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Different inflammatory profile in young and elderly STEMI patients undergoing primary percutaneous coronary intervention (PPCI): Its influence on no-reflow and mortality

Serena Del Turco [a,*], Giuseppina Basta [a], Alberto Ranieri De Caterina [b], Silverio Sbrana [a], Umberto Paradossi [b], Alessandro Taddei [b], Giuseppe Trianni [b], Marcello Ravani [b], Cataldo Palmieri [b], Sergio Berti [b], Annamaria Mazzone [b]

[a] CNR, Institute of Clinical Physiology, Via G. Moruzzi, 1, 56124 Pisa, Italy
[b] Fondazione G. Monasterio CNR-Regione Toscana Pisa, Massa, Italy

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ABSTRACT

Background: Coronary no-reflow phenomenon in ST-segment elevation myocardial infarction (STEMI) is associated with a poor clinical prognosis. Although its pathophysiology is not fully elucidated, a deregulated systemic inflammatory response plays an important role. Specifically, the relationship between age-associated differences in inflammatory markers and either no-reflow or mortality in STEMI patients undergoing primary percutaneous coronary intervention (pPCI) has never been investigated.

Methods and results: We retrospectively enrolled 625 consecutive STEMI patients undergoing pPCI for whom a complete laboratory inflammatory pattern was available. Routinely blood measured laboratory parameters were collected at the moment of admission. No reflow was defined as Thrombolysis in Myocardial Infarction (TIMI) flow-grade lower than 3. The population was divided into two groups using a cut-off centered at 65 years. Compared to younger patients, elderly patients had higher mean values of fibrinogen, brain natriuretic peptide (BNP), leukocytes, neutrophil-to-lymphocyte ratio (NLR), C reactive protein/albumin ratio (CAR). Conversely, lymphocyte count and albumin levels were higher in young patients. In elderly patients, the values of NLR, CAR as well as leukocytes, fibrinogen and neutrophils were associated with no-reflow, while in young patients only BNP value was associated. At multivariate Cox regression analysis, only BNP and NLR resulted as independent predictors of all-cause mortality in the whole population and in elderly patients.

Conclusions: Elderly STEMI patients on admission had a higher acute pro-inflammatory profile than young patients, associated to coronary no-reflow and mortality outcome. These results suggest that a different therapeutic approach between elderly and young STEMI patients should be agreed.

1. Introduction

Primary percutaneous Coronary intervention (pPCI) has become the standard of care for the treatment of ST-elevation myocardial infarction (STEMI) irrespectively of patient's age [1]. Despite the achievement of optimal coronary artery revascularization after pPCI, between up to 30% of STEMI patients do not achieve an effective reperfusion after infarct-related artery recanalization, a phenomenon known as no-reflow [2]. This condition is associated with increased risk for left ventricular dysfunction, progressive myocardial damage and higher mortality [3,4]. No-reflow is a complex and multifactorial phenomenon, caused by the combination of various mechanisms, such as distal embolization of thrombotic debris, prolonged myocardial ischemia and damage, microvascular obstruction and cellular edema [5] .

In STEMI patients, cardiac biomarkers such as troponin, and brain peptide natriuretic peptide (BNP) at hospital admission had an important role in diagnosis, risk stratification and prognosis, as evidenced by many studies focused on their predictive value on post-procedural no-reflow [6]. Nevertheless, there is a growing body of evidence indicating that inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP) [7], platelet and neutrophil number and lymphocytopenia, could be of interest to identify individuals at risk of no-reflow [8]. In addition, inflammation-based scores, such as neutrophil to lymphocyte ratio (NLR) [9,10], and more recently CRP/albumin Ratio (CAR) [11] were defined and used to predict adverse outcomes after pPCI.

* Corresponding author at: CNR, Institute of Clinical Physiology, San Cataldo Research Area, Via Moruzzi, 156124 Pisa, Italy.
E-mail address: serena@ifc.cnr.it (S. Del Turco).

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Despite considerable insight in recent years regarding single biomarkers or combination of theme used to establish the involvement of inflammation in no-reflow mechanism [7,11,12], no studies have been focused on the relationship between age-related differences in acute inflammation markers at the hospital admission and the incidence of no-reflow and mortality in STEMI patients.

