dan Rehospitalization		P value
	Yes N=18	No N=86	
Demographics			
Age, year	60,8 ± 4,6	56,7 ± 5,6	0,005 ^a
Sex, male	14 (77,7)	77 (88,5)	0,17 ^a
Weight, kg	67,6 ± 6,1	66,8 ± 7,0	0,63 ^a
BMI, kg/m ²	25,6 ± 2,9	25,4 ± 2	0,77 ^a
Hypertension	16 (88,8)	44 (51,2)	0,003 ^b
Smoker	13 (72,2)	70 (81,4)	0,37 ^b
Diabetes Mellitus	12 (66,7)	30 (34,9)	0,012 ^b
Dyslipidemia	12 (66,7)	51 (59,3)	0,56 ^b
Family History	2 (11,1)	5 (5,8)	0,41 ^b
Medical Therapy			
ASA	18 (100)	81 (94,2)	0,29 ^b
Clopidogrel	3 (16,7)	32 (37,2)	0,09 ^b
ACE-I	4 (22,2)	31 (36,0)	0,259 ^b
ARB	19 (77,8)	43 (50)	0,55 ^b
Beta Blocker	18 (100)	81 (94,2)	0,294 ^b
Nitrate	4 (22,2)	15 (17,4)	0,533 ^b
Diuretic	12 (66,7)	34 (39,5)	0,035 ^b
MRA	3 (16,7)	8 (9,3)	0,35 ^b
Statin	18 (100)	85 (98,8)	0,64 ^b
Echocardiography			
IVSD	12 ± 3,3	10,8 ± 2,3	0,09 ^a
IVSS	14,3 ± 3,4	13,3 ± 2,5	0,15 ^a
LVPWD	10,7 ± 2,2	11,5 ± 2,5	0,22 ^a
LVPWS	13 ± 2,3	14,4 ± 2,8	0,64 ^a
LVEDD	56,1 ± 4,5	48,5 ± 7,3	<0,001 ^a
LVEDS	34,1 ± 6,7	34,6 ± 7,9	0,81 ^a
LVEF	40,9 ± 5,2	54,7 ± 10,5	<0,001 ^a
TAPSE	20,3 ± 3,2	20,5 ± 2,5	0,86 ^a
6MWT			
Distance, meter	226,6 ± 67,1	329 ± 92,1	<0,001 ^a
METs	4,03 ± 1,1	5,7 ± 1,5	<0,001 ^a

^aIndependent test; ^bChi-Square test; ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; MRA : Mineralcorticoid Receptor Antagonist; 6MWT : Six Minute Walk Test; METs: Metabolic Equivalents

Optimal Cut-Off Value of 6MWT For Death and Rehospitalization Incidence for 3 Months

The 6MWT value data before the patient discharged from the hospital in post-CABG patients were analyzed for the cut-off value using the ROC curve (Figure 1). Then the area under the curve (AUC) to assess the prognostic strength of the parameters tested.

Table 3.
6MWT Test Results for Death and Rehospitalization based on ROC

Cut off	Sensitivity	Specificity	AUC	P value	95%CI
≤ 250 meters	83,3%	73,3%	0,810	<0,001	0,721-0,90

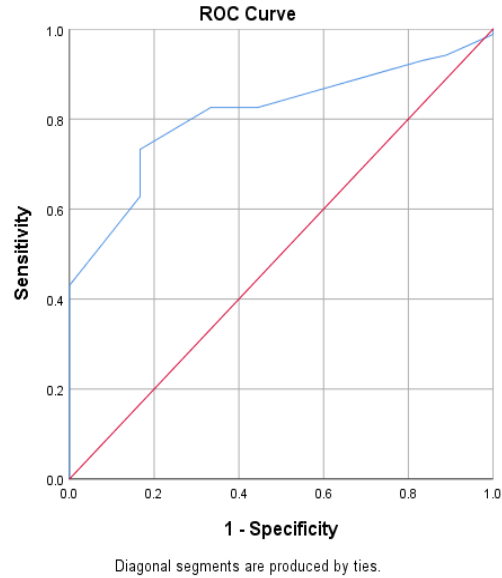


Figure 1. ROC Curve Optimal Cut Point Value of 6MWT before discharge for Death and Rehospitalization for 3 months

Multivariate Analysis of Variables with Incidence of Death and Rehospitalization for 3 Months

After bivariate analysis, multivariate analysis was performed to determine the prognostic variables that most influenced the incidence of rehospitalization and mortality in CABG patients. Results of multivariate analysis using the backward stepwise method (Table 4). From the results of multivariate analysis, it was found that the value of 6MWT had a significant relationship with the combined incidence of death and rehospitalization with a value of p = 0.008.

