The Impact of Frailty on 30-day Post-Elective Surgery Complications in Elderly Patients: a Prospective Cohort Study

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ABSTRAK

Latar belakang: *pembedahan pada usia lanjut memiliki risiko komplikasi dan mortalitas yang tinggi. Status frailty merupakan salah satu faktor yang dapat mempengaruhi luaran operasi pada usia lanjut. Penelitian ini bertujuan untuk mengetahui pengaruh status frailty terhadap komplikasi 30 hari pascabedah elektif pada pasien usia lanjut.* ***Metode:*** *studi dengan desain kohort prospektif dengan mengambil data pasien yang menjalani pembedahan elektif di RS Cipto Mangunkusumo. Penilaian frailty dengan menggunakan FI 40 items. Penilaian 30 hari komplikasi pasca bedah menggunakan klasifikasi Clavien-Dindo. Analisis multivariat dengan logistik regresi dilakukan untuk menghitung adjusted relative risk (RR) terjadinya komplikasi 30 hari pascabedah elektif.* ***Hasil:*** *total didapatkan 180 subjek dengan rerata usia 67.1 (SB 6.057) tahun. Sebagian besar subjek termasuk pre-frail (55.6%), diikuti frail (26.7%) dan fit (17.7%). Sebanyak 21.1% subjek mengalami komplikasi 30 hari pascabedah. Proporsi kejadian komplikasi 30 hari pada subjek frail lebih tinggi dibandingkan dengan kelompok pre-frail dan fit (41.7% vs 15% vs 9.4%). Pada analisis multivariat, didapatkan adjusted RR pada kelompok frail sebesar 4.579 (IK 95% 1.8-8.12), setelah memperhitungkan faktor perancu beratnya pembedahan. Pada subjek pre-frail, tidak ditemukan komplikasi yang berbeda bermakna walaupun terdapat kecenderungan komplikasi lebih tinggi dibandingkan kelompok fit.* ***Kesimpulan:*** *kondisi frail meningkatkan risiko komplikasi 30 hari pascabedah elektif pada pasien usia lanjut.*

Kata kunci: *status frailty, komplikasi pasca-operasi, bedah elektif, usia lanjut.*

ABSTRACT

Background: *late-life surgery poses a greater risk for complications and a higher mortality rate. Frailty has been noted to predict adverse outcomes after surgery in elderly patients. We aimed to investigate the impact of frailty on 30-day post-elective surgery complications in elderly patients.* ***Methods:*** *this prospective cohort study was conducted based on data collected from patients undergoing elective surgery in Cipto Mangunkusumo Hospital, Indonesia. Frailty was assessed using the Frailty Index 40 items, and 30-day post-surgery complications*

were assessed using Clavien-Dindo classification. Multivariate logistic regression analysis was performed to determined adjusted relative risk (RR) of the development of 30-day post-surgery complications. ***Results:*** *a total of 180 subjects were enrolled in the study, with average age of 67.1 (SD 6.06) years old. More than half of the subjects fell into pre-frail category (55.6%), followed by frail (26.7%) and fit (17.7%) respectively. About 21.1% experienced complications within 30 days post-surgery. Frail subjects (41.7%) showed higher incidence of complications compared to the pre-frail (15%) and fit (9.4%) group. Multivariate analysis revealed that adjusted RR in the frail group accounted for 4.58 (95% CI 1.8-8.12), considering the surgical severity as a confounding factor. No significant difference in the incidence of complications was observed between the pre-frail and fit groups, despite the pre-frail group having a higher complication rate.* ***Conclusion:*** *being frail increases the risk of 30-day post-elective surgery complications in elderly patients.*

Keywords: *frailty, post-surgery complication, elective surgery, elderly.*

INTRODUCTION

The elderly population worldwide, as well as nationwide in Indonesia, has been exponentially increasing in recent years.[1] Physical changes related to the ageing process contribute to elderly patients being more vulnerable to age-related degenerative diseases and surgical intervention.[2] Surgery in later life poses a detrimental risk of complication and a higher mortality rate compared to younger individuals. Incidence of post-surgery complications is believed to positively correlate with age, constituting a 4% increase at the ages of 40-60 years old and up to a 17% at >90 years old.[3]