2. Methods

2.1. Patients and study design

Between January 2006 and December 2012, 1542 consecutive patients with STEMI were admitted to the Cardiology Department (Massa) for primary PCI. Of these, 625 patients were enrolled regardless of door to balloon time (DTB), with no history of cardiogenic shock and cancer and with complete baseline data available. STEMI was defined according to the criteria formulated by the American College of Cardiology and the European Society of Cardiology [13]. STEMI is characterized by elevated cardiac biomarkers, with ST-elevation on electrocardiogram [13]. Coronary blood flow was analyzed according to TIMI flow grade. An arbitrary cut-off of 65 years was used to divide STEMI patients in young and elderly patients. According to TIMI flow grade score after pPCI, the two groups were divided into no-reflow group (TIMI grade ≤ 2) and reflow group (TIMI grade 3) (Supplemental Fig. 1). Written informed consent was obtained from all patients prior to participation and the local Ethic Committee approved the protocol.

2.2. Primary percutaneous coronary revascularization

No restrictions based on age and sex were applied. Before primary PCI, all patients received i.v. aspirin (500 mg) and a P2Y12 inhibitor (either clopidogrel [600 mg], prasugrel [60 mg] or ticagrelor [180 mg]). Unfractionated heparin (60 IU/Kg, intra-arterial), was administered in the catheterization laboratory before initiating the diagnostic angiography. Thrombus aspiration was preferred especially in the presence of a large thrombus burden [14] but left to the operator discretion. Similarly, downstream use glycoprotein IIb/IIIa was left to the operators' discretion in patients with large thrombus burden and/or angiographic complications (distal embolization, no reflow phenomenon) of pPCI according to the guidelines [15,16]. Cardiogenic shock was defined as persistent systolic blood pressure 90 mmHg, unresponsive to fluid administration and requiring vasopressors with echocardiographic evidence of severe dysfunction of the left ventricle, over a large infarction area. An intra-aortic balloon pump was positioned for all patients in cardiogenic shock. Culprit vessel TIMI flow grade was assessed after the PCI procedure as described [17] and procedural success was defined as post procedural TIMI 3 flow. Patients were classified into 2 groups based on post-intervention TIMI flow grade: no-reflow was defined as TIMI flow grades 0–2 (no-reflow group) and reflow was defined as TIMI 3 flow grade. To assess left and right ventricular systolic function, and rule out any mechanical complications, all patients, as internal protocol, received two-dimensional echocardiographic evaluation upon arrival in the catheterization laboratory before PCI, within the first 24 h after PCI, and during their in-hospital stay. Subsequent medical treatment included anti-ischemic, lipid-lowering and antithrombotic drugs according to current treatment guidelines [15,16].

2.3. Clinical assessment

Diabetes mellitus was defined by the patient self-report of history, current use of insulin or hypoglycemic agents, or serum HbA1c levels ≥ 6.5%. Hypertension was defined by physician-documented history of hypertension, or current use of antihypertensive medications. Dyslipidemia was defined by medical history or by the use of lipid-modulating medications in order to reduce lipids or fasting total cholesterol or low-density lipoprotein levels. Smoking status was ascertained by the medical history. Clinical and angiographic data, including sex, age, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary artery disease (CAD), previous MI, current smoking, culprit artery, TIMI flow, presence of multi-vessel, systolic blood pressure and ejection fraction were recorded.

2.4. Laboratory data

Venous blood samples were collected at admission in Intensive Care, immediately after performing pPCI, and used for routine blood chemistry and blood count. Specifically, high sensitivity- C reactive protein was measured by the Immulite System (Diagnostic Products Corporation, CA), troponin-I by the Access AccuTnI assay (BeckmanCoulter, Villepinte,France) and BNP by the Triage BNPtest (BiositeInc., San Diego, California). NLR was calculated by dividing neutrophil count by lymphocyte count, CAR by dividing CRP levels by albumin levels.

