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ORIGINAL ARTICLE

Mean Platelet Volume as Prognostic Marker in Patients with Acute Coronary Syndrome

Volumen plaquetario medio como marcador pronóstico en pacientes con síndrome coronario agudo

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ABSTRACT

Background: Mean platelet volume (MPV) has been described as a predictor of cardiovascular events in patients with acute coronary syndrome. However, there is limited evidence of its role as prognostic marker in elderly patients.
Objective: The aim of this study was to evaluate whether MPV is an independent predictor of events during follow-up of patients over 65 years of age with acute coronary syndrome.
Methods: This prospective study included patients over 65 years with ST-segment elevation or non ST-segment elevation acute coronary syndrome. They were divided into two groups: high MPV (≥ 10.9 fL- 3rd tertile) and low MPV (<10.9 fL -1st and 2nd tertile). Different clinical variables were analyzed and the TIMI and GRACE scores were calculated. The primary endpoint was the composite of all-cause mortality and cardiovascular readmission (for acute coronary syndrome, heart failure and stroke) over the follow-up period.
Results: A total of 250 patients were included in the study. Mean age was 74±7 years and 44% were women. Eighty-five patients presented with high and 165 with low MPV. Median follow-up was 302 days (interquartile range 130-558) and the primary endpoint was observed in 17.6% of cases (44 patients). In the multivariate Cox regression analysis, high MPV [HR 7.23 (95% CI 2.47-11.6); p=0.001], and TIMI [HR 3.10 (95% CI 1.46-6.59); p=0.03] and GRACE [HR 1.02 (95% CI 1.01-1.07); p=0.002] high risk scores were independent predictors of the primary endpoint. The area under the curve for MPV was 0.71 (95% CI 0.59-0.82), p=0.001.
Conclusions: In our population, MPV emerged as an independent predictor of the composite endpoint, adjusted for other variables as the TIMI and GRACE scores.

Key words: Acute Coronary Syndrome - Mean Platelet Volume - Biological Markers - Prognosis - Aged

RESUMEN

Introducción: El volumen plaquetario medio (VPM) se ha descripto como un predictor de eventos cardiovasculares en pacientes con síndrome coronario agudo. No obstante, la evidencia de su rol como marcador pronóstico en pacientes añosos es escasa.
Objetivo: Evaluar si el VPM es un predictor independiente de eventos en el seguimiento en pacientes con síndrome coronario agudo mayores de 65 años.
Material y métodos: Estudio prospectivo que incluyó pacientes mayores de 65 años con síndrome coronario agudo con y sin elevación del segmento ST. Se dividieron en dos grupos: VPM alto (≥ 10,9 fL - tercil 3) y VPM bajo (< 10,9 fL - terciles 1 y 2). Se analizaron diferentes variables clínicas y se calcularon los puntajes TIMI y GRACE. Se consideró el punto final combinado de mortalidad global y reinternación cardiovascular (por síndrome coronario agudo, insuficiencia cardíaca y accidente cerebrovascular) en el seguimiento.
Resultados: Se incluyeron 250 pacientes con una edad promedio de 74 ± 7 años, el 44% eran mujeres. Presentaron VPM alto 85 pacientes y VPM bajo 165. La mediana de seguimiento fue de 302 días (rango intercuartil 130-558) y el punto primario se observó en el 17,6% (44 pacientes). En el análisis multivariado por regresión de Cox, el VPM alto fue predictor independiente del punto primario [HR 7,23 (IC 95% 2,47-11,6); p = 0,001], al igual que el TIMI riesgo alto [3,10 (IC 95% 1,46-6,59); p = 0,03] y el puntaje GRACE [1,02 (IC 95% 1,01-1,07); p = 0,002]. El VPM presentó un área bajo la curva de 0,71 (IC 95% 0,59-0,82); p = 0,001.
Conclusiones: En nuestra población, el VPM se comportó como un predictor independiente del punto combinado, ajustado por otras variables como los puntajes TIMI y GRACE.

