Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-7

DOI: 10.1177/1076029620915994
journals.sagepub.com/home/cat
SAGE

Association of Frailty With Antiplatelet Response Among Elderly Chinese Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Yang Liu, MS[1,2], Shaoyan Liu, MS[3], Keyu Wang, MD[4], and Hongbin Liu, MD[1,2]

Abstract

Frailty has been implicated as a prognostic factor for ischemic cardiovascular diseases. However, the effects of frailty on platelet responses to aspirin and clopidogrel remain under investigation. In this study, we enrolled consecutive elderly patients with coronary artery disease (CAD) who were treated by percutaneous coronary intervention (PCI) to evaluate this association. A total of 264 patients (aged 70-95 years) were included. Patients were divided into 2 groups: a nonfrail (nFR) group and a frail (FR) group according to the Clinical Frailty Scale. Platelet reactivity was assessed with a light transmittance aggregometry method, and arachidonic acid and adenosine diphosphate induced maximum platelet aggregation (AA-MPA/ADP-MPA) were calculated to evaluate the platelet response to aspirin and clopidogrel. The results showed that the AA-MPA and ADP-MPA of the FR group were significantly higher than those in the nFR group (17.49 $\pm$ 6.65 vs 15.19 $\pm$ 6.33, $P < .01$; 56.13 $\pm$ 10.14 vs 45.45 $\pm$ 11.59, $P < .01$). High on-aspirin platelet response (HAPR) and high on-clopidogrel platelet response (HCPR) were significantly more common in the FR group than in the nFR group (24.67% vs 13.16%, $P = .028$, 37.33% vs 15.79%, $P < .01$). According to multivariable regression analyses, frailty was found to be independently associated with AA-MPA ($\beta_{coefficient} = 1.883$, $P = .042$) and ADP-MPA ($\beta_{coefficient} = 9.287$, $P < .001$), and it was an independent predictor of HAPR (odds ratio [OR]: 2.696, $P < .01$) and HCPR (OR: 2.543, $P < .01$). It was concluded that among elderly patients with CAD undergoing PCI, frailty is an independent predictor of HAPR and HCPR, and the state of frailty is independently associated with the platelet responses to clopidogrel and aspirin.

Keywords

aspirin, clopidogrel, coronary artery disease, frailty, percutaneous coronary intervention, platelet reactivity

Date received: 02 December 2019; revised: 20 February 2020; accepted: 05 March 2020.

Introduction

Frailty is a state of vulnerability in elderly adults that is characterized by poor clinical outcomes.[1] Frailty has been implicated as a prognostic factor in patients with cardiovascular diseases.[2,3] Relatively higher mortality outcomes have been found in frail patients with coronary artery disease (CAD) who are treated by percutaneous coronary intervention (PCI).[4] Compared with nonfrail patients, frail patients may suffer from more postoperative ischemic complications, such as myocardial reinfarction, stent restenosis, and thrombosis.[5,6] Aspirin and clopidogrel are oral antiplatelet agents that have been widely prescribed for the prevention of thrombotic events in patients undergoing PCI. Patients with high on-clopidogrel platelet response (HCPR) and high on-aspirin platelet response (HAPR) have been confirmed to be at increased risk of thrombotic events after undergoing PCI.[7]

The pathophysiological mechanisms underlying the relationship between frailty and the increased incidence of ischemic events after PCI remain unclear. Some studies have

[1] Medical School of Chinese People's Liberation Army, Beijing, China
[2] Department of Cardiology, The 2nd Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China
[3] Department of Cardiology, Laiyang Central Hospital, Yantai, China
[4] Clinical Laboratory, The 2nd Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China

Corresponding Author:
Hongbin Liu, Department of Cardiology, The 2nd Medical Center of Chinese People's Liberation Army General Hospital, Medical School of Chinese People's Liberation Army, No. 28. Fuxing Road, Beijing, China.
Email: cardiology301_lhb@126.com

suggested that frailty may lead to abnormal platelet function and coagulation.[8,9] In addition, some enzymes involved in drug metabolism seem to be impacted by frailty but not by chronological age, such as the enzymes involved in cytochrome P450-mediated phase I reactions.[10] These factors also play important roles in the metabolism of aspirin and clopidogrel.[11] Whether in terms of the effect of frailty on platelet function or the effect on drug metabolism, we speculate that frailty may have some effect on the antiplatelet effects of aspirin and clopidogrel. However, this hypothesis has not been confirmed. The aim of this prospective study was to examine whether frailty is related to low platelet responses to aspirin and clopidogrel in elderly patients who have undergone PCI.