2.5. Analysis

The sample size was based on mean value of log-transformed hs-CRP in STEMI patients. Assuming a difference of hs-CRP of between young and elderly patients of 30% (checked in a preliminary analysis of the database), with an error margin of 5% and a 95% confidence interval (95% CI), the required sample size was calculated to be at least 104 patients. We recruited in excess of this figure to be fully confident in our data. Continuous data were expressed as mean ± standard deviation or median (interquartile range) if not normally distributed and compared using independent Student's *t*-test. Variables with a non-normal distribution were logarithmically transformed before each analysis. Categorical variables were expressed as percentages and analyzed with the chi-square test. Univariate analysis was used to investigate the association with no-reflow. A Cox proportional hazard regression analysis was performed to evaluate predictive factors of mortality for all causes, CAD at two-year follow-up. Two-sided *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using Stat-View 5.0.1 program (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

3. Results

3.1. Characteristics of the population

Demographic, clinical, and angiographic characteristics of all patients are listed in Table 1 and the young and elderly patient's groups were compared. Among 625 STEMI patients (mean age 66 ± 13 years), 447 patients (71%) were male. The mean age of the study population in younger group was 55.4 ± 7.6 years (86% were male) and in older group 76 ± 7 years (57% were male). Elderly patients, at hospital admission, had a more frequent history of hypertension (70% vs. 48.2%) and diabetes (22% vs. 14.6%). Smokers were more frequent in the younger group (60% vs. 25%). Higher incidence of family history of CAD was observed in the younger group (47%) than that in the older group (18%) (Table 1). Elderly patients showed both higher longer DTB time (966 (76–122), $p = 0.006$) and incidence of no-reflow (18%) after pPCI compared with young patients (11%). No differences between two groups were found regarding single, double, or triple-vessel diseases.

3.2. Laboratory parameters

Among laboratory parameters, elderly patients had significantly higher values of BNP ($p < 0.0001$), glucose ($p < 0.014$), leukocytes ($P = 0.0037$), NLR ($p = 0.0001$), CRP ($p = 0.0003$), CAR ($p < 0.0001$), fibrinogen ($p = 0.005$) compared with young patients (Table 2). Conversely, the levels of serum albumin ($p < 0.0001$) and lymphocytes ($p < 0.0001$) were higher in young subjects. Both age group have comparable troponin and creatine kinase B (CKB) levels (Table 2).

3.3. Laboratory parameters, no-reflow and mortality

All patients, elderly and young groups were divided into two groups according to TIMI flow grade after pPCI. The percentage of patients with no-reflow in all population was 14%, among with 63% were elderly patients. In young and elderly subjects, the percentages of patients with no-reflow were 11% and 18%, respectively.

In the univariate comparisons, all patients who developed no-reflow (14%) during PCI were more likely to be older ($p = 0.04$), to have high BNP ($p = 0.0002$) (Fig. 1A), CAR ($p = 0.002$), and fibrinogen levels (0.004) (Fig. 1B–D).

In elderly patients who had the higher percentage of no-reflow than younger patients, higher levels of CAR ($p = 0.03$), and fibrinogen ($p = 0.03$) were significantly associated with no-reflow (Fig. 1B–D). Higher NLR levels tended to be associated with no reflow, but did not reach statistical significance ($p = 0.06$) (Fig. 1C). High levels of leukocytes (no reflow: 11.4 ± 4 *vs* reflow: 10 ± 3.7, $p = 0.023$) and neutrophils (no reflow 9.3 ± 4 *vs* reflow: 8 ± 3.6, $p = 0.022$) were also associated to no-reflow in elderly patients (data not shown). In young patients, only higher BNP levels were associated ($p = 0.0019$) with no-reflow (Fig. 1A). No differences by sex, disease type and medication class were found between no-reflow group and reflow group in the three classes of patients.

A multivariate Cox regression analysis identified BNP, NLR and age as independent predictors of all-cause mortality in all patients (Table 3) as well as in elderly patients, BNP and NLR were independent predictors of all-cause mortality (Table 3). BNP was also predictor of CAD death in all and in elderly patients (Table 3).

Table 1
Demographic, clinical and angiographic characteristics of STEMI patients.