Palabras clave: Síndrome coronario agudo - Volumen plaquetario medio - Marcadores biológicos - Pronóstico - Anciano

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Abbreviations

ACS	Acute coronary syndrome	**MPV**	Mean platelet volume
AMI	Acute myocardial infarction	**NSTE-ACS**	Non-ST-segment elevation acute coronary syndrome
ASA	Acetyl salicylic acid (aspirin)	**STE-ACS**	ST-segment elevation acute coronary syndrome
AUC	Area under the curve	**UA**	Unstable angina

INTRODUCTION

Atherothrombosis is the main pathophysiological mechanism of acute coronary syndromes (ACS), where platelet activation, adhesion and aggregation are essential events. (1, 2) Increased platelet reactivity has been associated to worse outcome and higher risk of events in patients with ACS. (3). Moreover, increased platelet reactivity is related to enhanced platelet volume, (2) and higher levels of procoagulable factors have been found in patients with increased mean platelet volume (MPV). (4, 5)

Automated cell counters can identify different hematimetric parameters together with standard complete blood count data; hence, MPV is easily available in the routine complete blood count of patients admitted with ACS.

Increased MPV has been reported in acute myocardial infarction (AMI) compared with unstable angina (UA) and control patients (6-8). Furthermore, MPV has been found to be a predictor of mortality and reinfarction in patients with ACS (8-10) or submitted to revascularization surgery. (11, 12) However, these studies included a large number of young patients below 65 years of age, with scarce relevance regarding the role of MPV as prognostic marker in elderly patients with ACS.

The aim of this study was thus to assess whether MPV is an independent risk factor of cardiovascular events in patients over 65 years admitted for ST-segment elevation or non-ST-segment elevation ACS.

METHODS

A prospective study including consecutive patients >65 years admitted for ST-segment elevation ACS (STE-ACS) or non-ST-segment elevation ACS (NSTE-ACS) was performed from June 2011 to December 2013. Previous history, clinical, laboratory and electrocardiographic characteristics were analyzed on admission, and MPV was obtained within 24 hours of admission. Values were divided according to MPV tertiles in: 1st tertile, MPV <10.2 fL (n=83); 2nd tertile, MPV between 10.3 and 10.8 fL (n=82) and 3rd tertile, MPV ≥10.9 fL (n=85). Patients with MPV ≥10.9 fL, corresponding to the 3rd tertile, were considered as high MPV and patients with MPV <10.9 fL, corresponding to tertiles 1 and 2, as low MPV. (11, 12) GRACE and TIMI STE-ACS or TIMI NSTE-ACS risk scores were calculated as appropriate. The only exclusion criterion was impossibility of measuring MPV.

After discharge, long-term follow-up was performed by telephone contact or medical visit.

The primary endpoint was all-cause mortality and readmission for cardiovascular causes (ACS, heart failure or stroke).

Definitions

Acute coronary syndrome was the presence of anginal pain, lasting 15 minutes or more, in functional class III-IV of the New York Heart Association, 24 hours prior to consultation, or presence of pain characterized as atypical angina during the previous 24 hours plus one of the following: elevated standard troponin I, changes in the electrocardiogram (ST-segment shift or inverted T wave in two or more leads), prior revascularization or documented coronary artery disease.

Acute myocardial infarction was diagnosed as the presence of defined ACS plus standard troponin I elevation and its subsequent decrease with at least one value above the 99th percentile (according to our laboratory >1.0 ng/dL). The diagnosis of STE-ACS required in addition to persistent ST-segment elevation of 1 mm in two contiguous leads, a new or presumably new, left ventricular bundle branch block. (13)

A score >5 for NSTE-ACS and >8 for STE-ACS was considered high risk TIMI. (15)

Sample collection

An EDTA-anticoagulated venous blood sample was withdrawn from all patients within 24 hours of admission for complete blood count including platelet count and MPV, and analysed at the Central Laboratory of the institutional Hematology Division with a Sysmex XT-2000i hematology analyzer.

Statistical analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as percentage. Student´s t test or the Mann Whitney test was used to compare high and low MPV groups for continuous variables with normal or non-normal distribution, respectively. The chi-square test or Fisher´s exact test was used to compare categorical variables, as appropriate. A p value <0.05 was considered as statistically significant.

Follow-up was monitored by univariate analysis using MPV as continuous variable, high MPV, TIMI high risk score, the GRACE score as continuous variable, ST-segment shift, elevated standard troponin I (>1 ng/dL), age, heart failure on admission (Killip and Kimball classification ≥II), previous AMI and prior use of aspirin (ASA). Variables presenting association with p≤0.1 entered a multivariate model using Cox regression analysis to establish independent predictors of the primary endpoint according to the hazard ratio (HR) and its 95% confidence interval (95% CI). Event-free survival was analysed using Kaplan-Meier curves. Finally, the area under the ROC curve (AUC) was calculated to evaluate MPV and GRACE score discrimination ability for the primary endpoint. Both AUCs were compared with the Hanley & McNeil test, using MedCalc 15.2.2. software. SPSS Statistics 18 and Statistix 7 software packages were used for the remaining analyses.