Methods

Study Population

This was a prospective study performed in the Department of Cardiology of the Chinese PLA General Hospital from December 2016 to September 2017. Patients aged more than 70 years with CAD who were undergoing PCI were consecutively enrolled in this cohort study. All enrolled patients were pretreated with a loading dose of antiplatelet drugs (300 mg clopidogrel and 300 mg aspirin) before PCI followed by clopidogrel (75 mg/d) and aspirin (100 mg/d). The detailed exclusion criteria were as follows: (1) a history of malignancy; (2) a history of hematological diseases, such as leukemia, thrombocytopenia, and thrombocytosis; (3) the combined use of anticoagulants; (4) active bleeding; (5) allergic reactions to aspirin and clopidogrel; (6) severe liver function disorders; and (7) the concomitant use of inhibitors of CYP2C19. The procedures were approved by the Institutional Ethics Committee of the Chinese PLA General Hospital. Written informed consent was obtained from all enrolled patients.

Frailty Assessment

The degree of frailty was evaluated using a global clinical measure, The Canadian Study of Health and Aging Clinical Frailty Scale, which is one of the most widely used evaluation methods.[4,12] It provides a global clinical measure of biological age, comorbidity, and disability and is reviewed on the 30th day after PCI during the outpatient review performed by 2 independent physicians who were blinded to the platelet aggregation treatment. The 2 raters independently determined the CFS score of each patient. If the 2 scores differed, a third rater was included to adjudicate conflicts. The enrolled patients were stratified into 2 groups according to CFS score: those with scores of 1 to 4 were included in the nonfrail group (nFR), and those with scores of 5 to 7 were included in the frail group (FR).

Laboratory Evaluation

Venous blood samples were collected on the 30th day after PCI. For both light transmittance aggregometry (LTA) aggregation tests and DNA isolation, the collection tubes contained sodium citrate buffer solution at a concentration of 0.109 M (3.2%). The counts of red blood cells, white blood cells, platelets, and lymphocytes were determined using a Coulter LH Series (LH750, Beckman Coulter, Brea, California). Creatinine levels, lipid profiles, high-sensitivity C-reactive protein levels, and interleukin 6 (IL-6) levels were also measured in all patients with an automatic analyzer (7600P, HITACHI, Tokyo, Japan). Estimated glomerular filtration rates (eGFRs) were evaluated. The values of eGFR were determined from the serum creatinine values using the prediction equation proposed by the Chinese Society of Nephrology.

Clopidogrel is oxidized by hepatic cytochrome P450, generating an active metabolite.[13] The presence of polymorphisms of CYP2C19 can modulate the cytochrome enzymes, which are considered to be major determinants of interindividual variability in clopidogrel-induced platelet inhibition. The CYP2C19*1 allele is the wild-type copy that has full enzymatic activity; the CYP2C19*2 and CYP2C19*3 alleles are the most common variants, resulting in the complete loss of enzymatic activity. Individuals with different CYP2C19 genotypes can be classified according to 3 main phenotypes: normal metabolizers (NM) carrying normal-function alleles, intermediate metabolizers (IM) carrying only one reduced-function allele, and poor metabolizers (PM) carrying 2 reduced-function alleles. Consequently, the genotype of NMs is CYP2C19*1/*1, the genotypes of IMs are CYP2C19*1/*2 and CYP2C19*1/*3, and the genotypes of PMs are CYP2C19*2/*2, CYP2C19*3/*3 and CYP2C19*2/*32. Genomic DNA was extracted from whole blood using the TIANamp Blood DNA Kit (TIANGEN BIOTECH, Beijing, China) according to the manufacturer's instructions. The CYP2C19*2 (681G>A, rs4244285) and CYP2C19*3 (636G>A, rs57081121) polymorphisms were genotyped by TaqMan Drug Metabolism Genotyping Assays (Applied Biosystems, Foster City, California, US) on the Applied Biosystems StepOneTM Real-Time PCR System (Applied Biosystems, Foster City, California, US).

