Effect of frailty on major bleeding in octogenarian patients undergoing percutaneous coronary intervention

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Abstract. – OBJECTIVE: There has been an increase in the number of percutaneous coronary intervention (PCI) procedures performed in octogenarian patients due to increased life expectancy and developments in modern medicine. Frailty is associated with the aging process, gradual loss of multiple body functions, and poor health outcomes. We examined the association between frailty and major bleeding in octogenarian patients undergoing PCI.

PATIENTS AND METHODS: We retrospectively analyzed the records of two local research hospitals in Turkey. In total, 244 patients were enrolled in this study. Patients were divided into two groups based on their Clinical Frailty Scale (CFS) score. The non-frail group included patients with CFS scores of 1 (very fit) to 4 (living with very mild frailty), while the frail group included those with CFS scores of 5 (living with mild frailty) to 9 (terminally ill).

RESULTS: Of the 244 patients, 131 were classified into the non-frail group and 113 into the frail group. Ticagrelor use was significantly more common in the non-frail group (31.3% *vs.* 20.4%, *p*=0.036). Major bleeding was more common in the frail than non-frail group (20.4% *vs.* 6.1%, *p*<0.001). The rates of stroke and all-cause death were higher in the frail than in non-frail group (stroke 15.9% *vs.* 3.8%, *p*<0.001, as well as all-cause mortality rate (27.4% *vs.* 2.3%, *p*<0.001).

CONCLUSIONS: Frailty is an independent predictor of major bleeding in patients undergoing PCI for acute coronary syndrome. Use of the P2Y12 inhibitor ticagrelor increases the risk of major bleeding in frail patients.

Key Words:
  Frailty, Elderly, Acute coronary syndrome, Dual antiplatelet therapy, Bleeding, Geriatric assessment, Clinical frailty scale.

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in octogenarian patients[1]. Given the increase in life expectancy and developments in modern medicine, we are now encountering more patients over the age of 80 years. Furthermore, these patients are undergoing interventional procedures more frequently than in the past[2]. Percutaneous coronary intervention (PCI) is the main treatment for acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) in both octogenarian and younger patients[3]. Dual antiplatelet therapy (DAPT) with aspirin and ticagrelor or clopidogrel is recommended to avoid thrombotic events after PCI for ACS, while DAPT with aspirin and clopidogrel is recommended after PCI for CCS in both older and younger patients[4].

Frailty refers to a decrease in the physiological reserves needed for daily activities and stress responses and occurs due to decreased organ and organ system function caused by biological aging[5]. Frailty predominantly affects the elderly; however, it is related to the biological rather than chronological age.

Frailty encompasses many conditions, including malnutrition, long bed rest, pressure sores, gait disturbances, weakness, loss of strength, balance deficits, delirium, confusion, and memory problems, which are related to biological aging[6]. Frailty is associated with abnormal platelet function and coagulation regardless of antithrombotic therapy, and it is an independent risk factor for bleeding[7].

The rate of frailty increases with age; about 30% of octogenarian patients are frail[8]. However,

octogenarian and frail patients are almost always excluded from randomized clinical trials of antiplatelet drugs. We examined the association between frailty and major bleeding in octogenarian patients undergoing PCI, and the effect of frailty on outcomes.

Patients and Methods

Trial Design and Population

We screened 451 patients who underwent primary and elective PCI between January 2019 and July 2021, and included 244 consecutive patients aged ≥ 80 years at presentation after exclusion criteria (Figure 1). This retrospective observational study based on electronic hospital records was performed at two research hospitals in Turkey. All enrolled patients were pre-treated with a loading dose of 300 mg of aspirin and either 300-600 mg of clopidogrel or 180 mg of ticagrelor according to the attending physician's preference. The exclusion criteria were as follows: use of anticoagulants, a history of severe intolerance or allergy to one of the drugs (acetylsalicylic acid, clopidogrel, or ticagrelor), a history of haematological disease or platelet count < 100,000/μL, a haemoglobin level < 10 g/dL, active bleeding, a known intracranial aneurysm, a cerebral arteriovenous malformation or intracranial mass, severe kidney failure requiring dialysis, a severe liver function disorder, mechanical complications due to ACS, concomitant use of CYP2C19 inhibitors, and a lack of online permission to access the patient's electronic health records.