Compared to chronological age, biological age is an important factor in the incidence of post-surgery complications. Frailty is one of the modern geriatric syndromes occurring as a result of accumulated deterioration of physiological function towards acute stress response. Frailty itself is closely associated with higher morbidity, mortality, and longer hospital stay in elderly patients undergoing surgery.[4,5]

Risk stratification can be evaluated using pre-surgical frailty assessment on patients undergoing surgery to optimize modifiable factors in achieving a better surgical outcome.[4,5] Despite studies showing a significant association between frailty and incidence of surgical complications[6-8], few studies have stated the opposite.[9,10] Furthermore, several studies on post-surgery complications related to frailty focused only on certain fields of surgery.[8-10] Since studies showed different results and no similar study has been conducted in Indonesia, we are intrigued to evaluate the impact of frailty as a predictor of complications following elective surgery in elderly patients admitted to Cipto Mangunkusumo Hospital. This study aims to investigate the impact of frailty on 30-day post-elective surgery complications in elderly patients.

METHODS

This is a prospective cohort study of elderly patients undergoing elective surgery in Cipto Mangunkusumo Hospital from April to July 2018. Frailty was assessed using 40-item Frailty Index (FI-40) and classified into three categories: fit/robust ($\leq$ 0.08), pre-frail (>0.08-0.25), and frail ($\geq$ 0.25).[11,12]

Post-surgery complications were evaluated using Clavien-Dindo classification on day 30 after elective surgery. This classification is based on the type of treatment required to alleviate imminent complications.[13] Complications were observed up to the 30th day following surgery based on data in medical records or obtained from contacted subjects. In subjects developing more than one complications, the most severe complication was considered as the final assessment. Based on Clavien-Dindo classification, complications were classified into five grades: (1) Grade I; any deviation from the normal condition postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological intervention. Allowed therapeutic regimens are using: antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy.

This grade also includes wound infections opened at the bedside; (2) Grade II; requiring pharmacological treatment with drugs other than allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included; (3) Grade III; requiring surgical, endoscopic or radiological intervention, Grade IIIa; intervention not under general anesthesia; and Grade IIIb; intervention under general anesthesia; (4) Grade IV; life-threatening complication (including central nervous system complications i.e brain hemorrhage, ischemic stroke, and subarrachnoidal bleeding) requiring intermediate care or intensive care unit management, Grade IVa; single organ dysfunction (including dialysis,), and Grade IVb; multi-organ dysfunction and (5) Grade V; death of a patient.[13]

The sample was consecutively collected using inclusion criteria of age ≥ 60 years, admission for elective surgery, and being given general or regional anesthesia. Subjects, who were given local anesthesia or who were unwilling to participate, were excluded from the study. Drop out criteria include all subjects who were out of reach and did not come to the clinic within the first 30 days following elective surgery. Potential confounding factors were patient age, type of anesthesia, surgical severity, and malignancy. Subjects were assessed for their nutritional status (Mini Nutritional Assessment), functional status (Activity of Daily Living/ADL Barthel Index), cognitive function (Mini Mental State Examination), depression (Geriatric Depression Scale), type and index of comorbidities (Carlson Comorbidity Index). The surgical severity was classified into three categories based on modified Johns Hopkins criteria; (1) Grade 1: minimal to mild risk independent to anesthesia, minimal to moderate invasive procedure, potential blood loss of less than 500 ml; (2) Grade 2: moderately to significantly invasive procedure, potential blood loss of 500 to 1500 ml, moderate risk to patient independent of anesthesia; (3) Grade 3: highly invasive procedure, potential blood loss greater than 1500 ml, major to critical risk to patient independent of anesthesia, and usual postoperative ICU stay with invasive monitoring.[14] All subjects provided written informed consent and approval was obtained from the Ethical Committee of the Faculty of Medicine, Universitas Indonesia (No.0162/UN2.F1/ETIK/2018).

