Impact of Frailty on the First 30 Days of Major Cardiac Events in Elderly Patients with Coronary Artery Disease Undergoing Elective Percutaneous Coronary Intervention

Rachmat Hamonangan, Ika P. Wijaya, Siti Setiati, Kuntjoro Harimurti

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Rachmat Hamonangan, MD. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. email: drmonang@yahoo.com.

ABSTRAK

Tujuan: *mendapatkan proporsi frailty (kerentaan), insidens major adverse cardiovascular events (MACE) 30 hari dan mengkaji peran frailty terhadap prognosis pasien usia lanjut dengan penyakit jantung koroner yang menjalani PCI elektif.* ***Metode:*** *studi kohort prospektif dilakukan untuk menilai kondisi frailty pasien usia lanjut dengan penyakit jantung koroner yang menjalani PCI elektif di RS Cipto Mangunkusumo dengan menggunakan kriteria frailty fenotipe. Pasien kemudian di follow-up selama 30 hari setelah tindakan PCI elektif untuk melihat apakah MACE terjadi atau tidak.* ***Hasil:*** *terdapat 100 pasien usia lanjut dengan penyakit jantung koroner yang menjalani PCI elektif dari bulan September 2014 - Juni 2015. Usia rerata pasien adalah 66,95 tahun (SD 4,875) dengan pasien terbanyak adalah laki-laki (69%). Sebanyak 61% pasien termasuk ke dalam kelompok frail. MACE terjadi pada 8,19% pasien pada kelompok frail dan 5,12% pada kelompok non-frail. Hubungan frailty terhadap MACE dapat dilihat pada hasil crude Hazard Ratio (HR) 1,6 (IK 95% 0,31-8,24). Pada penelitian ini, kesintasan 30 hari 95% pada kelompok frail, sementara pada kelompok non-frail kesintasan 30 hari adalah sebesar 98%.* ***Kesimpulan:*** *terdapat peningkatan risiko 1,6 kali untuk terjadinya MACE 30 hari pada subyek usia lanjut frail yang menjalani PCI elektif namun belum bermakna secara statistik.*

Kata kunci: *frailty, major adverse cardiac events, penyakit jantung koroner, percutaneous coronary interventions, usia lanjut.*

ABSTRACT

Aim: *to obtain the proportion of frailty and the incidence of 30-day major adverse cardiovascular events (MACE) as well as to review the impact of frailty on the prognosis of elderly patients with coronary heart disease who underwent elective PCI.* ***Methods:*** *this is a prospective cohort study to assess the frailty of elderly patients with coronary artery disease that underwent elective PCI in Cipto Mangunkusumo Hospital using the frailty phenotype criteria. They were subsequently followed-up for 30 days to see whether there was any MACE developed.* ***Results:*** *there were 100 elderly patients with coronary artery disease who underwent elective PCI between September 2014 and June 2015. The mean age of patients was 66.95 (SD 4.875) years and 69% of the patients were males. Frailty was present in 61% of the patients. MACE were occurred in 8.19% of frail patients and 5.12% were occurred in non-frail patients. The association between frailty and MACE was demonstrated by the result of crude HR of 1.6 (CI 95% 0.31-8.24). In our study, the 30-day survival rate was 95% in frail patients and 98% in non-frail patients.*

Conclusion: *there is a 1.6-fold increased risk of 30-day MACE in elderly frail patients undergoing elective PCI; however, it is not statistically significant.*

Keywords: *frailty, major adverse cardiac events, coronary artery disease, percutaneous coronary interventions, elderly.*

INTRODUCTION

According to the World Health Organization (WHO), cardiovascular disease is the number one cause of death in the world.[1,2] A total of 17.3 million people die annually from heart disease. Of all these deaths, 7.3 million people die due to coronary heart disease (CHD). In Indonesia, the incidence of heart disease in population aged over 15 years is 9.2% and about 4.8% of them have symptoms leading to angina pectoris. In addition, life expectancy in Indonesia is increasing every year. With the increasing number of aging population, the incidence of CHD is also increasing with age.[2]