The primary endpoints of this study were major bleeding (intervention and transfusion required) after PCI in first year, secondary endpoints are 1-year all-cause mortality, target vessel revascularization, and stroke. These data were obtained from a national Turkish electronic health record database. The study was conducted according to the principles outlined in the Declaration of Helsinki and was approved by the Ankara City Hospital Second Ethic Committee in Ankara/Turkey with number E2-22-3104.

Frailty Assessment

Frailty was assessed using the Clinical Frailty Scale (CFS) introduced in the Canadian Study of Health and Aging; the CFS has been shown to correlate with mortality in patients with cardiovascular disease[6-9]. Based on previous studies, the patients were divided into two groups based on their frailty scores. The non-frail group included those with CFS scores of 1 (very fit) to 4 (living with very mild frailty), while the frail group included those with CFS scores of 5 (living with mild frailty) to 9 (terminally ill). The CFS scores of the patients were evaluated by two physicians according to hospital records and nurse follow-up file.
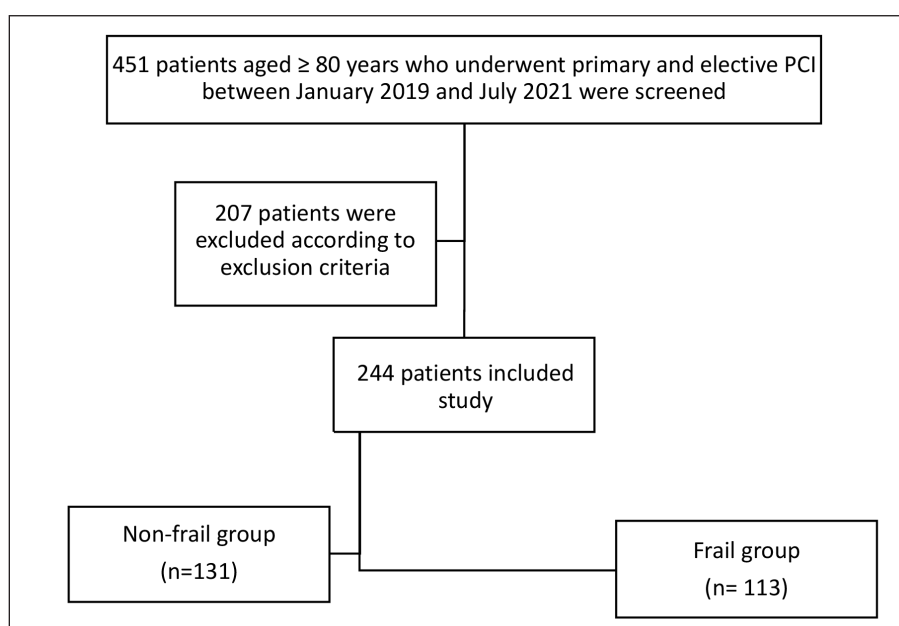

Figure 1. Study flow diagram..

Statistical Analysis

SPSS for Windows software (ver. 23.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Normally distributed continuous variables are presented as means and standard deviations, and means were compared using Student's *t*-test. Non-normally distributed continuous variables are shown as median (min–max) values and were compared using the Mann-Whitney U test. Categorical variables are shown as numbers and percentages and were compared using the chi-square test and Fisher's exact test. Kaplan-Meier plots and the log-rank test were used to compare survival between groups with and without a major adverse cardiovascular or cerebrovascular event. Cox proportional hazard models were used to evaluate the association between DAPT regime and outcomes, after adjusting for predefined clinically relevant comorbidities and demographic variables. Logistic regression was used to study the secondary outcome measures. All tests were two-sided and *p*-values <0.05 were considered significant.

Results

Overall, 244 patients who met the inclusion criteria were enrolled in this study. At the time

Table I. Baseline characteristics of the frail and non-frail patients.