Sample size was estimated by proportion difference formula for 3 groups. Using alfa of 0,05 and power of 80% and assuming the difference of proportion 25%, total subjects to include at least 162 elderly patients underwent surgery. Subject characteristics were presented using descriptive statistics, and data was analyzed using SPSS (Statistical Product for Social Science) software version 20.0. The association between frailty status and post-surgery complications was analyzed using chi-square test. Relative risk of frail and pre-frail for complications was calculated compare to the fit group. Chi-square test was used

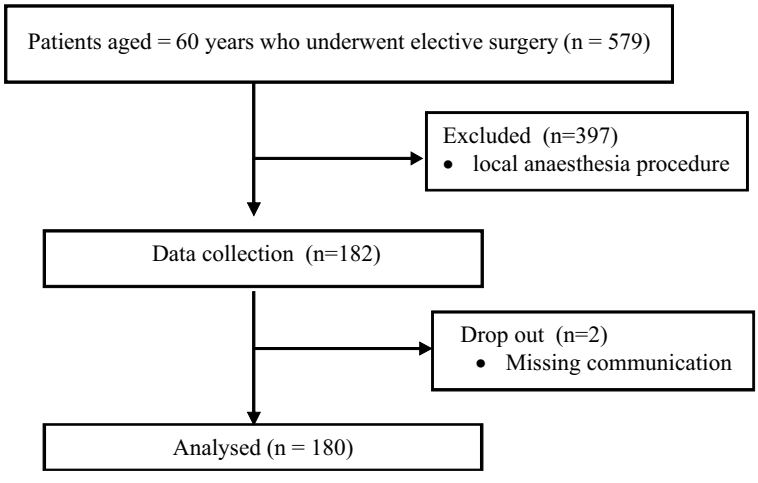

Figure 1. Participant flow diagram.

to analyzed confounding factors (age, type of anesthesia, surgical severity, and malignancy) with complications, and then significant confounding factor/s ($p<0.25$) would be included in multivariate analysis. Multivariate logistic regression analysis was used to adjust the association between frailty status and post-surgery complications with significant confounding factor/s. As odds ratio (OR) naturally overestimates the RR value, we converted the adjusted OR obtained by logistic regression analysis to adjusted RR with formula proposed by Zhang et al.[15] Statistically significant p value for regression analysis was < 0.05.

RESULTS

During the period of April to July 2018, 579 subjects above 60 years old opted for elective surgery in Cipto Mangunkusumo Hospital. Of these, 397 were excluded because they were given local anesthesia. At the start of the study,182 patients were enrolled, but during the study period, two patients dropped out because of missing communications, leaving 180 participants for analysis in the study.

The majority of participants were female (55.5%), with average age of 67.1 (SD 6.06) years, ranging between 60 and 86 years. More than half of the subjects fell into the pre-frail category, followed by the frail and fit group, respectively. Nutritional status of most subjects was considered normal, and the majority of subjects also had relatively normal cognitive ability, independent functional status, normal geriatric depression score, and received general anesthesia for their elective surgeries (**Table 1 and 2**).

Post-surgery complications were found in 21.1% of all cases. Complications occurred in 41.7% of the frail group, but only 15% of the pre-frail group and 9.4% of the fit group. Bivariate analysis comparing frail and fit subjects showed a considerable difference in the incidence of complications within 30 days following elective surgery (RR 4.44, 95% CI 1.44-13.73; $p = 0.009$), as shown in **Table 3**. Of the subjects in all three groups, the greatest proportions of complication Grade I to V were found in the frail subjects and consecutively followed by the pre-frail and fit group.

Two of the frail subjects died after the surgery during their hospital stay due to septic shock, while another one died in outpatient care. The first two casualties shared similar baseline characteristics, including cognitive impairment, malnutrition, and severe to total dependency, while the last one had risk of malnutrition, cognitive impairment, mild to moderate dependency with CCI score of 4. One pre-frail subject died due to septic shock during rehospitalization after previously being discharged. This pre-frail individual was malnourished, functionally independent, had no cognitive impairment and had CCI score of 2.

Bivariate analysis between the confounding factors (age, surgical severity, type of anaesthesia, and malignancy) and the incidence of complications revealed significance only for surgical severity ($p<0.25$) (**Table 4**), suggesting the need to do a multivariate analysis for this factor.