Ethical considerations

The protocol was evaluated and approbed by the Institutional Review Board.

RESULTS

Among the 278 patients admitted for ACS, 15 had no

MPV assessment, 5 died during hospitalization and 8 were lost to follow-up; thus, 250 patients were included in the study. Mean age was 74±7 years, and 44% were women with MPV of 10.6±0.6 fL. Eighty-five patients presented high MPV (11.3±0.5 fL) and 165 low MPV (10.2±0.4 fL). The high MPV group was composed of a lower number of women (34.1% vs. 48.4%; p=0.04), with enhanced GRACE score (141±27 vs. 129±26; p=0.002), greater high risk TIMI (34.1% vs. 15.1%; p=0.003) and higher rate of troponin I elevation (63.5% vs. 43.6%; p=0.006), with a trend to increased incidence of prior AMI (28.2% vs.16.9%; p=0.052). There were no differences between groups for the remaining variables (Table 1).

Median follow-up was 302 days with interquartile range of 130-558. The primary endpoint was observed in 44 patients (17.6%), with an overall mortality of 5.2% (13 patients). The high MPV group presented higher prevalence of the primary endpoint, mortality and readmission for cardiovascular causes than the low MPV group (Table 2).

Table 3 shows univariate and multivariate analyses for the primary endpoint. In the univariate analysis, the primary endpoint was associated with MPV

Table 1. Baseline characteristics

	Total (n=250)	High MPV group (n=85)	Low MPV group (n=165)	p
Age, years	74 ± 7	74 ± 6	74 ± 7	0.5
Female gender, n (%)	(109) 43.6	(29) 34.1	(80) 48.4	0.04
Hypertension, n (%)	(204) 81.,6	(67) 78.8	(137) 83.0	0.3
Diabetes, n (%)	(65) 26.0	(20) 23.5	(45) 27.2	0.5
Dyslipidemia, n (%)	(147) 58.8	(53) 62.3	(94) 56.9	0.5
Smoking, n (%)	(65) 26.0	(19) 22.3	(46) 27.8	0.6
Prior AMI, n (%)	(52) 20.8	(24) 28.2	(28) 16.9	0.052
Prior PCI, n (%)	(46) 18.4	(17) 20.0	(29) 17.5	0.6
Prior CABG, n (%)	(32) 12.8	(13) 15.2	(19) 11.5	0.2
Prior use of ASA, n (%)	(131) 52.4	(52) 61.1	(79) 47.8	0.07
Prior use of clopidogrel, n (%)	(25) 10	(8) 9.4	(17) 10.3	0.9
Admission and hospitalization data				
MPV, fL	10.6 ± 0,6	11,3 ± 0,5	10,2 ± 0,4	
Platelets, cells/ml	210x103 ± 75x103	200x103 ± 75x103	218 103 ± 74x103	0.1
Hematocrit, %	37 ± 5	38 ± 5	37 ± 5	0.1
Leukocytes, cells/ml	8,850 ± 3,800	9,100±3,390	8,720±4,016	0.4
Creatinine, mg/dL	1.00±0.5	1.07±0.4	0.97±0.4	0.1
CRCL, ml/min	76 ±30	72±30	77±29	0.2
SBP, mmHg	146±29	148±25	145±29	0.4
HR, bpm	75±17	76±19	74±16	0.4
KK >1, (n)%	(16) 6.4	(5) 5.8	(11) 6.6	0.7
Tn I >1 ng/dL, (n) %	(126) 50.4	(54) 63.5	(72) 43.6	0.006
ST-segment shift, (n) %	(110) 44	(44) 52	(72) 43.6	0.1
GRACE score	133 ± 27	141 ± 27	129 ± 26	0.0002
High risk TIMI, (n) %	(54) 21.6	(29) 34.1	(25) 15.1	0.003
STE-ACS, (n) %	(55) 22.0	(23) 27.0	(32) 19.4	0.21
NSTE-ACS, (n) %	(195) 78.0	(62) 72.9	(133) 80.6	0.2
Non-STE AMI, (n) %	(67) 26.8	(29) 34.1	(35) 21.2	0.04
UA, (n) %	(128) 51.2	(33) 38.8	(98) 59,3	0.04
Revascularization during hospitalization, (n) %	(118) 47.2	(41) 48.2	(77) 46.6	0.2