In the past half decade, a number of studies conducted in New York have reported that the mortality rate of Major Adverse Cardiac Events (MACE) at the age of 60-80 years and over 80 years is 4.1% and 11.5%, which is far higher than those with age less than 60 years old who has 1% mortality rate.[3-5] Most of studies reported that there is an increased risk of vascular access complications as well as increased incidence of major bleeding on PCI procedure in elderly patients, which subsequently rising the mortality risk.[5,6] Frailty itself is a physiological decline that could occur in every organ system, which is characterized by loss of function, loss of physiologic reserve, and increased susceptibility to disease and death.[3] In several studies, frailty is often associated with elderly because frailty becomes more common with age.[7] The prevalence of frailty in people aged 65 years and older is as much as 6.9%.[8] Woodhouse et al[8] specifically provide a definition that frail people are those aged over 65 years who rely on others for daily activities and even under the supervision of the institution.[9] There are differences regarding the definition of elderly between developed countries and developing countries. Most developing countries around the world, including Indonesia set a chronological age of 60 years to define the term "elderly". While WHO has suggested the age of 65 years and over as a definition for elderly people in developed countries.[10] There is a correlation between frailty and cardiovascular diseases, i.e. cardiovascular disease can accelerate the development of frailty. Frailty occurs in 25-50% of patients with cardiovascular disease depending on the measurement scale of frailty that being used. Frail patients with cardiovascular disease, especially those undergoing invasive methods such as PCI are more likely have more adverse effects than people without frailty.[11-13]

Until now, there are only two studies that have been published about the effect of frailty in patients undergoing PCI.[14,15] Both studies were conducted at the same health center, Mayo Clinic, a tertiary health care center in Rochester, Minnesota and Franciscan Skemp Hospital in La Crosse, Wisconsin. Gharacholou et al[15] conduct a study assessing the incidence of MACE (death, myocardial infarction, and re-revascularization) in patients undergoing PCI within 30 days and they reveal that the incidences of death, myocardial infarction, and re-revascularization in 30 days of frail patients are 0.8%, 6% and 5%, respectively. Moreover, Sigh et al[14] perform a study assessing the incidence of MACE (death and myocardial infarction) in patients aged 65 years over a period of 35 months. They demonstrate that there are 12% of patients have died, 11% has experienced non-fatal myocardial infarction and 22% have died or have myocardial infarction. Upon further analysis, they also reveal that during 3-year follow up, the mortality of patients with frail is 28% and it is 6% in non-frail patients. Frail patients are more likely having 4-fold risk of death and 2.5-fold risk for having myocardial infarction. The study was conducted at Mayo Clinic with patients aged over 65 years. It included in definition of elderly age for developed countries. Furthermore, another study

has been conducted at the Division of Cardiology in Cipto Mangunkusumo Hospital (RSCM), the national referral hospitals in Indonesia. The study was carried out in 2011 and included 510 PCI procedures and 224 of them were performed in elderly patients (>60 years). There were approximately 513 PCI procedure had been conducted in RSCM for the last 3 years.

Although studies on the association between frailty and MACE following PCI procedure have been performed in other countries, but there are differences in population, epidemiology, comorbidites and hospital technologies between developed and developing countries, including Indonesia. Therefore, it becomes the basic reason to perform our study.

METHODS

Our study used an observational method with a prospective cohort design to evaluate the association between frailty and MACE. Moreover, our study has also been approved for ethics review issued by University of Indonesia on October 19, 2015, number 945 / UN2.F1/ ETHICS / X / 2015.

The study was conducted at Cipto Mangunkusumo Hospital, Jakarta. Data sampling was carried out for 8 months, i.e. from October 2014 until June 2015. General population for the study was an elderly group of patients who underwent elective PCI. The target population was elderly patients who had undergone the procedure at Cipto Mangunkusumo Hospital, Jakarta. The eligible population was selected as samples using exclusion and inclusion criteria.

By estimating the magnitude of α (type I error) as 5% and the power for the study (β-1) as 80%, we calculated that the minimal sample size required for our study was 100 subjects.

The inclusion criteria for our study were all patients aged over 60 years old who had been diagnosed with coronary heart disease who had undergone elective PCI at Cipto Mangunkusumo Hospital, Jakarta. Moreover, the exclusion criteria were: 1) Post-stroke patient with persistent neurological deficit, severe Parkinson or dementia; 2) patient who had difficulties to communicate and any lack of clinical information to determine the frailty of the patient; 3) patients with disabilities e.g unable to walk; 4) patient who rejected to participate in the study.