	All (n: 244)	Non-frail Group (n: 131)	Frail Group (n: 113)	*p*-value
Demographics				
Age (Years)	84.6 ± 3.4	82.9 ± 2.3	86.4 ± 3.5	**<0.001**
Sex, n (%)				
Male	131 (53.7)	77 (58.8)	54 (47.8)	0.056
Female	113 (46.3)	54 (41.2)	59 (52.2)	
Comorbidity, n (%)				
Diabetes Mellitus	85 (34.8)	43 (32.8)	42 (37.2)	0.28
Hypertension	200 (82.0)	105 (80.2)	95 (84.1)	0.26
Current smoker	46 (18.9)	29 (22.1)	17 (15.0)	0.10
Heart Failure	9 (3.7)	3 (2.3)	6 (5.3)	0.18
Stroke	35 (14.3)	11 (8.4)	24 (21.2)	**0.004**
Previous PCI	46 (18.9)	24 (18.3)	22 (19.5)	0.47
Previous CABG	22 (9)	14 (10.7)	8 (7.1)	0.22
Presentation, n (%)				
STEMI	98 (40.2)	52 (39.7)	46 (40.7)	0,84
NSTEMI	133 (54.5)	71 (54.2)	62 (54.9)	
UA	13 (5.3)	8 (6.1)	5 (4.4)	
Laboratory examinations				
WBC, (µ/µL)	9.7 ± 3.5	9.3 ± 3.3	10.2 ± 3.7	0.044
HGB, (g/dL)	12.6 ± 1.6	12.9 ± 1.5	12.3 ± 1.7	0.09
PLT, (µ/µL)	228.2 ± 67.2	228.5 ± 63.4	227.9 ± 71.7	0.94
Cre, (mg/dL)	1.07 ± 0.3	1.02 ± 0.27	1.1 ± 0.35	0.03
TotChol, (mg/dL)	172.8 ± 43.5	177 ± 43.39	167.5 ± 43.39	0.10
LDL, (mg(dL)	107.8 ± 39.5	110.8 ± 41.7	103.9 ± 36.4	0.19
HDL, (mg/dL)	45.4 ± 13.2	46 ± 14.1	44.8 ± 12.2	0.52
P2Y12 inhibitors, n (%)				
Clopidogrel	179 (73,4)	90 (68.7)	90 (79.6)	**0.036**
Ticagrelor	65 (26,6)	41 (31.3)	23 (20.4)	
Other data				
Precise Score	30.4 ± 9.2	27.06 ± 7.8	34.3 ± 9.1	**<0.001**
DAPT duration (Days)	278.6 ± 128.2	330.5 ± 81.9	218.4 ± 145.2	**<0.001**
DAPT Dyspnea, n (%)	9 (3.7)	4 (3.1)	5 (4.4)	0.40
Left Ventricular Ejection Fraction, (%)	51.9 ± 9.4	53.8 ± 8.1	49.6 ± 10.3	0.001
Systolic Blood Pressure, (mmHg)	125.8 ± 21.5	128 ± 20.1	123.1 ± 22.7	0.077
Diastolic Blood Pressure, (mmHg)	71.1 ± 13.9	72.8 ± 14.6	69 ± 12.9	**0.035**
Heart Rate, (bpm)	79.3 ± 13.8	77.3 ± 12.6	81.7 ± 14.8	**0.014**