AMI: Acute myocardial infarction. PCI: Percutaneous coronary intervention. CABG: Coronary artery bypass graft surgery. MPV: Mean platelet volume. CRCL: Creatinine clearence. SBP: Systolic blood pressure. HR: Heart rate. KK: Killip and Kimball classification. Tn I: standard troponin I. STE-ACS: ST-segment elevation acute coronary syndrome. NSTE-ACS: Non-ST-segment elevation acute coronary syndrome. Non-ST AMI: Non-ST-segment elevation acute myocardial infarction. UA: Unstable angina.

[HR 1.14 (95% CI 1. 07-1.21); p=0.005], high MPV [HR 8.2 (95% CI 3.80-17.6); p=0.001)], GRACE score [HR1.03 (95% CI 1.01-1.08); p=0.0001], high TIMI score [HR 3.33 (95% CI 1.65-6.62); p=0.001], ST-segment shift [HR 2.42 (95% CI 1.19-4.89); p=0.01] and elevated standard troponin I [HR 2.43 (95% CI 1.21-4.87); p=0.01]. In the multivariate analysis adjusted for high TIMI score, GRACE score, ST-segment shift, elevated standard troponin I and previous use of aspirin, high MPV remained as independent predictor of the primary endpoint [HR 7.23 (95% CI 2.47-11.6); p=0.0001], same as high risk TIMI [HR 3.11 (95% CI 1.43-6.59); p=0.02] and the GRACE score [HR 1.02 (95% CI 1.01-1.07); p=0.02].

Figure 1 shows Kaplan-Meier curves, where high MPV presents lower event-free survival compared with the low MPV group (p=0.0001, log-rank test).

The AUC for MPV was 0.71 (95% CI 0.59-0.82; p=0.0001). The cut-off point was set at ≥10.8 fL, with 71.4% sensitivity and 74.1% specificity for the primary endpoint. In the analysis not adjusted by log-rank test, the HR was 5.42 (95% CI 2.56-11.4; p=0.0001). The AUC for the GRACE score was 0.67 (95% CI 0.59-0.74; p=0.001). Non-significant differences in the

Table 2. Primary endpoint in high and low MPV groups

	Total (n=250)	High MPV group (n=85)	Low MPV group (n=165)	p
Primary endpoint, n (%)	(44) 17.6	(31) 36.4	(13) 7.8	0.00001
Death, n (%)	(13) 5.2	(11) 12.9	(2) 1.2	0.00001
Cardiovascular readmission, n (%)	(31) 12.4	(20) 23.5	(11) 6.7	0.0001

*Chi-square test. MPV: Mean platelet volume

Table 3. Univariate and multivariate analysis for the primary endpoint. Cox regression analysis

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
MPV	1.14	1.07-1.21	0.0001	1.14	1.07-1.21	0.0001
High MPV	8.20	3.8-17.6	0.0001	8.20	3.8-17.6	0.0001
High risk TIMI	3.31	1.65-6.62	0.001	3.31	1.65-6.62	0.001
GRACE score	1.03	1.01 -1.04	0.01	1.03	1.01 -1.04	0.01
Troponin I >1ng/dL	2.42	1.21- 4.87	0.01	2.42	1.21- 4.87	0.01
ST-segment shift	2.41	1.19-4.84	0.01	2.41	1.19-4.84	0.01
Killip-Kimball >1	1.19	0.40-3.89	0.7	1.19	0.40-3.89	0.7
Prior AMI	1.58	0.75-3.31	0.22	1.58	0.75-3.31	0.22
Prior use of ASA	1.96	0.98-3.91	0.05	1.96	0.98-3.91	0.05