Data was obtained through history taking and direct physical examination after the patients had given their written informed consent. The criteria to evaluate the frailty phenotype such as hand grip strength were evaluated by Natong Hand Dynamometer using the dominant hand. Subseqeuntly, another criterion of phenotype frailty such as delayed walking was measured by asking the patient to walk 6 meters, which then observer could measure the velocity using a stopwatch in seconds. The frailty was evaluated by the investigators prior to the elective PCI procedure and the follow-up was carried out for 30 days following the elective PCI.

Data obtained from history taking dan direct physical examination was tabulated and statistically analyzed using program SPSS version 21 and it was then presented using diagram. Data such as subject characteristics of socio-demographic, anthropometric and clinical diagnosis were presented by using descriptive statistics. Numeric data was presented as mean/ median value including the standard deviation. Nominal data was translated as proportion and confidence interval.

Statistical Analysis

Bivariate analysis was used to obtain data about the effect of frailty on MACE. The data was presented as different survival rate of developing MACE in elderly patients, both in frail and non-frail patients, which was described in Kaplan-Meier curve using Log-Rank test. Multivariate analysis was carried to adjust the confounding factors using the analysis of Proportional Hazard Regression Model. With such analysis, the effect of frailty on MACE was presented as the adjusted hazard ratio and 95% confidence interval.

Each subject (or their family) received both direct and written explanation about the aim, procedures and advantages of our study. The subject was then asked for their written consent to participate in the study. All data obtained from the history taking and medical records used in our study were strictly confidential.

RESULTS

In our study, the data of patients treated in Cipto Mangunkusumo Hospital was accumulated from September 2014 until June 2015. Within the period of study, 165 patients were treated with a primary diagnosis of coronary heart disease (CHD). About 31 patients could not have PCI procedure because there was no indication and the remaining 34 patients had not undergone the procedure since more time was needed for further examination of any underlying disease as well as preparing additional equipment for revascularization procedure, which could probably performed during the surgery. As many as 100 patients who met the inclusion criteria were recruited as the study subjects and they were followed up to 30 days following the elective PCI procedure. There was no subjects drop out.

Within the study period, we found that most subjects were male (69%) with an average age of 66.95 years (SD 4.875). From the sample population, we found that most had an education level that was equal to high school (37%) and undergraduates (31%) with an occupation as retired civil employee. Using the BMI criteria, 44% of the sample population was overweight, 28% was obese, 26% was normal and 2% was underweight.

Furthermore, we also found the following underlying disease, i.e. hypertension (80%) type II diabetes mellitus (54%), congestive heart failure (51%), chronic liver disease (6%), dyslipidemia (24%), cataract (4%) and arrhythmia (17%). Based on the medication use, we found that most subjects often used statin (79%), combined-dose of aspirin and clopidogrel (71%), and beta-blockers (58%). Other medications that had also been used were nitrates (32%), ACE Inhibitor (29%), ARB (25%), CCB (18%), aspirin (12%), clopidogrel (8%), and diuretics (6%)

In our study, the frailty was evaluated using frailty phenotype criteria. The criteria contained 4 out of 5 objective (measureable) items that had been extensively validated to predict the health outcomes. Those items were shrinkage (25 subjects), debility (49 subjects), lack of energy and endurance (35 subjects), tardiness (40 subjects) and poor physical activities (13 subjects).

The phenotype frailty criteria categorized the subjects into 3 group i.e. non-frail, pre-frail and frail groups. Considering the small sample size and limited amount of time in our study, we only categorized the subjects into the non-frail and frail groups in order to optimize data analysis. There were 61 elderly patients (61%) with coronary heart disease undergoing elective PCI procdure with phenotype frailty score of ≥3 in the frail group; while 39 patients (39%) with score of 0-2 were included in the non-frail group. The subject characteristics are presented in the **Table 1**.

In our study, the incidence of MACE in elderly patients with coronary heart disease underwent elective PCI procedure was 8.19% in the frail group and 5.12% in the non-frail groups. The MACEs were 1 event of death, 1 event of re-stenosis, 4 events of myocardium infarct and 1 event of stroke. The Kaplan Meier test showed insignificant result, i.e. 0.57 (p Log Rank >0.05). Based on the results, we could identify that in the first seven days, non-frail patients had a survival rate of 98%; while the frail patient had 97% survival rate. On the 14th day,the patients in non-frail group had a survival rate of 98%, while those in frail group had 96%. On the 21st day, the non-frail patients had 98% survival rate and the frail group had 95% survival rate.