Variable	All patients $n = 625$	Young (≤65 years) $n = 307$	Elderly (>65 years) $n = 318$	P value
Age (years)	66 ± 13	55 ± 7.6	76 ± 7	<0.0001
Men, gender, n (%)	447 (71)	265 (86.3)	182 (57.2)	<0.0001
Hypertension, n (%)	370 (13.3)	148 (48.2)	222 (70)	<0.0001
Diabetes, n (%)	117 (19)	45 (14.6)	72 (22)	0.01
Smoking, n (%)	262 (42)	183 (59.6)	79 (25)	<0.0001
Family history of CAD, n (%)	200 (32)	144 (47)	56 (17.6)	<0.0001
BMI (kg/m^2)	27 ± 4	27.6 ± 4	26 ± 4.3	0.0002
Systolic blood pressure, SBP (mmHg)	138 ± 27	135 ± 24	141 ± 28	0.0024
No. of coronary artery narrowed				
1	333	172 (56)	161 (51)	0.18
>1	292	135 (40)	157 (45)	
Disease vessel, n (%)				
LAD	76 (14)	41 (15)	35 (12.4)	0.05
LCX	230 (41)	116 (42)	114 (40.3)	
RCA	252 (45)	118 (43)	134 (47.3)	
Ejection fraction, (%)	46 ± 10	47.2 ± 10	45 ± 10	0.05
Door-to-balloon time, DTB (min)	92 (75–120)	90 (73–111)	96 (76–122)	0.006
TIMI flow grade 0–2	89 (14.2)	33 (11)	56 (17)	0.0141
TIMI flow grade 3	536(85)	274 (89)	262 (82.4)	0.07
Previous medication, n (%)				
Beta-blockers	482(77)	241 (78)	241 (76)	0.41
Statins	531(85)	266 (87)	265 (83)	0.25
Aspirin	608 (97)	307	301 (95)	0.24
Sartans	348 (56)	169 (55)	179 (56)	0.75
Ace-inhibitors	491 (78)	239 (78)	252 (79)	0.67
Clopidogrel	293 (93)	142 (46)	151 (47)	0.33

Data are expressed as mean ± SD, median (interquartile range, IQR) or n (%). CAD: coronary artery disease; BMI: body mass index; SBP: systolic blood pressure; LAD: Left anterior descending; LCX: Left Circumflex Artery; TIMI Thrombolysis in Myocardial Infarction; RCA: Right Coronary Artery.

4. Discussion

In the present paper, we aimed at assessing whether a different biohumoral inflammatory pattern with respect of the age of presentation could have an impact on the incidence of no-reflow and mortality in a cohort of STEMI patients. First, we found a differential inflammatory pattern between young and elderly STEMI patients at the hospital admission that confirms the presence of a higher acute pro-inflammatory systemic response in elderly patients. Second, in elderly patients the cellular and humoral aspects of acute inflammation were associated to coronary no-reflow, while in young patients only BNP resulted to be associated to no-reflow. Third, BNP and NRL resulted as predictor of mortality in elderly patients at 2-years of follow-up.

4.1. Higher inflammatory burden in elderly STEMI patients

Coronary atherosclerosis is associated with an increased systemic and local inflammatory response that can act as a precipitating factor leading to plaque destabilization and rupture and acute myocardial infarction (AMI) [18]. In addition to local inflammation in the myocardium, which serves to repair heart, AMI is associated with acute systemic inflammation response, characterized by elevation of circulating levels of CRP, fibrinogen or of other soluble markers as cytokines and chemokines, as well as activation of peripheral leukocytes [19]. These markers are predictors of adverse clinical outcomes, such as death, recurrent myocardial infarction MI and heart failure in patients with AMI [20]. Recently, high levels of vascular endothelial growth factors

Table 2
Laboratory characteristics at the admission of STEMI patients.