Venous blood samples for the platelet function tests were processed within 3 hours of collection. Platelet reactivity was evaluated by LTA using a 2-channel platelet aggregometry system (700, Chrono-Log, Havertown, Pennsylvania). The platelet-rich plasma was prepared by centrifugation of the sample at 150 g for 15 minutes, and platelet-poor plasma (PPP) was prepared by centrifugation at 1500 g for 20 minutes. The resulting platelet count for analysis was adjusted to 200-250 $\times$ 10^9 platelets/L by dilution with autologous PPP. The aggregation results are expressed as percentages of the maximal platelet aggregation (MPA) using PPP from the same patient as the reference. Arachidonic acid (AA) at a concentration of 1 mM was used for the measurement of AA-induced MPA (AA-MPA), which can reflect the platelet response to aspirin. For the detection of the platelet response to clopidogrel, adenosine diphosphate (ADP)-induced MPA (ADP-MPA) was measured by ADP at a concentration of 20 μM. In the absence of baseline platelet reactivity measurements, the high aspirin/clopidogrel platelet response (HAPR/HCPR) is preferred over the "reduced platelet response to aspirin/clopidogrel" in regard to the

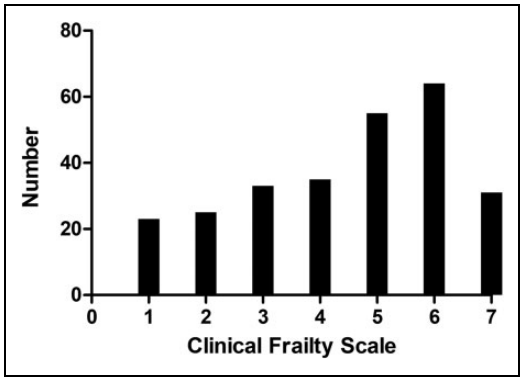

Figure 1. The distribution of clinical frailty scores among the enrolled patients.

description of the platelet response to an antiplatelet drug. The cutoff point of ADP-MPA for the determination of HCPR is 60%, and the cutoff point of AA-MPA for the determination of HAPR is 20%.[14]

Statistical Analysis

Data are expressed as frequencies and percentages for categorical variables and as the means ± standard deviations or as medians with interquartile ranges for continuous variables. Continuous variables were compared using Student's *t* test (if normally distributed) or the Mann-Whitney *U* test (if nonnormally distributed). Univariate correlation analyses were evaluated using Spearman analysis. Variables relevant to the multivariable models were selected by their clinical significance and a threshold *P* value <.1 from the univariate analyses. Multiple linear regression analysis was performed to assess independent factors associated with AA-MPA or ADP-MPA. Multicollinearity of variables was assessed using variance inflation factors with a reference value of 10 before interpreting the final output. Multivariable logistic regression was used to determine the independent predictors of HCPR or HAPR. All analyses were performed using SPSS version 20.0 (SPSS, Chicago, Illinois). A *P* value < .05 was considered statistically significant.

Results

Enrolled Patients and Clinical Features

A total of 304 consecutive patients were enrolled in this study, and 264 patients (aged 70-95 years) ultimately underwent outpatient follow-up on the 30th day after PCI. During outpatient follow-up, frailty was evaluated, electrocardiograms were recorded, and venous blood samples were taken. The distribution of the degree of frailty is shown in Figure 1. Patients were assigned based on the CFS to 2 groups: a frail (FR, n = 150) group and a nonfrail (nFR, n = 114) group. The baseline clinical characteristics of the 2 groups are shown in Table 1. The FR group had a significantly higher age and lower body mass index (BMI) than the nFR group (age: 81.37 ± 10.11 vs 74.34 ± 8.74, $P < .01$; BMI: 23.96 ± 3.7 vs 26.25 ± 3.69, $P < .01$). The results showed that the baseline laboratory characteristics of the 2 groups in this study were well matched. More nFR patients than FR patients underwent PCI because of acute coronary syndrome (56% vs 71.93%, $P < .001$). After treatment, no ischemic changes were observed in any of the enrolled patients. Compared with the nFR group, the FR group had a higher burden of comorbidities, including higher rates of chronic obstructive pulmonary disease, congestive heart failure, hypertension, stroke, and moderate-to-severe renal impairment (eGFR < 60 mL/min/1.73 m^2). In terms of drug therapy, there was no significant difference between the 2 groups in the proportion of patients taking aspirin regularly before the operation; a lower proportion of patients in the FR group were taking clopidogrel regularly before the operation, but the difference did not reach statistical significance ($P = .053$). There was a higher proportion of proton pump inhibitors use in the FR group. Although the prevalence of hypertension increased, there was not a significantly greater use of calcium channel blockers and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker drugs in the FR group.