CABG: coronary artery bypass graft, DAPT: dual antiplatelet therapy, PCI: percutaneous coronary intervention, WBC: White Blood Cell Count, HGB: Hemoglobin, PLT: Platelet Count, Cre: Creatinine, TotChol: Total Cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

of discharge, frailty was evaluated, and the patients were divided into two groups (non-frail group, n=131; frail group, n= 13) based on their CFS scores. The baseline demographic and clinical characteristics of the two groups are shown in Table I. The mean age of the patients was 84.6±3.4 years, and 53.7% were male. The frail group was significantly older than the non-frail group (86.4±3.5 *vs.* 82.9±2.3 years, *p*<0.001). There were no significant group differences in the rates of hypertension, diabetes mellitus, heart failure, prior PCI, or prior coronary artery bypass graft surgery. The sex ratio and number of active smokers were similar between the two groups. The frail group had a higher prevalence of stroke (21.2% *vs.* 8.4%, *p*=0.004). The proportions of patients with an ST-elevation myocardial infarction (STEMI) in the frail and non-frail groups were 40.7% and 39.7%, respectively. For DAPT, the P2Y12 receptor blocker used was clopidogrel in 73.4% of patients and ticagrelor in 26.6% of patients. The use of ticagrelor was significantly more common in the non-frail group (31.3% *vs.* 20.4%, *p*=0.036). Patients in the frail group had higher leukocyte counts (10.2 ± 3.7 μ/μL *vs.* 9.3 ± 3.3 μ/

μL, *p*=0.044) and creatinine levels (1.1 ± 0.35 mg/dL *vs.* 1.02 ± 0.27 mg/dL, *p*=0.09), and lower haemoglobin levels (12.3 ± 1.7 g/dL *vs.* 12.9 ± 1.5 g/dL, *p*=0.09). However, there were no significant group differences in the platelet counts or lipid profiles. The duration of DAPT was significantly shorter in the frail group (218.4 ± 145.2 days *vs.* 330.5 ± 81.9 days, *p*<0.001). Also, the patients in the frail group had a significantly lower left ventricular ejection fraction (49.6 ± 10.3% *vs.* 53.8 ± 8.1%, *p*<0.001) and diastolic blood pressure (69 ± 12.9 mmHg *vs.* 72.8 ± 14.6 mmHg, *p*=0.035), and a significantly higher heart rate (81.7 ± 14.8 bpm *vs.* 77.3 ± 12.6 bpm, *p*=0.014) at admission. Finally, the Predicting Bleeding Complications in Patients Undergoing Stent Implantation (PRECISE) scores were higher in the frail group (34.3 ± 9.1 *vs.* 27.06 ± 7.8, *p*<0.001).

Clinical outcomes according to CFS group are shown in Table II. The rate of major bleeding was higher in the frail than non-frail group (20.4% *vs.* 6.1%, *p*=0.001), and Kaplan-Meier analysis revealed a significant difference between the frail and non-frail groups (*p*<0.001) (Figure 2). Moreover, the rates of stroke and all-cause death were
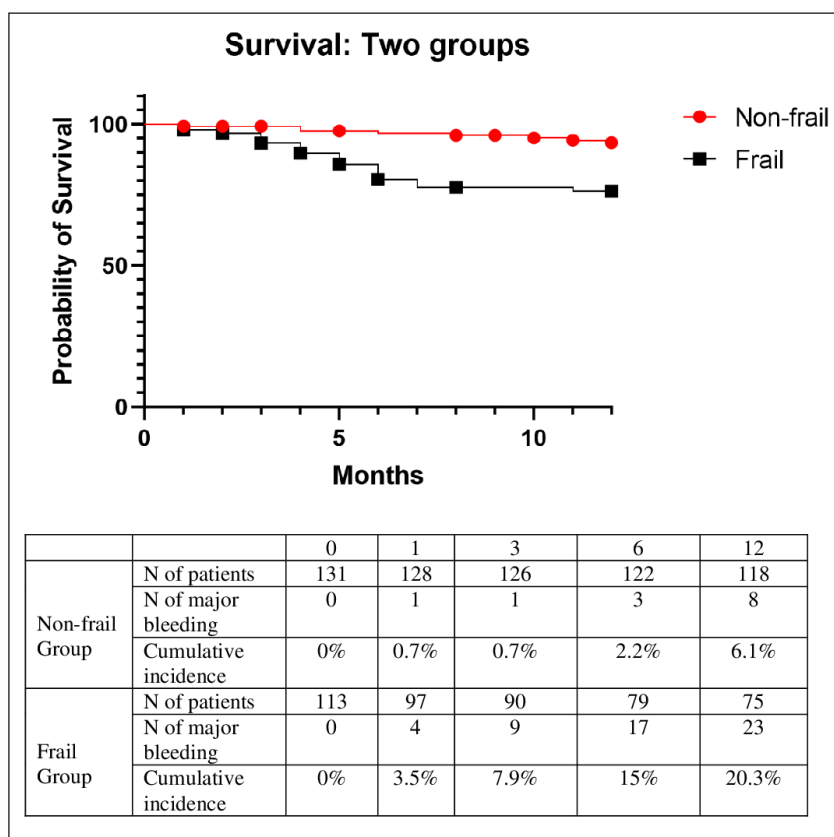