Variable	All n = 625	Young (≤65 years) n = 307	Elderly (>65 years) n = 318	P value
Troponin (ng/mL)	13 (3–42)	11.5 (2.5–38)	13.3 (3.7–49)	0.09
Creatine kinase-MB (U/L)	106 (36261)	102 (35–241)	112 (38–273)	0.34
BNP (pg/mL)	87 (48–280)	66 (31–142)	197 (91.5–436)	<0.0001
Triglyceride (mg/dL)	111 ± 75	97 ± 53	126 ± 90	<0.0001
LDL (mg/dL)	128 ± 39	133 ± 40	123 ± 37	0.0021
HDL (mg/dL)	47 ± 13	45 ± 12	48.4 ± 13.7	0.0015
Glucose (mg/dL)	131 ± 57	124 ± 60	136 ± 53	0.0146
Hemoglobin (g/dL)	14 ± 1.6	14.1 ± 1.4	13.2 ± 1.7	<0.0001
Creatinine (mg/dL)	0.99 ± 0.4	0.9 ± 0.3	1.1 ± 0.5	<0.0001
Serum albumin (g/L)	3.6 ± 0.4	3.7 ± 0.4	3.5 ± 0.4	<0.0001
Platelet count ($\times 10^9$)	222 ± 67	225 ± 64	216 ± 68	0.07
Leukocytes ($10^3/\mu L$)	11 ± 3.5	10.4 ± 4	11 ± 3	0.0037
Neutrophils ($10^3/\mu L$)	8.4 ± 3.4	8.6 ± 3	8.3 ± 3.7	0.27
Lymphocytes ($10^3/\mu L$)	1.6 ± 0.7	1.83 ± 0.8	1.4 ± 0.6	<0.0001
Monocytes ($10^3/\mu L$)	0.7 ± 0.35	0.74 ± 0.3	0.7 ± 0.36	0.05
Neutrophil-to-lymphocyte ratio (NLR)	6.8 ± 5	6 ± 4.5	7.5 ± 5	0.0001
C-reactive protein/albumin (CAR) ratio	0.16 (0.66–0.43)	0.12 (0.056–0.309)	0.2 (0.08–0.7)	<0.0001
Fibrinogen (mg/dL)	300 ± 92	289.6 ± 84	310.5 ± 97	0.0049
hs-CRP (mg/dL)	0.6 (0.25–1.52)	0.45 (0.29–2.61)	0.7 (0.22–1.17)	0.0003

Data are expressed as mean ± SD, median (IQR). BNP: brain natriuretic peptide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BMI: body mass index; hs-CRP: high sensitive C-reactive protein.