Frailty and Platelet Reactivity

The AA-MPA and ADP-MPA in the FR group were significantly higher than those in the nFR group (ADP-MPA: 56.13 ± 10.14 vs 45.45 ± 11.59, $P < .01$; AA-MPA: 17.49 ± 6.65 vs 15.19 ± 6.33, $P < .01$). Moreover, the percentage of HCPR was significantly higher in the FR group than in the nFR group (37.33% vs 15.79%, $P < .01$). Similarly, the percentage of HAPR was significantly different between the 2 groups (24.67% vs 13.16%, $P = .028$). (Figure 2)

We further analyzed the proportion of frailty and the platelet response to antiplatelet drugs among the enrolled patients stratified by sex. The results showed that there were no significant differences in the proportions of frailty or the platelet responses to antiplatelet drugs between male and female patients (frailty: 55.86% vs 57.98%, $P = .803$; AA-MPA: 16.69 ± 6.56 vs 16.34 ± 6.65, $P = .67$; ADP-MPA: 50.76 ± 12.5 vs 52.44 ± 11.36, $P = .26$; HAPR: 19.31% vs 20.17%, $P = .88$; HCPR: 26.21% vs 30.25%, $P = .49$). In addition, we compared the platelet responses to antiplatelet drugs between the FR patients and nFR patients stratified by sex. The results showed that the ADP-MPA and AA-MPA were significantly different in each sex subgroup (ADP-MPA in males: 55.66 ± 10.36 vs 44.56 ± 12.27, $P < .01$; ADP-MPA in females: 56.68 ± 9.92 vs 46.58 ± 10.67, $P < .01$; AA-MPA in males: 17.68 ± 6.99 vs 15.32 ± 5.7, $P = .04$; AA-MPA in females: 17.32 ± 6.39 vs 15.09 ± 6.82, $P = .04$). With regard to the proportions of HAPR and HCPR, there were significant differences between the FR patients and nFR patients in each sex subgroup except for the proportion of HAPR in males (HAPR in females: 26.09% vs 12%, $P = .047$; HAPR in males: 23.46% vs 14.06%, $P = .2$; HCPR in females: 40.58% vs 16%, $P = .005$; HCPR in males: 34.57% vs 15.63%, $P = .013$).

Table 1. Baseline Clinical and Laboratory Characteristics of Enrolled Patients.

Variable	All, n = 264	Frail, n = 150	Nonfrail, n = 114
Age (years)[a]	78.33 ± 10.15	81.37 ± 10.11	74.34 ± 8.74
Male	145 (54.93%)	81 (54%)	64 (56.14%)
Body mass index (kg/m^2)[a]	25.89 ± 3.61	25.62 ± 3.94	26.25 ± 3.69
Current smoker	36 (13.64%)	19 (12.7%)	17 (14.9%)
Hypertension[a]	198 (75%)	122 (81.3%)	76 (66.7%)
Diabetes mellitus	103 (39.02%)	66 (44%)	37 (32.5%)
Stroke[a]	51 (19.32%)	38 (25.3%)	13 (11.4%)
COPD[b]	38 (14.39%)	28 (18.67%)	10 (8.77%)
Congestive heart failure[a]	32 (12.12%)	25 (16.67%)	7 (6.14%)
Acute coronary syndrome[b]	166 (62.88%)	84 (56%)	82 (71.93%)
Lipid parameters at admission			
Total cholesterol (mmol/L)	4.78 ± 1.49	4.79 ±1.5	4.76 ± 1.49
LDL-C (mmol/L)	2.96 ± 1.13	3.62 ± 1.09	2.91 ± 1.18
HDL-C (mmol/L)	1.1 (0.92-1.29)	1.1 (0.92-1.3)	1.1 (0.91-1.28)
Triglycerides (mmol/L)	2.37 (1.21-4.05)	2.42 (1.32-4.1)	2.22 (0.97-3.89)
eGFR < 60 mL/min/1.73 m^2	165 (62.5%)	70 (73.7%)	46 (50.5%)
IL-6 (pg/mL)	5.14 ±3.71	5.23 ± 3.92	5.03 ± 3.44
hs-CRP (mg/L)	2.61 ± 1.46	2.73 ± 1.5	2.46 ± 1.4
White blood cells (10^9/L)	7.29 (5.05-9.26)	7.52 (4.94-9.19)	7.01 (5.22-9.48)
Red blood cells (10^9/L)	4.11 ± 0.84	4.08 ± 0.88	4.22 ± 0.8
Platelet count (10^9/L)	225.38 ± 98.45	227.2 ± 95.86	221.54 ± 103.35
Hemoglobin (g/L)	117.34 ± 18.4	117.01 ± 19.14	118.98 ± 18.09
Creatinine (μmol/L)	91.37 ± 30.56	90.07 ± 30.89	94.11 ± 30.33
Medication before admission			
Aspirin	167 (63.26%)	93 (62%)	74 (64.91%)
Clopidogrel	30 (11.36%)	12 (8%)	18 (15.79%)
NSAIDs	16 (6.06%)	12 (8%)	4 (3.51%)
Beta blocker	51 (19.32%)	28 (18.67%)	23 (20.18%)
Statin	249 (94.32%)	141 (94%)	108 (94.7%)
ACEI/ARB	119 (45.08%)	62 (41.3%)	57 (50%)
PPI[b]	52 (19.7%)	37 (24.7%)	15 (13.2%)
CCB	48 (18.18%)	30 (20%)	18 (15.8%)