After adjusted for surgical severity, frailty independently increased the risk of developing complications 30 days after elective surgery in elderly patients with adjusted RR 4,58 (CI 95% 1.8-8.12; p=0,004), while pre-frail didn't have association with 30 days complications with adjusted RR 1,46 (CI 95% 0.42-4.05; p=0.54).

DISCUSSION

The study showed that 21.1% of geriatric patients opting for elective surgery developed complication during the first 30 days following the surgery. The results reveal a higher incidence of complications 30 days after elective surgery in frail subjects, with adjusted RR value of 4.58 (CI 95% 1.8-8.12). Similar results were produced in a study by Tan et al[6], which evaluated the impact of frailty on post-surgery complications using the same Clavien-Dindo classification, with OR value of 4.08 (p=0.006). However, the subjects participating in the aforementioned study were limited to patients with colorectal cancer. In their research, frail subjects had complications ranging from grade II to grade IV (anastomosis leakage, surgical site bleeding, intra-abdominal collection, abdominal obstruction, rectal perforation, neurological disorder, thoracic infection, arrhythmia, acute coronary syndrome,

Table 1. Baseline Subject Characteristics.

Characteristics	Fit (n=32)	Pre-frail (n=100)	Frail (n=48)	Total (n=180)
Age (year-old), average (SD)	64.5 (3.869)	67 (6.21)	68.8 (6.41)	67.1 (6.06)
Age category, n (%)				
- ≥ 80 years old	0 (0)	4 (4)	3 (6.3)	7 (3.9)
- 70-79 years old	4 (12.5)	24 (24)	18 (37.5)	46 (25.6)
- 60 - 69 years old	28 (87.5)	72 (72)	27 (56.2)	127 (70.5)
Gender, n (%)				
- Female	14 (43.8)	58 (58)	28 (58.3)	100 (55.5)
- Male	18 (56.2)	42 (42)	20 (41.7)	80 (44.5)
Nutritional Status, n (%)				
- Malnourished (MNA score < 17)	2 (6.2)	8 (8)	19 (39.6)	29 (16.2)
- Risk of Malnutrition (MNA score 17 – 23.5)	5 (15.6)	25 (25)	14 (29.2)	44 (24.4)
- Normal (MNA score >23,5)	25 (78.1)	67 (67)	15 (31.2)	107 (59.4)
Cognitive Status, n (%)				
- Cognitive Impairment (MMSE < 24)	4 (12.5)	11 (11)	16 (33.3)	31 (17.3)
- Normal (MMSE ≥ 24)	28 (87.5)	89 (89)	32 (66.7)	149 (82.7)
Functional Status, n (%)				
- Severe-total dependency (ADL <9)	0 (0)	0 (0)	14 (29.2)	14 (7.8)
- Mild-moderate dependency (ADL 9-19)	4 (12.5)	21 (21)	31 (64.6)	56 (31.1)
- Independence (ADL = 20)	28 (87.5)	79 (79)	3 (6.2)	110 (61.1)
Charlson Comorbidity Index (CCI), n (%)				
- CCI score ≥5	0 (0)	9 (9)	5 (10.4)	14 (7.8)
- CCI score 3-4	5 (15.6)	29 (29)	15 (31.2)	49 (27.2)
- CCI score 1-2	21 (65.6)	58 (58)	25 (52.1)	104 (57.8)
- CCI score 0	6 (18.8)	4 (4)	3 (6.2)	13 (7.2)
Comorbidity, n (%)				
- Hypertension	7 (21.9)	62 (62)	30 (62.5)	100 (55.6)
- Malignancy	20 (62.5)	50 (50)	14 (29.2)	84 (46.7)
- Diabetes mellitus	2 (6.25)	15 (15)	15 (31.25)	32 (17.8)
- Congestive heart failure	1 (3.1)	11 (11)	11 (22.9)	23 (12.8)
- Moderate-severe kidney disease	0 (0)	1 (1)	2 (4.2)	3 (1.7)
- Chronic lung disease	0 (0)	1 (1)	3 (6.2)	4 (2.2)
Depression scale, n (%)				
- Depression (GDS score ≥ 10)	0 (0)	0 (0)	1 (2.0)	1 (0.6)
- Possibility of depression (GDS score 5-9)	1 (3.1)	11 (11)	9 (18.8)	21 (11.7)
- Normal (GDS score <5)	31 (96.9)	89 (89)	38 (79.2)	158 (87.7)
Polypharmacy (≥5 medication), n (%)	1 (3.1)	20 (20)	9 (18.8)	29 (16.3)
Albumin, (n=155) (%)				
- < 3 mg/dL	0 (0)	3 (5)	11 (30.6)	14 (12.2)
- ≥ 3 mg/dL	19 (100)	57 (95)	25 (69.4)	101 (87.8)
Hb, n (%)				
- <10 mg/dL	1 (3.1)	3 (3.0)	3 (6.2)	7 (4.0)
- ≥ 10 mg/dL	31 (96.9)	94 (97)	45 (93.8)	172 (96)
Random Blood Glucose, (n=167) (%)				
- ≥ 200 mg/dL	1 (3.4)	1 (1.1)	1 (2.2)	3 (1.8)
- <200 mg/dL	28 (96.6)	91 (98.9)	45 (97.8)	164 (98.2)