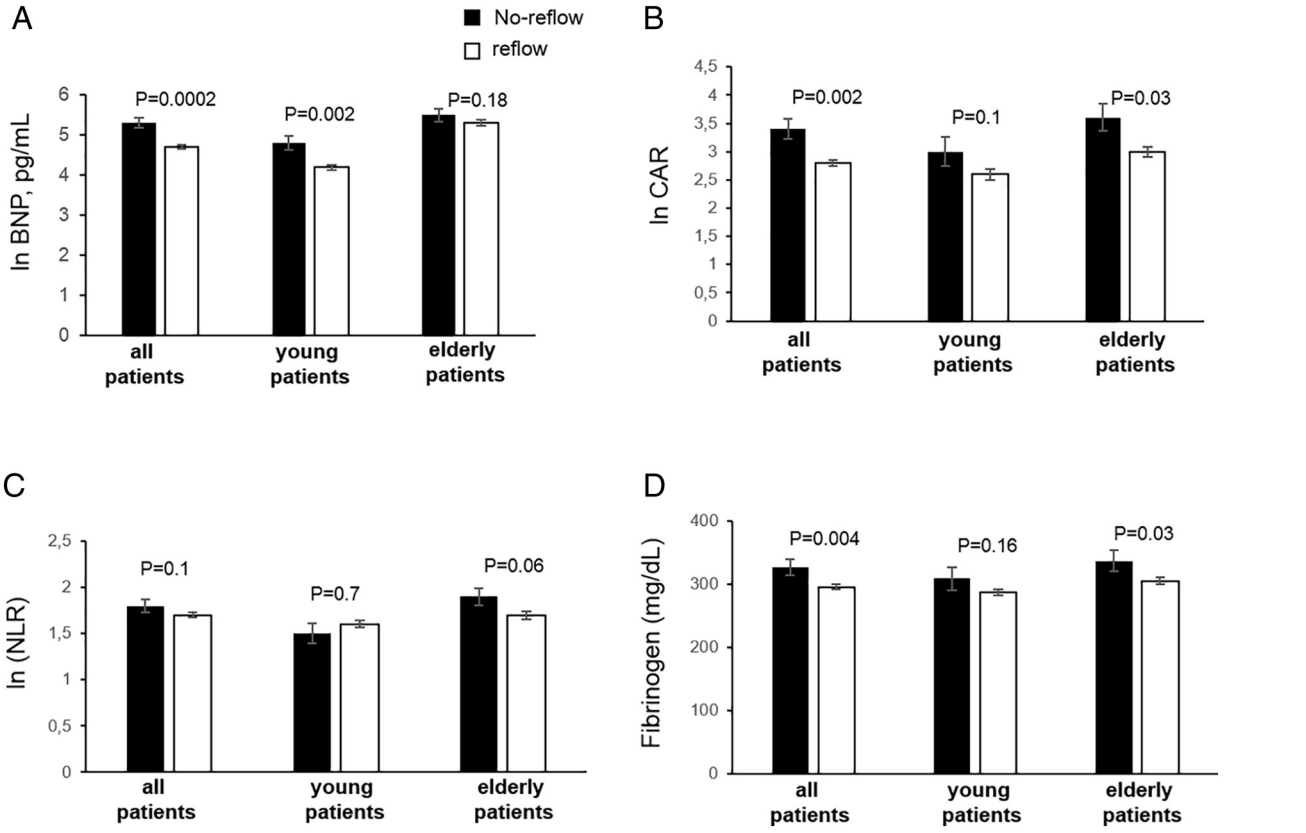

Fig. 1. Comparisons of plasma levels of BNP (A), CAR (B), NLR (C) and fibrinogen (D) between no-reflow and reflow in all, young and elderly patients. BNP: brain natriuretic peptides; NLR: Neutrophil-to-lymphocyte ratio; CAR: C-reactive protein/albumin ratio.

(VEGF), a pro-angiogenetic, pro-inflammatory factor and a vascular permeability inducer released during AMI, were independently associated with microvascular obstruction in STEMI patients [21]. We found that elderly STEMI patients at the admission show increased inflammatory marker levels, as NLR, CAR fibrinogen, compared to younger STEMI patients. This unfavorable inflammatory status in elderly patients can derive from the association between acute inflammatory insult due to STEMI and chronic low-grade inflammatory status typical of aging [22,23].

Other mechanisms such as decline in adaptive and innate immunity, malnutrition, and comorbidities likely contribute and are intertwined with age-related inflammation, characterizing the elderly frailty [24,25]. Our results showed that elderly STEMI patients have also a number of lymphocytes lower than young patients, suggesting that immunity component is affected. In fact, one of the main sign of an immune system aging is a significant reduction of native lymphocytes in blood, which has been mainly attributed to a reduction of thymic output and imperfect peripheral maintenance [26,27]. Lower albumin levels that we have found in elderly patients may reflect both a malnutrition status common in older individuals [28] and an acute inflammatory response, as albumin is a negative acute-phase reactant, related inversely with the inflammatory status [29].

In addition to inflammatory markers, elderly STEMI patients showed higher BNP levels on admission. BNP is a biomarker of biomechanical stress stored mainly in the ventricular myocardium and early released into the circulation in response to ventricular dilatation and pressure overload and ischemic injury [30,31]. Furthermore, several aging-related changes influence BNP levels in older individuals as biomarker of myocardial remodeling by fibrotic tissue [32].

Table 3
Cox proportional hazard regression analysis of risk of all-cause mortality, CAD death during 2 years of follow-up in the all and elderly STEMI patients.

	All-cause mortality		CAD	
	HR (95% CI)	*P* value	HR	(95% CI) *P* value
All patients				
BNP	2.14 (1.3–3.4)	0.0012	3.9 (1.4–10)	0.007
NLR	2.32 (1.1–4.9)	0.03	0.79 (0,1-4,3)	0.78
Age	1.05 (1–1.12)	0.03	1 (0.9–1-15)	0.58
Elderly patients				
BNP	2.52 (1.62–3.9)	<0.0001	3.3 (1.2–8.8)	0.01
NLR	2.6 (1.1–6.2)	0.028	0.4 (0.05–3.3)	0.41

BNP: brain natriuretic peptide; CAD: coronary artery disease; HR: hazard ratio; NLR: Neutrophil-to-lymphocyte ratio.