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C reactive protein; IL 6, interleukin 6; LDL-C, low density lipoprotein cholesterol; NSAIDs, nonaspirin non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors.
[a] $P < .01$.
[b] $P < .05$.

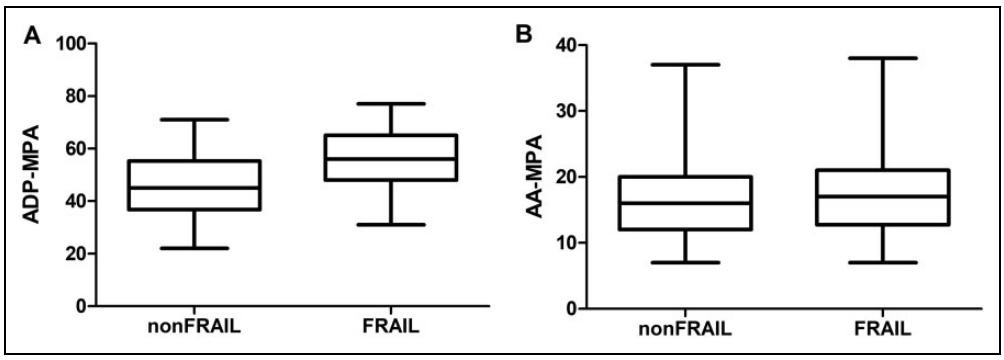

Figure 2. Platelet activation test parameters in the frail and nonfrail groups. A, ADP-MPA in the frail (right box) and nonfrail (left box) groups (56.13 ± 10.14 vs 45.45 ± 11.59, $P < .01$). B, AA-MPA in the frail (right box) and nonfrail (left box) groups (17.49 ± 6.65 vs 15.19 ± 6.33, $P < .01$). AA-MPA indicates arachidonic acid-induced maximal platelet aggregation; ADP-MPA, adenosine diphosphate-induced maximal platelet aggregation.

Table 2. Association of Adenosine Diphosphate- and Arachidonic Acid-Induced Maximal Platelet Aggregation With Other Independent Variables Determined by the Multivariable Linear Regression Models.

	$\beta_{coefficient}$		
	Value	SE	*P*
Factors related to ADP-MPA. Variables included frailty, age, body mass index, current smoker, diabetes mellitus, CCB, statin, PM.			
Frailty	9.287	1.511	<.001
Age	0.030	0.070	.665
Body mass index	−0.234	0.181	.196
Current smoker	−2.252	1.958	.251
Diabetes mellitus	−0.350	1.362	.798
CCB	2.125	1.735	.222
Statin	−2.483	2.876	.389
PM	4.524	1.628	.006
Factors related to AA-MPA. Variables included frailty, age, body mass index, current smoker, diabetes mellitus, NSAIDs.			
Frailty	1.883	0.920	.042
Age	0.038	0.043	.375
Body mass index	0.006	0.110	.957
Current smoker	−0.270	1.181	.819
Diabetes mellitus	0.572	0.834	.494
NSAIDs	1.929	1.699	.257

Abbreviations: AA-MPA, arachidonic acid-induced maximal platelet aggregation; ADP-MPA, adenosine diphosphate-induced maximal platelet aggregation; CCB, calcium channel blockers; PM, the CYP2C19 genotype of poor metabolizers; NSAIDs, nonaspirin nonsteroidal anti-inflammatory drugs; SE, standard error.

Table 3. Association of High On-Clopidogrel/Aspirin Platelet Response With Other Independent Variables as Determined by Multivariable Logistic Regression.