SD=standard deviation; MNA = Mini Nutritional Assessment; MMSE=Mini Mental State Examination; ADL= Activities of Daily Living; GDS= Geriatric Depression Scale, Hb = Hemoglobin

Table 2. Subject Characteristics of Surgeries and Complications.

Characteristic	Fit (n=32)	Pre-frail (n=100)	Frail (n=48)	Total (n=180)
Surgical severity, n (%)				
- Grade I	23 (71.9)	55 (55)	22 (45.8)	100 (55.6)
- Grade II	7 (21.9)	35 (35)	25 (52.1)	67 (37.2)
- Grade III	2 (6.2)	10 (10)	1 (2.1)	13 (7.2)
Surgery type based on specialty, n (%)				
- Digestive Surgery	3 (9.4)	18 (18)	3 (6.2)	24 (13.3)
- Orthopaedic Surgery	1 (3.1)	7 (7)	17 (35.4)	25 (13.9)
- Vascular Surgery	1 (3.1)	4 (4)	8 (16.7)	13 (7.2)
- Neurosurgery	0 (0)	4(4)	3 (6.2)	7 (3.9)
- Cardio-Thoracic-Vascular Surgery	0 (0)	3 (3)	1 (2.1)	4 (2.2)
- Plastic Surgery	0 (0)	0 (0)	1 (2.1)	1 (0.6)
- Urology Surgery	8 (25)	22 (22)	2 (4.2)	32 (17.8)
- Oncology Surgery	4 (12.5)	7 (7)	4 (8.3)	15 (8.3)
- Obstetric Gynaecology Surgery	2 (6.2)	3 (3)	2 (4.2)	7 (3.9)
- Ophthalmology Surgery	9 (28.1)	16 (16)	7 (14.6)	32 (17.8)
- Otorhinolaryngology Surgery	4 (12.5)	14 (14)	0 (0)	18 (10)
- Oral Surgery	0 (0)	2 (2)	0 (0)	2 (1.1)
Type of Anaesthesia, n (%)				
- General	23 (71.9)	73 (73)	32 (66.7)	128 (71.1)
- Regional	9 (28.1)	27 (27)	16 (33.3)	52 (28.9)
Complications, n (%)				
- Grade I-V	3 (9.4)	15 (15)	20 (41.7)	38 (21.1)
- Grade I	1 (3.1)	5 (5.1)	4 (8.3)	10 (5.6)
- Grade II	2 (6.2)	9 (9.1)	7 (14.6)	18 (10.2)
- Grade III	0 (0)	0 (0)	5 (10.4)	5 (2.8)
- Grade IV	0 (0)	0 (0)	1 (2.1)	1 (0.6)
- Grade V (death)	0 (0)	1 (1)	3 (6.25)	4 (2.3)

Table 3. Bivariate Analysis between Frailty Impact on 30-day Post-Elective Surgery Complications in Elderly Patients.