4.2. Potential impact of age-related inflammation on impaired myocardial reperfusion

Despite the recent progress in PCI, however, a proportion of STEMI patients develops acute reduction in coronary blood flow, named as no-reflow, which is associated at an increased risk for left ventricular dysfunction and progressive myocardial damage [4]. Although data on association between age and no-reflow in STEMI patients are limited, some studies have underlined that older patients are more likely to have no reflow, probably linked to co-morbidities and more severe coronary artery disease [33,34]. Among all STEMI patients, 14% developed no-reflow phenomenon during pPCI, of these 63% were elderly. The rate of no-reflow phenomenon after primary PCI in our study was similar to that reported (5–40%) by other studies [4,35].

When elderly patients were classified according to TIMI flow grade, we found that higher levels of CAR, CRP, neutrophils, fibrinogen, and lower levels of albumin were significantly associated with no-reflow. Compared to normal reflow group, higher NLR levels tended to be associated with no-reflow. However, among all these inflammatory markers, only NLR results independent predictor of mortality in all and elderly patients.

Recently it has been demonstrated that CAR is an index that resulted to have clinical value in no-reflow prediction of STEMI patients [11]. An increase in CRP levels and a decrease in albumin levels can be linked to no-reflow in STEMI patients [36,37]. CRP induces the release of inflammatory mediators and oxygen free radicals, thus resulting in vascular intimal injuries, unstable plaque and increasing luminal stenosis caused by atherosclerosis [38]. Hypoalbuminemia, besides being an important indicator of malnutrition, increases blood viscosity, diminishes endothelial function and predicts no-reflow [37] and mortality in older STEMI patients undergoing pPCI [39,40]. High fibrinogen concentration is associated with no-reflow, likely because of enhanced erythrocyte aggregation and higher plasma viscosity, which elevate blood flow resistance in the microvasculature, resulting in impaired reperfusion [41].

Many studies have demonstrated that NLR, a simple and inexpensive marker of subclinical inflammation, is associated with no-reflow and is a strong predictor of adverse outcomes after pPCI [12,42,43]. In this study, elderly STEMI patients on admission had higher NLR levels compared to young patients, and elevated NLR persisted in the no-reflow group. Recently it has been demonstrated that elevated NLR in elderly patients with AMI results potential predictor of in-hospital mortality [44]. This ratio has high value because integrates information that derive from two immune pathway, the neutrophils, responsible for ongoing inflammation, and the lymphocytes that represent the regulatory pathway [45,46]. Neutrophils are an important component of innate immunity, secrete mediators responsible of inflammatory response, infiltrate coronary plaques and infarcted myocardium and contribute to endothelial damage contributing to impaired reperfusion [47]. A high count of neutrophils was associated to short-term post-MI adverse outcomes and worse angiographic findings [48]. We found that NLR was independent predictor of all-cause mortality in all patients and in elderly patients.

The predictive value of NLR on mortality in elderly patients but not in young patients suggests that enhanced inflammatory status in elderly patients, likely deriving from basal aging-derived inflammation and acute inflammatory insult of STEMI, plays an important role in increasing risk of mortality.

Conversely, in young patients, BNP level on admission was the only laboratory parameter associated with no-reflow, suggesting that no-reflow phenomenon is mainly dependent on the pre-procedural myocardial dysfunction in this group. Changes in ventricular wall-stress secondary to ischemia, but above, transient myocardial ischemia/hypoxia per se could contribute to raising BNP levels in the early phase of myocardial ischemia [49].

4.3. Conclusion

The above findings show differential inflammatory pattern in young and elderly STEMI patients at the admission confirming the presence of a higher acute pro-inflammatory condition in elderly patients. In addition, simple and easy routine biomarkers of inflammation and tissue remodeling resulted to be associated with both no-reflow and global mortality in older STEMI patients. Since the elderly individuals represent a growing cohort of STEMI patients treated with pPCI and given their highest risk of morbidity and mortality, they could derive more benefits with targeted anti-inflammatory treatments. At the same time, the possibility of use new tools as targeted perfusion microcatheter to assure effective coronary arteries concentration of drugs could reduce the occurrence of general side effects [50]. However, further studies are necessary to validate a tailored age-dependent approach to acute care management of STEMI patients undergoing pPCI.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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