*Chi-square test. MPV: Mean platelet volume

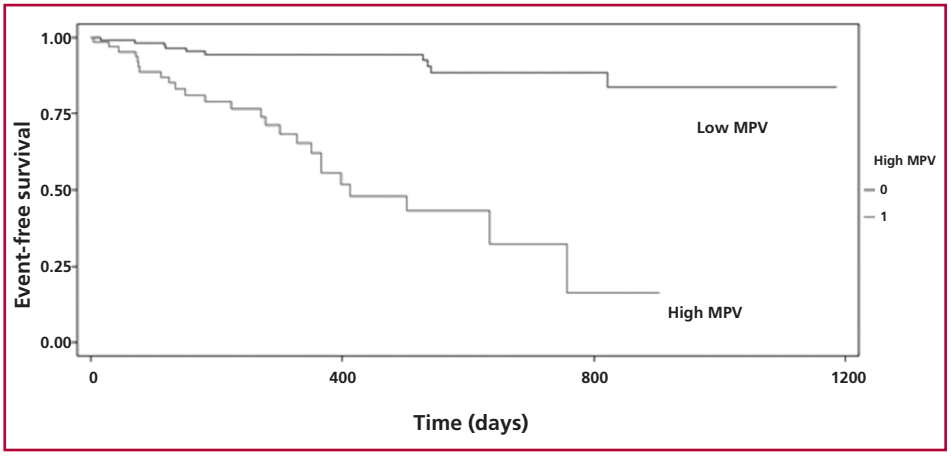

Fig. 1. High and low mean platelet volume (MPV) Kaplan-Meier curves for the primary endpoint

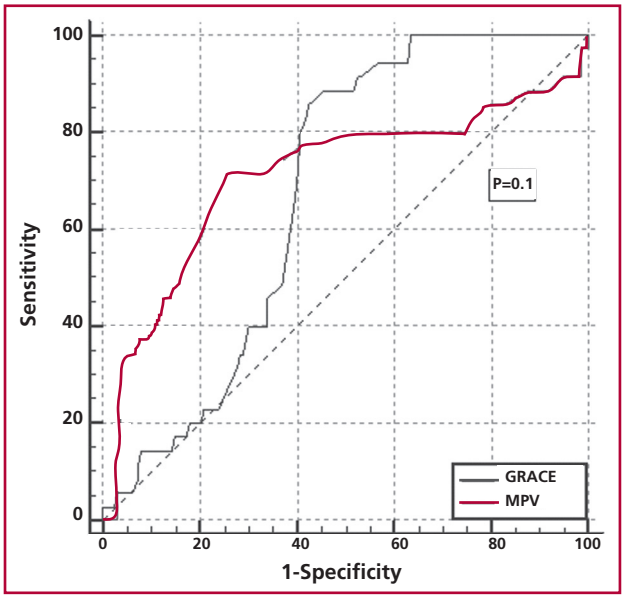

Fig. 2. Mean platelet volume (MPV) and GRACE score ROC curves for the primary endpoint

AUC were found between MPV and the GRACE score (p=0.1). Figure 2 shows the MPV and GRACE ROC curve for the primary endpoint.

DISCUSSION

The present study showed that MPV is an independent predictor of mortality and readmission for cardiovascular causes in a population of patients over 65 years of age in a center treating exclusively senior patients [proper PAMI effector: Programa de Atención Médica Integral - Instituto Nacional de Servicios Sociales para Jubilados y Pensionados, Rep. Argentina (Comprehensive Medical Attention Program – National Institute of Social Services for Retirees and Pensioners, Argentina)]. Patient age was 74 years, older than in the SCAR registry in our country (16) and the GRACE registry. (17) Among studies evaluating MPV in ACS, only one assessed elderly patients with age similar to the one presented here. (18) Both in studies included in Chu et al.'s meta-analysis (8) as in later studies average age was not over 68 years. (12-22)

The role of MPV as event predictor has been analysed in several studies. In Chu et al.'s meta-analysis, three studies evaluated the predictive role of MPV and found that high MPV was associated with increased mortality. (8) In one unselected cohort of more than 200,000 patients with ACS and other causes of hospitalization, the risk of overall and cardiovascular mortality was greater at higher MPV quintile. (19) In another study evaluating 1,400 patients undergoing percutaneous coronary intervention, 77% of whom presented ACS, MPV >9.1fL was independent predictor of mortality and re-AMI at follow-up, with a predictive profile similar to troponin. (12) In another series, high MPV (≥10.3 fL) was associated with more severe coronary artery disease in patients with ACS, presenting with higher Syntax and Gensini score. (20) Another study evaluating 392 NSTE-ACS patients, MPV correlated with the combined endpoint of cardiovascular death and readmission for ACS, but following adjustment by the TIMI score, MPV lost its predictive value. (21) A recently published work, evaluating STE-ACS and NSTE-ACS patients, found that high MPV (≥11.9 fL) improved the performance of the GRACE score as risk predictor. The authors suggest that incorporation of MPV to the GRACE score might help risk stratification. (22)