		0	1	3	6	12
Non-frail Group	N of patients	131	128	126	122	118
	N of major bleeding	0	1	1	3	8
	Cumulative incidence	0%	0.7%	0.7%	2.2%	6.1%
Frail Group	N of patients	113	97	90	79	75
	N of major bleeding	0	4	9	17	23
	Cumulative incidence	0%	3.5%	7.9%	15%	20.3%

Figure 2. Kaplan-Meier curves of major bleeding according to frailty.

Table II. Clinical outcomes of two groups distinguished based on the Clinical Frailty Scale Score.

	All (n: 244)	Non-frail Group (n: 131)	Frail Group (n: 113)	*p*-value
Major Bleeding, n (%)	31 (12.7)	8 (6.1)	23 (20.4)	**<0.001**
Minor Bleeding, n (%)	28 (11.5)	13 (9.9)	15 (13.3)	0.268
Stroke, n (%)	23 (9.4)	5 (3.8)	18 (15.9)	**<0.001**
Target Vessel Revascularization, n (%)	14 (5.7)	6 (4.6)	8 (7.1)	0.287
All-cause death, n (%)	34 (13.9)	3 (2.3)	31 (27.4)	**<0.001**

Table III. Results of Cox proportional hazard regression analysis of major bleeding during the 12-month follow-up.

Multivariate	OR (95% CI)	*p*
Age	1.003 (0.883-1.138)	0.967
Diabetes Mellitus	2.175 (0.993-4.746)	0.052
Hypertension	2.375 (0.679-8.313)	0.176
Current smoker	3.035 (1.211-7.604)	0.018
Ticagrelor	2.393 (1.109-5.162)	**0.026**
Left Ventricular Ejection Fraction	0.994 (0.994-1.029)	0.728
Hemoglobin	0.870 (0.721-1.050)	0.146
Creatinine	1.144 (0.378-3.465)	0.811
Frailty	6.220 (2.449-15.479)	**0.001**
Creatinine	1.144 (0.378-3.465)	0.811
Frailty	6.220 (2.449-15.479)	0.001

Table IV. Associations of ticagrelor and clopidogrel use with bleeding outcomes in the frail group.

	Events (n) and events rate (year/%)				Adjusted analyses HR for ticagrelor (95% CI)	
	Non-Frail Group (131)		Frail Group (113)		Non-Frail Group	Frail Group
	Ticagrelor (41)	Clopidogrel (90)	Ticagrelor (23)	Clopidogrel (90)		
Major Bleeding	5 (12.2)	3 (3.3)	9 (39.1)	14 (15.6)	1.999 (0.410-9.739)	2.214 (0.880-5.572)

higher in the frail than non-frail group (stroke 15.9% *vs.* 3.8%, *p*<0.001), as was the all-cause mortality rate (27.4% *vs.* 2.3%, *p*<0.001). There were no significant group differences in the minor bleeding or target-vessel revascularization rate.

A multivariate Cox proportional hazard regression analysis showed that frailty (hazard ratio [HR]= 6.220, 95% confidence interval [CI] = 2.449-15.479) was a more important risk factor for major bleeding than active smoking (HR = 3.035, 95% CI = 1.211-7.604) and the DAPT drug used (HR = 2.393, 95% CI = 1.109-5.162). Age, diabetes mellitus, hypertension, left ventricular ejection fraction, haemoglobin, and creatinine were not associated with major bleeding (Table III).