Frailty Status	Complication		Total (%)	Relative Risk	95% CI	P value*
	Yes (%)	No (%)				
Frail	20 (41.7)	28 (58.3)	48 (100)	4.44	1.44-13.73	0.009
Pre-frail	15 (15.0)	85 (85.0)	100 (100)	1.60	0.5-5.18	0.43
Fit	3 (9.4)	29 (90.6)	32 (100)	Ref		

*Chi-square test

sepsis, delirium, acute kidney failure, cerebral vascular accident).[6] A study by Kristjansson et al[7] similarly showed significant result on the impact of frailty and 30-day post-surgery complications using the Clavien-Dindo classification, showing the OR value of 3.13 (95% CI 1.65-5.92). Their study featured Grade I to Grade IV Clavien-Dindo-based complications, comprising of surgical site infection, urinary tract infection, pneumonia/lung disease requiring mechanical ventilation, heart problems featuring arrhythmia/lung edema/acute coronary syndrome, delirium, intraabdominal abscess, diarrhea, blood loss requiring transfusion, intestinal obstruction, and cerebrovascular accident.[7] Study by Kistler et al.[8] focused on subjects undergoing hip fracture surgery and used modified Fried criteria. It showed more complications in frail participants compare to non-frail participants (p=0.028). The study selectively enrolled 35 subjects undergoing

Table 4. Bivariate Analysis Between Confounding Factors and Surgery Complications.

Variables	Complication		Total	P value*
	Yes	No		
Age (n,%)				
- >70 year	12 (22.6)	41 (77.4)	53	0.75
- 60-69 year	26 (20.5)	101 (79.5)	127	
Surgical severity (n,%)				
- Grade III	6 (46.2)	7 (53.8)	13	0.03
- Grade II	16 (23.9)	51 (76.1)	67	
- Grade I	16 (16)	84 (84)	100	
Type of anaesthesia (n,%)				
- General	25 (19.5)	103 (80.5)	128	0.42
- Regional	13 (25)	39 (75)	52	
Malignancy (n,%)				
- Yes	19 (22.6)	65 (77.4)	84	0.64
- No	19 (19.8)	77 (80.2)	96	

*Chi-square test

hip surgery and observed possible arising complications such as pneumonia, myocardial infarction, arrhythmia, heart problem, bleeding, surgical site infection, deep vein thrombosis, kidney failure, and delirium.

In contrary to our study, other publications by Green et al.[9] and Charest-Morin et al.[10] revealed an insignificant correlation between frailty and post-surgery complications at 30 days or between frailty and any adverse events. Some differences observed were due to diverse frailty assessment, type of surgery, and outcome measurement, including complication classification. Green et al.[9] carried out their study on patients undergoing transcatheter aortic valve replacement using combination of four marker (serum albumin, hand grip strength, gait speed, Katz ADL) for frailty assessment. Frailty was found in 45% subjects. Post-surgery outcome parameters included mortality, rehospitalization, stroke, bleeding, vascular complication, kidney problems, and permanent pacemaker use. Study by Charest-Morin et al.[10] used the modified Frailty Index on subjects undergoing elective surgery for lumbar spine. They found no significant relationship between frailty and peri-operative adverse events.

Our study has confirmed that frailty significantly influences the incidence of complications 30 days after elective surgery. Surgery is a stressful condition in the elderly patient and can result in deteriorating physical function. Functional capacity reserves may decrease and impair homeostatic balance in the frail elderly. Inflammation is thought to be the main contributor to clinical deterioration in the frail and patients with many complications. Surgery enhances the production of inflammatory markers, oxidative stress, and free radicals that accumulatively induce more secretion of inflammatory mediators, thus causing dysregulation of the immune response. This condition may compromise the organ function and put frail patients into more dysregulated homeostasis, aggregating the risk of complications and mortality post-surgery.[4,9]

To the best of our knowledge, this is the first study in Indonesia that determine the impact of frailty in the elderly population in terms of 30-day post-elective surgery complications. One of the limitations of the study is that its location in a national tertiary referral hospital in Indonesia may have provided results which might not be applicable nationwide to other hospitals. Another limitation was that since this study did not specify the type of surgery, its outcome parameters may be too broad and not specialized for each surgical type.

CONCLUSION

Being frail increases the risk of developing complications 30 days after elective surgery in elderly patients.

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DISCLOSURE STATEMENTS

The authors declare no conflict of interest.

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