Factors	OR (95% CI)	*P*
Model 1: including the factors related to reduced platelet response to clopidogrel		
Frailty	2.623 (1.339-5.137)	.005
Age	1.004 (0.974-1.034)	.814
Body mass index	0.945 (0.873-1.022)	.156
Current smoker	1.204 (0.528-2.749)	.659
Diabetes mellitus	1.031 (0.580-1.834)	.917
IL6	1.048 (0.974-1.129)	.211
CCB	1.008 (0.474-2.148)	.983
Statin	0.596 (0.187-1.896)	.381
PM	1.434 (0.738-2.788)	.288
Model 2: including the factors related to reduced platelet response to aspirin		
Frailty	2.696 (1.382-5.260)	.004
Age	1.003 (0.974-1.033)	.843
Body mass index	0.946 (0.875-1.023)	.163
Current smoker	1.269 (0.570-2.826)	.560
Diabetes mellitus	1.036 (0.583-1.839)	.905
NSAIDs	1.732 (0.588-5.102)	.0319
IL6	1.041 (0.967-1.120)	.288

Abbreviations: CCB, calcium channel blockers; CI, confidence interval; IL-6, interleukin 6; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PM, the CYP2C19 genotype of poor metabolizers.

A significant correlation was observed between ADP-MPA and frailty ($r = 0.428$, $P < .01$). A similar significant correlation was also found between AA-MPA and frailty ($r = 0.192$, $P < .01$). The factors included in the models for evaluating the independent correlationship with ADP-MPA or AA-MPA were chosen by univariate correlationship analysis between the items and ADP-MPA or AA-MPA. The factors included in the model are shown in Table 2. Multivariable linear regression analysis showed that frailty and PM were independently associated with ADP-MPA (frailty: $\beta_{coefficient} = 9.287$, $P < .001$; PM: $\beta_{coefficient} = 4.524$, $P = .006$, Table 2). Moreover, frailty was found to be independently associated with AA-MPA ($\beta_{coefficient} = 1.883$, $P = .042$, Table 2).

To explore the independent predictive factors for HCPR and HAPR, multivariate logistic regression analyses were used. The factors involved in the models for the evaluation of the independent predictors of HCPR and HAPR were chosen by analyses of the differences between the group with a high platelet response on antiplatelet drugs and the group with a normal platelet response on antiplatelet drugs and the significant clinical factors affecting platelet function.[14] The factors included in the model for the evaluation of the independent factors affecting HCPR or HAPR are shown in Table 3. The results showed that frailty was an independent predictor of HCPR (odds ratio [OR]: 2.543, 95% confidence interval [CI]: 1.296-4.989, $P = .007$, model 1 in Table 3) and HAPR (OR: 2.696, 95% CI: 1.382-5.26, $P = .004$, model 2 in Table 3).

Discussion

To the best of our knowledge, this is the first prospective study assessing the relationship between frailty and the platelet responses to aspirin and clopidogrel. The results of this study demonstrate that frailty is an independent predictor of HCPR and is independently associated with the platelet responses to clopidogrel and aspirin among elderly patients with CAD undergoing PCI. These results prompted us to pay more attention to the platelet reactivity of elderly patients with frailty and to develop more individualized antithrombotic strategies to improve patient prognosis.

In this study, we found that frail elderly patients with CAD were more likely to have HCPR. Because of the limitation of the HAPR sample size, the independent factors related to HAPR were not analyzed in this study. However, through a correlation analysis between frailty and AA-MPA, we identified a negative correlation between platelet reactivity to aspirin and the degree of frailty. A similar conclusion about the relationship between frailty and the decreased effectiveness of aspirin has also been reported in another study.[15] Frailty is an independent factor that negatively affects prognosis in elderly patients with CAD. Previous research studies have found that the incidence of ischemic events in frail patients was higher than that in nonfrail patients.[5,6] However, regarding hemorrhagic events, no uniform conclusion has been reached in different trials.[16-18] Identifying the causes underlying the greater number of ischemic events among frail patients than among nonfrail patients will be helpful in improving the prognosis of frail

patients undergoing PCI. The finding of correlation between frailty and the platelet responses to aspirin and clopidogrel provided a partial explanation for this phenomenon from the perspective of the effect of frailty on the platelet response to antiplatelet drugs.

However, the underlying mechanisms of frailty-related high platelet response remain unclear. Drug metabolism is significantly different in patients with frailty than in those without frailty due to changes in inflammation, oxidative stress, and gut microbiota.[10,19] Similarly, the pharmacokinetics and pharmacodynamics of clopidogrel and aspirin may be altered by the individual's frail state. From the view of intestinal microecology, previous studies have found that the metabolism of clopidogrel can be changed significantly by changes in the gut microbiota,[20,21] and the antiplatelet effect of aspirin has been shown to change because of the disturbances to the gut microbiota caused by the use of antibiotics.[22] The intestinal microecology of frail patients is significantly different from that of nonfrail patients due to comorbidities.[23] Therefore, the change in gut microbiota may be one of the causes of the frailty-related high platelet response. Moreover, frailty is closely related to oxidative stress, which plays a pivotal role in the mechanism of platelet activation.[24] Therefore, significant changes in oxidative stress may be one of the main causes of a high platelet response in frail patients.