In the non-frail group, 2 patients had MACE and 37 patients did not have MACE; while in the frail group, 5 patients experienced MACE and 56 patients did not experience MACE. The effect of frailty on MACE can be seen based on the crude HR, which was 1.6 (CI 95% 0.31-8.24).The data shown here indicates that the frailty increases the risk for MACE as much as 1.6 times higher.

DISCUSSION

Our study is a retrospective cohort study, which was conducted in 100 elderly patients with CHD who underwent elective PCI procedure at Cipto Mangunkusumo Hospital between September 2014 and June 2015.

Our study showed that there was a greater proportion of male (69%) than female subject (31%). We recorded that 55.07% male subjects and 74.2% female subjects undergoing elective PCI procedure were frail patients. The tendency

Tabel 1. Characteristics of subjects

Variables	Overall population (n=100)	Non-Frail (n=39)	Frail (n=61)
Sex, n (%)			
- Male	69 (69)	31 (79)	38 (62.3)
- Female	31 (31)	8 (20.5)	23 (37.7)
Range of age, n (%)			
- 60-69 years old	75 (75)	29 (74.3)	46 (75.4)
- 70-79 years old	25 (25)	10 (25.7)	15 (24.6)
Education, n (%)			
- Post bachelor	5 (5)	3 (7.7)	2 (3.3)
- Bachelor	31 (31)	9 (23.1)	22 (36.1)
- Vocation	6 (6)	2 (5.1)	4 (6.5)
- High-school	37 (37)	15 (38.5)	22 (36.1)
- Middle high	10 (10)	5 (12.8)	5 (8.2)
- Elementary	11 (11)	5 (12.8)	6 (9.8)
Jobs n (%)			
- Housewives	14 (14)	4 (10.2)	10 (16.4)
- Retired civil employees	32 (32)	7 (18)	25 (41)
- Retired private employees	15 (15)	10 (25.6)	5 (8.2)
- Enterpreneurs	14 (14)	3 (7.7)	11 (18)
- Others	24 (24)	14 (35.9)	10 (16.4)
- Unemployed	1 (1)	1 (2.6)	0 (0)
IMT, n (%)			
- Underweight (<18.5)	2 (2)	1 (2.6)	1 (1.7)
- Normal (18.5-22.9)	26 (26)	13 (33.3)	13 (21.3)
- Overweight (23-27.4)	44 (44)	15 (38.5)	29 (47.5)
- Obese (>27.5)	28 (28)	10 (25.6)	18 (29.5)
Comorbid diagnosis, n (%)			
- Hypertension	80 (80)	30 (76.9)	50 (81.9)
- Type 2 diabetes mellitus	54 (54)	20 (51.3)	34 (55.7)
- Congestive heart failure	51 (51)	19 (48.7)	32 (52.4)
- Cerebrovascular disease	10 (10)	4 (10.2)	6 (9.8)
- Chronic kidney disease	21 (21)	9 (23.1)	12 (19.7)
- Chronic liver disease	6 (6)	1 (2.5)	5 (8.2)
- Dyslipidemia	24 (24)	9 (23)	15 (24.6)
- Cataracs	4 (4)	0 (0)	4 (6.5)
- Arythmias	17 (17)	4 (10.2)	13 (21.3)
Medication, n (%)			
- Aspirin + Clopidrogel	71 (71)	26 (66.7)	45 (73.7)
- Aspirin	12 (12)	6 (15.4)	6 (9.8)
- Clopidrogel	8 (8)	3 (7.7)	5 (8.2)
- Statin	79 (79)	28 (71.8)	51 (83.6)
- Beta Blocker	58 (58)	23 (59)	35 (57.3)
- ARB	25 (25)	12 (30.7)	13 (21.3)
- CCB	18 (18)	4 (10.2)	14 (23)
- Nitrat	32 (32)	7 (18)	25 (41)
- ACE Inhibitor	29 (29)	12 (30.8)	17 (27.9)
- Diuretics	6 (6)	3 (7.7)	3 (4.9)

