

Leukocyte Count as Predictor of Angiographic Findings and Clinical Events in Non-ST-Segment Elevation Acute Coronary Syndromes. Sub-analysis of the PACS Angiographic Study

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ABSTRACT

Background

Previous studies have analyzed the relationship between inflammatory markers and acute coronary syndromes. Prognosis in Acute Coronary Syndromes (PACS) was a prospective, multicentric study conducted between January 2000 and May 2002 in 11 coronary care units of Argentina. It determined the prognostic value of different biomarkers, alone or in combination, to stratify risk in patients with non-ST-segment elevation acute coronary syndromes (NSTEMACS). However, there are few studies on the relationship of increased leukocyte levels with angiographic findings and mid-term events.

Objective

The aim of the study was to establish whether leukocyte count at admission is associated with complex coronary disease and adverse prognosis at 6-month follow-up in patients with NSTEMACS.

Methods

The angiographic PACS substudy was conducted in 1253 patients from the core PACS study cohort (with a total population of 1500 patients) and it included centers with coronary angiography facilities (CA). Out of the 1253 substudy patients, CA was performed in 633 patients (50.5%) (mean of 48 hours after admission, percentiles 25-75, 24-72 hours).

To perform the sub-analysis, complete data were obtained from 580 patients (46.2%). In this group, leukocyte count within 24 hours of admission was analyzed in addition to tests performed in the biomarker PACS protocol. The population was divided in percentiles according to admission leukocyte count. Patients with initial leukocytes $< 7700/\text{mm}^3$ were included in the lower percentile, patients with leukocyte count between 7700 and $11500/\text{mm}^3$ in the middle percentile and those with leukocyte count $> 11500/\text{mm}^3$ in the higher percentile.

Results

Most of the 580 patients were men (72.9%), and mean age was 66 ± 12 years. Among these patients, 64.4% had history of hypertension, 17.9% of diabetes, 22.2% of previous infarction, 60% presented high clinical risk (ACC/AHA) and 61.1% had ECG at admission with ST-segment or T wave alterations. Leukocyte count $> 11500/\text{mm}^3$ was associated with higher rate of visible thrombus, presence of complicated plaque and more extensive coronary disease ($p = 0.019$, 0.033 and 0.07 , respectively). At the 6-month follow-up, patients in the higher percentile had greater tendency of death or infarction than patients in the lower percentile (14.2% vs. 7.5%; $p = 0.026$).

Conclusion

In patients with NSTEMACS, a high leukocyte count at admission is associated with complex coronary disease and worse prognosis at 6 months.

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Key words

> Acute Coronary Syndromes - Leukocytes - Coronary Disease

Abbreviations

AMI	Acute myocardial infarction	NSTEACS	Non-ST segment elevation acute coronary syndrome
BNP	Brain natriuretic peptide or type B	PTCA	Percutaneous transluminal coronary angioplasty
CA	Coronary angiography	TNF-α	Tumor necrosis factor alpha
CRP	C-reactive protein	Tn T	Troponin T
ECG	Electrocardiogram	WBC	Leukocytes
IL	Interleukin		
MRS	Myocardial revascularization surgery		

INTRODUCTION

Inflammation has been related to atherogenesis and in recent studies it has been associated with the pathogenesis of acute coronary syndromes. (1-4) Elevation of systemic inflammatory markers as C-reactive protein (CRP) is associated with coronary atherosclerosis, (3) with a significant increase of patients with acute coronary syndromes. (4-6) It has been recently demonstrated that inflammatory markers are potent predictors of major clinical events (6-8) in patients with non-ST-segment elevation acute coronary syndromes (NSTEACS).

However, the relationship between inflammatory marker levels and angiographic findings in patients with NSTEACS is still controversial, based on studies with a limited number of patients. (4, 9, 10)

The purpose of this study is to establish whether leukocyte level at admission in patients with NSTEACS is related with complex coronary lesions and adverse outcome at 6 months.