In the subgroup analysis of bleeding outcomes according to the use of ticagrelor or clopidogrel (Table IV), the HR for major bleeding was 2.214 (95% CI = 0.880-5.572) in the frail group and 1.999 (95% CI = 0.410-9.739) in the non-frail group. In the adjusted analyses, ticagrelor was consistently associated with a higher risk of major bleeding compared to clopidogrel based on the patients' CFS scores.

Discussion

The likelihood of frailty increases with age, and it is associated with increased rates of morbidity, mortality, complications and falling, as well as higher healthcare costs[10]. Octogenarian

and frail patients are vulnerable groups not usually included in clinical trials, and no randomized controlled studies have investigated the outcomes of DAPT in these groups. In this study, frailty in octogenarians after PCI was associated with adverse outcomes, such as major bleeding, stroke, and death from all causes. However, there were no significant group differences in the minor bleeding or target-vessel revascularization rates. In addition, DAPT with ticagrelor increased the incidence of major bleeding in all octogenarians, while DAPT with ticagrelor resulted in an even greater likelihood of major bleeding in frail patients. Mortality, stroke, and major bleeding were significantly more common in the frail group despite the shorter DAPT duration (due to the high PRECISE score). The patients in the frail group were older than those in the non-frail group, and they also had a higher likelihood of a history of stroke and a lower ejection fraction.

In a meta-analysis[11] of eight studies including 2,332 patients with a mean age of 68 years, frailty after PCI was an important cause of mortality. In another study involving 190 patients aged > 75 years who presented with ACS, frailty was associated with an increased rate of major bleeding in the early period (first 30 days of follow-up)[12]. Similar to these studies, in our study, which included 244 patients, fragility was associated with mortality and major bleeding in patients aged > 80 years.

PCI may also increase the likelihood of progression to frailty in elderly patients. In a study of 288 octogenarian patients who underwent PCI for STEMI, the rate of progression to frailty increased after PCI[13]. Another study[14] of 608 patients with a mean age of 77 years showed that nutritional status is an important prognostic factor after PCI in frail elderly patients.

In the open label randomized controlled POPular AGE trial[15] that compared clopidogrel and ticagrelor in patients aged ≥ 70 years with non-ST elevation ACS, clopidogrel resulted in less bleeding, without any increase in the composite endpoint of stroke, all-cause mortality, and myocardial infarction. Similar results were obtained in our study; clopidogrel was associated with a lower likelihood of major bleeding.

Adding ticagrelor to acetylsalicylic acid in dual antiplatelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention reduces both stent thrombosis and cardiovascular mortality, despite a slight increase in the risk of non-procedural bleeding without increasing major bleeding[16]. It is important to underline that frailty should be taken into consideration rather than age in order to avoid major bleeding if ticagrelor is the preferred drug in dual antiplatelet therapy in octogenerians.

Limitations

Our study had several limitations, of which the most important was its retrospective, non-randomized design. The CFS is a semiquantitative scale for assessing frailty; although our participants were assessed by the same medical professionals, progression to frailty after discharge was not evaluated. Therefore, we do not have any data on frailty status during the 1-year follow-up period. Moreover, this study was based on hospital registries and minor bleeding data may have been missing in some patients due to difficulty in accessing health services.

Conclusions

Frailty is an independent predictor of major bleeding in octogenarian patients undergoing PCI for ACS. During the 1-year follow-up period, major bleeding, all-cause mortality, and stroke were more common in our frail patients. The use of the P2Y12 inhibitor ticagrelor increased the risk of major bleeding in frail patients.

Authors' Contributions

K. Özbek is the principal author of this study, and designed the study with resources acquisition, data collection and processing data, data analysis and interpretation, writing-original draft preparation, and editing. A. Balun and K. Özbek conceived the idea for the article, framing the hypothesis, designed the methods to generate results, data collection and processing data, data analysis and interpretation, writing-original draft preparation, critical review, and editing. Both authors have read and approved the paper.

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