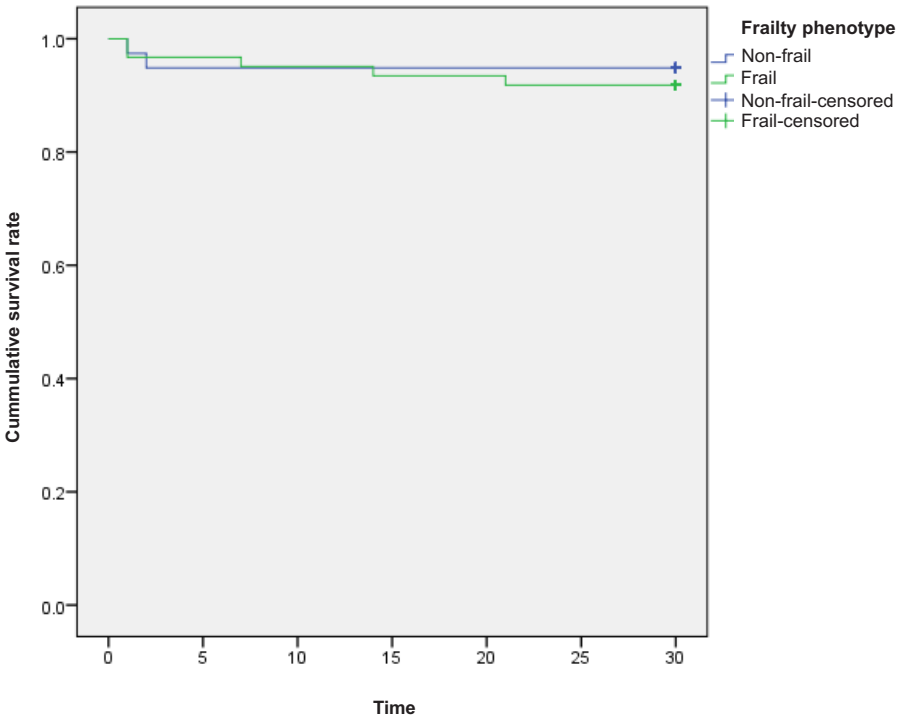

Figure 1. Kaplan Meier chart the survival of elderly patient with coronary heart disease on PCI elective.

of women experiencing frailty had been studied by a large scale study conducted by Fried et al.[16-18] Female is often associated with intrinsic risk factors of frailty since women have greater body mass and weaker than men of the same age. Thus, loss of body mass in women can cause frailty.[18-20]

The proportion of frail subjects in this study is 61%. The mean age of subjects was 66.95 years (SD 4.875) years. There were 75 subjects aged 60-69 years, in which 46 (61.33%) of them were frail and 15 subjects out of 25 subjects aged 70-79 year (60%) were frail. The mean age of frail subjects was 67.1 years compared to 66.8 years in the non-frail subjects. A study by Fried et al. that evaluated 5317 elderly subjects aged 65 – 101 years found that the prevalence of frailty is 6.9%. The study had three grops categorized by age, i.e. 3.2% of subjects were at 65-70 years, 5.3% aged 71-74 years and there were 95% with 75-79 years of age. The prevalence of frailty in the study was found greater than similar studies such as the study conducted by Murali-Krishnan (11% subjects with mean age of 61 (SD 12 years), Mandeep-Singh (18.6% subjects with mean age of 74.3 (SD 6.4) years.

The criteria that had been used in the study are the same with those in Mandeep-Singh study; while Murali-Krishnan used the criteria of Canadian Study of Health and Aging Clinical Frailty Scale, which is simpler and more subjective. The discrepancy of frailty prevalence may be due to differences in subject characteristics and the study site. Frailty has been often associated with cardiovascular disease. Fried in his large-scale population study, the Cardiovascular Health Study, has also found that 62% of frail subjects had cardiovascular disease and there were three-fold incidence of frailty in subjects with cardiovascular disease.[19]

The elderly frail subjects in our study had more comorbidities than the non-frail subjects. Approximately, frail subjects had 2.96 comordities; while the non-frail subjects had 2.46 comorbidities. Hypertension was found in 81.9% frail subjects compared to 76.9% in the non-frail subjects. Similar conditions were also found in patients with type 2 diabetes mellitus (frail vs. non-frail: 55.7 vs. 51.3%), congestive heart failure (52.4% vs. 48.7%), cerebrovascular disease (9.8% vs. 10.2%), chronic kidney disease

(19.7% vs. 23.1 %) and arrhythmia (21.3% vs. 10.2%). The result is consistent with several studies related to frailty and elderly patients who underwent PCI procedure.[14,17,18]

In our study, there were more frail subjects using combined medication than those in the non-frail group (4.52 vs. 3.76). It was associated with the number of comorbidities, which was indeed found greater in the frail subjects.