METHODS

Prognosis in Acute Coronary Syndromes (PACS) was a cohort, prospective, multicentric study performed in Argentina between January 2000 and May 2002 which included 1500 consecutive patients admitted for NSTEACS in 11 coronary care units (see Appendix) to assess the prognostic value of a multimarker strategy [ultrasensitive CRP, troponin T (Tn T), myoglobin and brain natriuretic peptide (BNP)] at hospital admission. (11, 12) The angiographic PACS substudy (10) was conducted in a subgroup of 1253 patients of the core PACS study cohort (total n = 1500 patients) corresponding to centers with coronary angiography facilities (CA). Out of the 1253 substudy patients, CA was performed in 633 patients (50.5%) (mean of 48 hours after admission, percentiles 25-75, 24-72 hours). For the present subanalysis complete data were obtained from 580 patients (46.2%).

Inclusion criteria in the PACS study were angina at rest within 24 hours of hospital admission. Patients with secondary angina, persistent ST-segment elevation, those who were candidates for reperfusion therapy and patients with percutaneous coronary intervention or myocardial revascularization surgery (MRS) within 6 months prior to enrollment were excluded from the study. In addition, patients presenting conditions that might alter biomarker results (active infection within the 2 previous weeks or chronic inflammatory diseases or cancer) were also excluded from the study.

Predefined events (12) at 180 days comprised a composite of death for any cause or new non-fatal myocardial infarction, the latter as new episode of angina and characteristic electrocardiographic changes (ST/T changes or new Q waves) and peak CK twice the upper normal limit or after

percutaneous transluminal coronary angioplasty (PTCA) for new Q waves or CK three times above normal and after MRS for new Q waves. All patients were followed-up for 180 days since hospital admission or up to event occurrence [non-fatal acute myocardial infarction (AMI) or death]

Coronary angiographies were evaluated in a central angiographic laboratory following a pre-specified protocol. Two interventional cardiologists reviewed the studies blinded to leukocyte level (WBC) or clinical outcome. When reviewers were in disagreement, a third party defined lesion characteristics. A complex coronary lesion was defined as presence of at least one of the following characteristics: 1) intracoronary thrombus, 2) ulcerated plaque or 3) abnormal TIMI flow. Coronary lesions were also classified according to their complexity in types A, B1, B2 or C conforming to the American College of Cardiology/American Heart Association classification. (13). Coronary disease extension was determined according to the number of involved vessels.

Troponin-T, ultrasensitive CRP, myoglobin and BNP were determined in all patients (samples were stored in a freezer at -70 °C, and read at a central laboratory in agreement with the PACS protocol). All patients had a complete WBC count as part of routine tests at admission in each center and were divided into percentiles according to their initial WBC count. Patients with initial WBC count < 7700/mm³ were considered in the lower percentile, patients between 7700 and 11500/mm³ in the middle percentile and those > 11500/mm³ in the higher percentile. Blood samples were taken between 8 and 12 hours after the last chest pain determining hospital admission. Researchers were blinded to the results of specific protocol measurements until the end of the study.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and percentile range according to their distribution. Goodness of fit tests were used to analyze normal distribution. The chi-square test was used to compare categorical variables. The analysis of cumulative incidence of death or infarction at 180 days was performed using the Kaplan-Meier method and compared with the log rank test. Finally, a multiple logistic regression analysis was performed where death or non-fatal myocardial infarction at 180 days was the dependent variables and basal characteristics (Table 1), biomarkers (Tn T, CRP and myoglobin) and WBC count at admission were the independent variables. A p value < 0.05 was considered statistically significant for two-tailed tests. Statistical analyses were performed with the SPSS software package, version 10.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Most of the 580 patients included in the subanalysis were men (N = 423; 72.9%), with mean age of 66