The RR value for 6MWT against the incidence of death and rehospitalization is 16.74 (CI 95% (2.53-110.78)) which indicates that a value of 6MWT < 250 meters will increase the risk of death and rehospitalization 3 months after CABG by 16.74 times higher than with patients who have a value of 6MWT >250 meters.

From echocardiographic parameters, the RR value for the ejection fraction (EF) against the incidence of rehospitalization was 26.46 (CI 95% (2.35-297.37)) which indicates that EF <40% will increase the risk of rehospitalization 3 months after CABG by 26.46 times more. higher compared to patients who have an EF> 40%. This shows that apart from the value of 6MWT, the parameter of ejection fraction (EF) through echocardiography also has a prognostic value for the incidence of rehospitalization 3 months after CABG.

Table 4.
Multivariate Analysis of Factors Associated with Death and Rehospitalization

Variable	RR (95% CI)	Nilai p
Age	2.59 (1.20-27.92)	0.432
LVEF	26.46 (2.35-297.37)	0.003
6MWT	16.74 (2.53-110.78)	0.008

Survival Analysis for Mortality and Rehospitalization Based on 6MWT value

During the 3 month observation period, death and rehospitalization occurred in 15 subjects with 6MWT before discharge <250 meters. In contrast, the incidence of death and rehospitalization occurred in 3 subjects with 6 MWT before discharge > 250 meters. The survival test was performed using the Kaplan Meier curve. On this Kaplan Meier curve it was found that patients with a value of 6MWT > 250 meters had a better prognosis up to 3 months of follow-up for mortality and rehospitalization.

Based on the curve it can be seen that after 10 weeks, patients with a value of 6MWT >250 meters had a 5% incidence of death and rehospitalization, while patients with a value of 6MWT <250 meters had a 52% incidence of rehospitalization. During 3 months of follow-up, the incidence of rehospitalization was found in patients with a value of 6MWT <39.4%, while patients with a value of 6MWT >250 meters were 4.5%. It can be interpreted that the relative risk of mortality and rehospitalization (RR) was 16.74 times at a value of 6MWT <250 meters compared to patients with a value of 6MWT > 250 meters (95% CI 2.68 - 28). This can be seen in Figure 2.

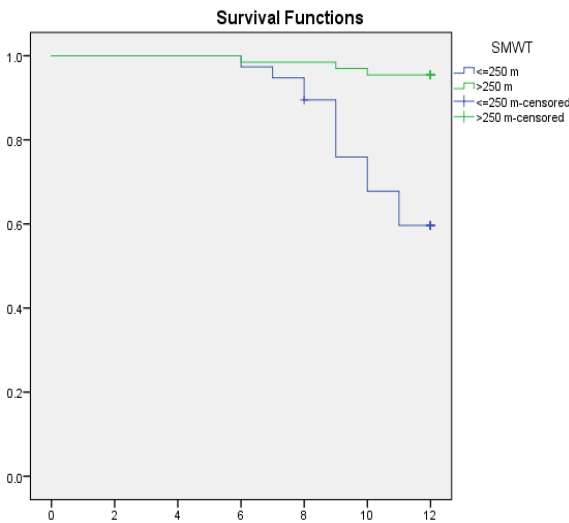


Figure 2. Kaplan-Meier Survival Curve values of 6MWT for mortality and rehospitalization

Discussion

The 6MWT value before discharge was a predictor of incidence of death and rehospitalization 3 months after CABG surgery. From the baseline characteristics of the sample, it was found that the majority of post-CABG patients were male (87.5% vs. 12.5%), smokers, had hypertension, had dyslipidemia, the average age in this study was 57.4 ± 5.7 years. There was a study of patients with coronary artery bypass surgery, the mean age was 65.8 + 9.3 years with about 84.1% of the study sample being men with 30.3% smokers, 59.2% hypercholesterolemia, 48.6% hypertension, and 25.7% suffering from diabetes mellitus.¹³ Whereas in the

epidemiological study of CABG surgery in the last two decades, the average age of patients who underwent the CABG procedure was 67.86 years and 80.5% of the sample were men with about 82.8% suffering from hypertension and 34.4% suffering from diabetes mellitus.¹⁴