Pretreatment platelet reactivity has good predictive value for antiplatelet drug reactivity.[25] Some studies have described an increase in pretreatment platelet activity among the frail from the perspective of hyperglycemia.[26] Therefore, we speculated that hyperglycemia may be another reason for the reduced platelet reactivity to antiplatelet drugs among the frail population. However, unlike previous studies[26,27] there was no significant difference in the incidence of diabetes between the frail group and the nonfrail group. The reasons for this phenomenon may be as follows: (1) Ethnic differences: In another study of frail elderly Chinese patients, the authors also found no significant difference between the frail group and the nonfrail group[28]; (2) Sample size: Although the differences in the test for diabetes between the 2 groups was not significant in our study, the trend was clear ($P = .06$), and the relatively small sample size may be the reason why the result was different from those in previous studies.

Frailty is a common state, with prevalence rates among the elderly population ranging from 34.6% to 50.9% in different trials; however, the state and degree of frailty are often underestimated due to a lack of awareness.[1] Frailty is an independent factor affecting the poor prognosis of elderly patients with CAD. This study confirms that frailty is an independent risk factor for a high platelet response to antiplatelet drugs. This conclusion provides a new explanation for the high incidence of ischemic events in patients with frailty after PCI. Therefore, more attention should be paid to recognizing frailty among the elderly population, and treatment strategies need to be more individualized. Current solutions to a hyporesponse to antiplatelet drugs are limited to adjusting the type or increasing the dose of the drug. However, current clinical practice has shown that these solutions have inevitably brought about an increase in bleeding events in elderly patients. For example, the application of ticagrelor is increasing; however, the high risk of bleeding in non-Caucasian older patients still limits its use to some extent.[29] Shifting our focus to improving the platelet response to antiplatelet drugs could lead to new benefits with regard to antithrombotic therapy in elderly patients. From the independent relationship between frailty and a high platelet response to antiplatelet drugs, we inferred that improving frailty could enhance the antiplatelet effect of clopidogrel. This hypothesis needs to be further confirmed by other prospective trials.

Limitations

Some limitations of our study must be noted. First, we did not collect data pertaining to the long-term clinical outcomes of the included patients. There was no further analysis of whether frailty-related clopidogrel resistance had an impact on prognosis. Second, limited by the incidence rates of HCPR and HAPR, the sample size in this study was not large enough, which may have had some influence on the ability to draw clinically valuable conclusions.

Conclusion

In conclusion, there is a consensus that the platelet responses to aspirin and clopidogrel may vary according to clinical, cellular, and genetic conditions. We confirmed that frailty is an independent predictor of HCPR and that the degree of frailty is independently associated with the platelet responses to clopidogrel and aspirin among elderly patients with CAD undergoing PCI.

Authors' Note

Liu Y. conceived the study, participated in the design, performed the statistical analyses, and drafted the manuscript. Liu S.Y. participated in collecting the samples, and helped to draft the manuscript. Wang K.Y. undertook genotyping and the measurement of platelet function. Liu H.B. conceived the study and help to draft the manuscript. All authors read and approved the final manuscript. Written informed consent was obtained from patients for their anonymized information to be published in this article.

Acknowledgments

The authors are grateful to the patients and staff involved with the collection of samples at the Department of Cardiology of Chinese PLA General Hospital.

Declaration of Conflicting Interests

The author(s) declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study

was funded by the National Key Research Program of China (2017YFC0840100 and 2017YFC0840103) and the Central Health Care Fund (W2015ZD02).