MACE might occur in long term and short term. In our study, the incidence of 30-day MACE was evaluated by the investigator in order to identify the shor-term incidence, i.e. during hospitalization (in-hospital MACE) and during the ambulatory care in the outpatient clinic in patients had been followed-up for 30 days. The overall MACE incidence was 7%. The MACE incidence included 1 event of death, 1 event of restenosis, 4 events of myocardium infarct and 1 event of stroke. In the frail group, the 30-day MACE was 8.19%; while in the non-frail group the incidence was approximately 5.12%.

Furthermore, four of seven MACEs were the in-hospital MACEs. Overall, there was only one death event; therefore, the mortality rate in one-month period was 1%. The rate found in our study is higher than other available studies. The Multi-Kharisnan study demonstrated that the 30-day mortality was 1.5% for all subjects. When they categorized the subjects into groups, the mortality rate of frail group was 4.9% and the non-frail group was 1.1%. According to the Murali-Kharisnan study, frail patients have 5-fold greater risk of death in 30-days after PCI than the non-frail patients. Lo et al.[20] who studied 54 elderly patients aged over 80 years who underwent PCI procedure showed that there was 1.9% MACE in one month. There was no in-hospital mortality within a month.

Gharacholou[14] performed a study in 629 elderly patients aged 65 years or older who underwent PCI and showed that there was 18.6% proportion of frailty and the mortality or myocardium infarct occurred within 30 days was 6%. Moreover, even when the short-term MACE included mortality, myocardium infarct and revascularization, the 30-day MACE was 9%. The high rate of MACE found in the study may occur since Gharacholou did not only include elective PCI for inclusion criteria; while in our study, we only included the elective PCI procedure in our inclusion criteria.[20]

In our study, three patients who experienced MACE were at the age less than 70 years; while the remaining 4 patients aged more than 70 years. Most patients had two or more comorbidities, whereas five patients had three or more. Patients who experienced MACE also had high body mass index (overweight or obese).

The multivariate analysis showed that the crude HR was 1.6 for the variable of frailty against MACE in elderly patients with CHD, meaning that the subjects with frailty had 1.6-fold greater risk for MACE within 30 days than those in the non-frail group. The number was smaller than those in Murali-Kharisnan study, which found HR of 4.8 (95% CI 1.4 to 16.3) for mortality in frail subjects undergoing PCI procedure.[20]

Multivariate analysis was performed for frailty and confounding variables with $p<0.25$; therefore, the adjusted HR of frailty against MACE was found. After an adjustment was made gradually for other variables affecting MACE including hypertension and arrhythmia, we found that the adjusted HR was 1.5 (95% CI 0.29-7.71).

In our study, the incidence of 30-day MACE in elderly patients with coronary heart disease who underwent elective Percutaneous Coronary Intervention was not significant since the restenosis or progression of disease rarely occurs within 1 month period; therefore, it can be concluded that the complication that develops within 1 month following the PCI is more correlated to the procedure or patient selection.[21]

The limitation of our study is that the study was only conducted at one hospital; thus, the obtained subject characteristics were the characteristic of elderly patients who sought treatment at the hospital. The number of sample size is relatively small since it was based on the assumed number of hazard ratio used in the study. Our study also did not compare the results with younger age population.

In previous studies, subjects were categorized into the non-frail, pre-frail and frail group. Such categories enable investigators to perform analysis on study subjects. In our study, the non-

frail and pre-frail group were included into the non-frail group.

CONCLUSION

The proportion of frailty in elderly subjects with coronary heart disease undergoing elective PCI procedure is 61%. The incidence of 30-day MACE in frail elderly patients with coronary heart disease following the elective PCI procedure is 8.19%; while in the non-frail group, the incidence is 5.12%. Elderly frail patients with coronary heart disease undergoing the PCI procedure have a high risk - 1.6 times more than the non-frail group - in experiencing MACE.

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