In this study, the mean left ventricular ejection function was 52.3 + 11, while in the previous study, the mean left ventricular ejection function was 56.1+ 7.6. As for the 6MWT value in this study, the average value was 311.4 + 96.2 meters. Another observational study also obtained a mean value of 6MWT after heart valve surgery and coronary artery bypass surgery of + 277.3 meters before the patients were discharged from hospital. In this study, there were about 6 people (5.8%) of the study sample who experienced mortality during the follow-up period of 3 months after CABG. The combined incidence of death and rehospitalization in this study was found around 18 people (17.3%) of the study sample where the most common causes of rehospitalization were heart failure (17.3%), cardiogenic shock (3.8%), arrhythmia (1.9%) and stroke (1.9%). In another study found that out of 1022 patients who were involved in the study, about 32 patients (3%) died within the first few months after CABG surgery.¹³ Previous study of post-CABG patients at the Harapan Kita National Heart Hospital (RSJNHK) obtained from 186 patients after CABG found 3 patients died (1.6%) and 16 people experienced rehospitalization (8.6%) during 6 months follow-up.¹⁵

The results of bivariate analysis showed a difference in the 6MWT distance performed by the patient and the ventricular ejection fraction between the group that experienced death and rehospitalization and the group that did not, where the mean distance of 6MWT was 226.6 + 67.1 meters (p <0.001) and the mean ejection fraction was 40.9 + 5.2% (p <0.001) in the group that experienced mortality and rehospitalization. This shows that there is a strong relationship between the 6MWT variable and the ejection fraction with the incidence of rehospitalization and death 3 months after CABG surgery. This is consistent with previous studies where the 6MWT value at the start of phase II cardiac rehabilitation had a strong association with the incidence of rehospitalization and the incidence of death during 6 months of follow-up (p = 0.05).

Another study also showed ejection fraction > 50% and 6MWT > 300 meters independently as protective variables against mortality in CABG patients before cardiac rehabilitation. However, the protective role of these two variables depends on age. In fact, an ejection fraction > 50% is protective in adults but not in elderly (> 65 years) while 6MWT > 300 m is protective in elderly but not in adult patients.¹² In this study, it was found that the cut-off value of 6 MWT was considered significant to be <250 meters based on AUC 0.81 for a combination of mortality and rehospitalization, thus showing high predictive accuracy. This result is similar to the results of previous studies which stated that patients after CABG using the cutoff value of 6MWT <240 meters had a higher risk of rehospitalization and death.¹⁵ Another study that evaluated how the prognostic value of 6MWT after heart

valve surgery found a value of 6MWT <215 meters associated with the combined incidence of rehospitalization and mortality ($p = 0.003$) after 18 months of follow-up.¹¹

In this study, Based on results of multivariate analysis using the backward stepwise method, the value of Six Minute Walk Test (6MWT) <250 meters will increase the risk of death and rehospitalization 3 months after CABG by 16.74 times greater and has a good prognostic value for combined incidence of death and rehospitalization 3 months after CABG. In the previous study, a value of 6MWT <240 meters was also obtained as a strong predictor variable for rehospitalization and mortality with an RR value of 4.25 (95% CI: 1.646 to 10.962) and $p = 0.003$ in the follow-up 6 months after CABG so that it can be concluded that patients with Results 6MWT less than 240 meters had a 4.25 times greater risk of hospital rehospitalization and death compared with patients who traveled more than 240 meters.¹⁵

A previous study said that the multivariate test results found a value of 6MWT <215 meters to be a strong predictor of the combined incidence of rehospitalization and death (HR = 0.95, 95% CI: 0.90-0.99, $P = 0.02$) in patients after heart valve surgery with 18 months follow-up.¹¹ Another study concluded that for patients undergoing a post cardiac surgery rehabilitation program, 6MWT before discharge (<320 meters, HR 0.97 (95% CI 0.95–0.99)) provided strong independent prognostic information for all causes of death ($p = 0.0038$) after cardiac surgery with a median follow-up of 23 months.¹⁰

There are several limitations of this study. The number of subjects in the study was only 104 people. It needs a larger number of samples involving more factors to get a more representative UJ6M value as a predictor of death and rehospitalization 3 months after CABG. This research was only conducted in one center. Monitoring of study subjects in this study was only carried out for 3 months. Long-term monitoring of the role of the UJ6M as a predictor of mortality and rehospitalization is needed in further studies.

Conclusion

6MWT before discharge was a predictor of incidence of death and rehospitalization 3 months after CABG surgery. Patients who walked in shorter distance group <250 meters would increase the risk of re-hospitalization rate and mortality 16.74 greater than patients with distance more than 250 meters.

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