ORCID iD

Hongbin Liu https://orcid.org/0000-0002-6093-6164

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762.
2. Alonso Salinas GL, Sanmartin Fernandez M, Pascual Izco M, et al. Frailty is a short-term prognostic marker in acute coronary syndrome of elderly patients. *Eur Heart J Acute Cardiovasc Care*. 2016;5(5):434-440.
3. Dewiasty E. Impact of frailty on cardiovascular disease (and the other way around). *Acta Med Indones*. 2016;48(2):83.
4. Tse G, Gong M, Nunez J, et al. Frailty and mortality outcomes after percutaneous coronary intervention: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2017;18(12):1097 e1-e10.
5. Hamonangan R, Wijaya IP, Setiati S, Harimurti K. Impact of frailty on the first 30 days of major cardiac events in elderly patients with coronary artery disease undergoing elective percutaneous coronary intervention. *Acta Med Indones*. 2016;48(2): 91-98.
6. Klein LW, Garcia CA. Is patient frailty the unmeasured confounder that connects subacute stent thrombosis with increased periprocedural bleeding and increased mortality? *J Am Coll Cardiol*. 2012;59(20):1760-1762.
7. Vila PM, Zafar MU, Badimon JJ. Platelet reactivity and nonresponse to dual antiplatelet therapy: a review. *Platelets*. 2009; 20(8):531-538.
8. Fuentes F, Palomo I, Fuentes E. Platelet oxidative stress as a novel target of cardiovascular risk in frail older people. *Vascul Pharmacol*. 2017;93-95:14-19.
9. Phan HM, Alpert JS, Fain M. Frailty, inflammation, and cardiovascular disease: evidence of a connection. *Am J Geriatr Cardiol*. 2008;17(2):101-107.
10. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69(3): 319-326.
11. Ford NF.The metabolism of clopidogrel: CYP2C19 is a minor pathway. *J Clin Pharmacol*. 2016;56(12):1474-1483.
12. Tonet E, Pavasini R, Biscaglia S, et al. Frailty in patients admitted to hospital for acute coronary syndrome: when, how and why? *J Geriatr Cardiol*. 2019;16(2):129-137.
13. Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese EP, Goch A. Genetic determinants of platelet response to clopidogrel. *J Thromb Thrombolysis*. 2011;32(4):459-466.
14. Le Quellec S, Bordet JC, Negrier C, Dargaud Y.Comparison of current platelet functional tests for the assessment of aspirin and clopidogrel response. A review of the literature. *Thromb Haemost*. 2016;116(4):638-650.
15. Nguyen TN, Pepperell D, Morel Kopp MC, Cumming RG, Ward C, Hilmer SN. Effect of frailty and age on platelet aggregation and response to aspirin in older patients with atrial fibrillation: a pilot study. *Cardiol Ther*. 2016;5(1):51-62.
16. Alonso Salinas GL, Sanmartin M, Pascual Izco M, et al. The role of frailty in acute coronary syndromes in the elderly. *Gerontology*. 2018;64(5):422-429.
17. Dodson JA, Hochman JS, Roe MT, et al. The association of frailty with in-hospital bleeding among older adults with acute myocardial infarction: insights from the ACTION registry. *JACC Cardiovasc Interv*. 2018;11(22):2287-2296.
18. White HD, Westerhout CM, Alexander KP, et al. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: insights from the targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes (TRILOGY ACS) trial. *Eur Heart J Acute Cardiovasc Care*. 2016;5(3):231-242.
19. Waring RH, Harris RM, Mitchell SC. Drug metabolism in the elderly: a multifactorial problem? *Maturitas*. 2017;100:27-32.
20. Amin AM, Sheau Chin L, Teh CH, et al. Pharmacometabolomics analysis of plasma to phenotype clopidogrel high on treatment platelets reactivity in coronary artery disease patients. *Eur J Pharm Sci*. 2018;117:351-361.
21. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell*. 2016;165(1):111-124.
22. Kim IS, Yoo DH, Jung IH, et al. Reduced metabolic activity of gut microbiota by antibiotics can potentiate the antithrombotic effect of aspirin. *Biochem Pharmacol*. 2016;122:72-79.
23. Meehan CJ, Langille MG, Beiko RG. Frailty and the microbiome. *Interdiscip Top Gerontol Geriatr*. 2015;41:54-65.
24. Soysal P, Isik AT, Carvalho AF, et al. Oxidative stress and frailty: a systematic review and synthesis of the best evidence. *Maturitas*. 2017; 99:66-72.
25. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting. *Circulation*. 2003;107(23):2908-2913.
26. Hernandez B, Fuentes E, Palomo I, Alarcon M. Increased platelet function during frailty. *Exp Hematol*. 2019;77:12-25 e2.
27. Peng PS, Kao TW, Chang PK, Liang CW. Association between HOMA-IR and frailty among U.S. middle-aged and elderly population. *Sci Rep*. 2019;9(1):4238.
28. Kang L, Zhang SY, Zhu WL, et al. Is frailty associated with short-term outcomes for elderly patients with acute coronary syndrome? *J Geriatr Cardiol*. 2015;12(6):662-667.
29. Andreotti F, Rocca B, Husted S, et al. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J*. 2015; 36(46):3238-3249.