Finally, an Italian study evaluated 1,042 NSTE-ACS patients with age similar to this study (76 years) and found that the 4th MPV quartile (>8.9 fL) was associated with the combined endpoint of cardiovascular mortality and re-AMI at one-year follow-up. This association then allowed the inclusion of MPV in a risk model with different variables as age, systolic blood pressure, heart rate, Killip and Kimball classification, ST-segment shift, and troponin and creatinine levels among others. (18) Although this is the only study presenting a population with age similar to that of our study, some differences should be mentioned. We included patients with ACS with and without ST-segment elevation, as in most published works. Our population had a lower risk profile, as for example lower GRACE score (133 vs. 149), lower prior AMI (21% vs. 38%) and less heart failure (6.5% vs. 30%). This might be explained by the fact that our patients presented UA as cause for admission. It might also account for the lower rate of the combined endpoint in our population (17% vs. 20%) and the lower rate of mortality (5.3% vs. 15%). However, other series of younger patients have reported rates of infarction or death between 5.5% (12) and 12% (22) at follow-up.

An elevated MPV has been found in AMI compared with UA and controls. (8) In this sense, we found that the high MPV group presented with higher troponin I elevation, and elevated GRACE and TIMI scores. Similarly, after adjusting for these risk predictors, MPV was independently associated with the primary endpoint, similarly to TIMI and GRACE scores. We used a TIMI score divided in high and low risk TIMI to compare with STE-ACS and NSTE-ACS populations. As validated, a TIMI score >5 was used for NSTE-ACS and a TIMI score >8 for STE-ACS. (14, 15) The GRACE score was continuously evaluated, since it has been developed and validated for both populations. (23, 24)

The results of this study complement a series of studies where MPV has been found to be an independent predictor of events in patients with ACS. However, different cut-off points have been used, as MPV in the populations studied had different average values. This precludes the standardization of this parameter for analysis and its incorporation to known risk scores. We divided the population in tertiles to define the group of patients with high MPV as previously performed in other studies. (11, 12) The 3rd tertile

value was ≥10.9 fL, similar to the one found in the ROC curve (10.8 fL). A recently published study has directly used ROC curve analysis to establish the cut-off point to classify the high MPV population, defining an MPV value >11.9 fL. (25) The predictive MPV profile in that work was similar to the one obtained here (AUC 0.73 and 0.71, respectively).

The pathophysiological mechanism whereby MPV is associated to the prognosis of patients with ACS is not yet clear. It is known that platelets have a life span of approximately 8 to 12 days, so MPV would be increased prior to ACS (5, 10, 25) Moreover, larger platelets have higher levels of thromboxane A2 per unit (26) and greater expression of GP IIb-IIIa receptors (5, 26) than smaller platelets. Other studies have shown elevated MPV in diabetic patients or with other risk factors (27) and that, in the general population, elevated MPV is a risk factor of AMI occurrence. (28) In the present work MPV was nor correlated with any of these risk factors, but evidenced greater trend to be associated with previous AMI. It has been shown that larger platelet size correlates with larger number of reticulated platelets (29) and greater residual platelet reactivity in patients treated with ASA or clopidogrel. (29, 30) Finally, MPV has been found to be associated with thromboembolic risk in patients with atrial fibrillation (31) and also in patients with stroke compared with controls. (32) These findings support the notion that enhanced MPV might indicate greater prothrombotic state. In addition, it is a parameter easily obtained in a routine lab test enabling its incorporation to the pool of predictive risk variables in patients with ACS.

Study limitations

A limitation of the current study was that MPV was measured within 24 hours of admission, so in some patients its value was nor assessed on the admission lab test but later. This was due to central lab exclusive sample processing for the protocol, leading to exclusion of several patients.

Moreover, it was a single-center study, focused exclusively in senior patients. Therefore, results cannot be extrapolated to other populations. Owing to the relatively small size of our population, we could not analyse whether the inclusion of MPV as risk variable increases the ability of the GRACE and TIMI scores to predict events.

CONCLUSIONS

In our population of patients over 65 years of age, MPV was a predictor of the combined endpoint of overall mortality and readmission due to cardiovascular events, even after adjusting for other risk variables as TIMI and GRACE scores, elevated troponin and ST-segment shift. However, MPV was a moderate predictor of the combined endpoint when the AUC was considered. High TIMI and GRACE scores were also independent predictors of the combined endpoint.

Conflicts of interest

None declared

(See author´s conflicts of interest forms in the web / Supplementary Material)

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