years (± 12). Among these patients, 374 (64.4%) had history of hypertension, 104 (17.9%) of diabetes, 129 (22.2%) of previous myocardial infarction, 180 (31%) of smoking, 75 (12.9%) of previous angioplasty, 62 (10.6%) of previous MRS and 348 (60%) of high clinical risk (ACC/AHA). The admission ECG showed ST-segment/T alteration in 61.1% of patients. In-hospital treatment was: 99% aspirin, 21.3% clopidogrel, 91% beta-blockers, and 68.5% heparin. Revascularization at 180 was: PTCA in 318 patients (72.4%) and MRS in 121 patients (27.5%). The incidence of adverse events (AMI or death) was 9.8% (57 patients: 31 had non-fatal AMI and 26 died). Median population WBC count was 9300/mm³ (range between 3500 and 37000). Table 1 details patient characteristics grouped according to the initial WBC count and divided into percentiles. Patients with initial WBC count < 7700/mm³ were included in the lower percentile, patients between 7700 and 11500/mm³ in the middle percentile and those > 11500/mm³ in the higher percentile. There was greater prevalence of men smokers in the higher percentile and of previous angina in the lower percentile.

Table 2 shows CA findings. The higher percentile WBC count was associated with greater rate of visible thrombus, presence of complicated plaque and greater extension of coronary disease ($p = 0.019, 0.033$ and 0.07 , respectively).

Figure 1 depicts the relationship between complicated plaque and intracoronary thrombus angiographic findings and percentile initial WBC count. In the higher percentile group of patients, thrombus

incidence was 23.4% and complicated plaque 51% ($p < 0.03$ and < 0.019 , respectively). Figure 2 illustrates the relationship between WBC levels and markers of necrosis (myoglobin and Tn T) and inflammation (ultrasensitive CRP).

During the 180-day follow-up, independent predictors (including demographic variables and WBC count) of AMI or death were age, history of diabetes and WBC count (Table 3). Upon addition of biomarkers to the multivariate model, WBC levels were not significant (Table 4).

The 6-month clinical follow-up analysis (Figure 3) showed a tendency of greater risk of AMI or death in the group of patients in the higher percentile (14.2%, $n = 20$) compared with the lower percentile (7.5%, $n = 11$; $p = 0.026$); however, there was no significant difference between patients in the intermediate and higher percentiles.

The analysis of the population according to the pre-established CRP cut-off level ($>$ or $<$ 3 mg/dL) in the PACS protocol showed that in the higher percentile WBC count added significant prognostic information (Figure 4).

DISCUSSION

The present study shows that elevated WBC count at admission in patients with NSTEMI correlated with angiographic findings (more anatomical complexity) and, as shown in Figure 4, added prognostic information of greater risk of myocardial infarction or death in the 6-month follow-up of the subgroup of patients

Table 1. Demographic and clinical characteristics according to leukocyte count

	Low (n = 146) n (%)	Intermediate (n = 293) n (%)	High (n = 141) n (%)	p
Age > 65	41 (28.1)	70 (23.9)	30 (21.3)	ns
Male	90 (61.6)	223 (76.1)	110 (78)	0.002
HT	91(62)	190 (65)	93 (66)	ns
DM	22 (15.1)	52 (17.7)	30 (21.3)	ns
Smoking	31 (21.2)	88 (30)	61 (43.3)	0.001
Dyslipidemia	96 (66)	163 (55.6)	83 (59)	ns
Previous chest pain	72 (49.3)	100 (34.1)	45 (31.9)	0.003
Previous AMI	31 (21.2)	70 (23.9)	28 (19.9)	ns
Previous angioplasty	22 (15.1)	35 (11.9)	18 (12.9)	ns
MRS	14 (9.6)	37 (12.6)	11 (7.8)	ns

ns: Not significant. HT: Hypertension. DM: Diabetes mellitus. AMI: Acute myocardial infarction. MRS: Myocardial revascularization surgery.

Table 2. Coronary angiography findings according to leukocyte count

	Low (%)	Intermediate (%)	High (%)	p
Angiographic findings				
Complicated plaque	36.3	46.4	51.1	0.033
Presence of thrombus	11	19.1	23.4	0.019
Three-vessel disease	17.8	25	29.3	0.07

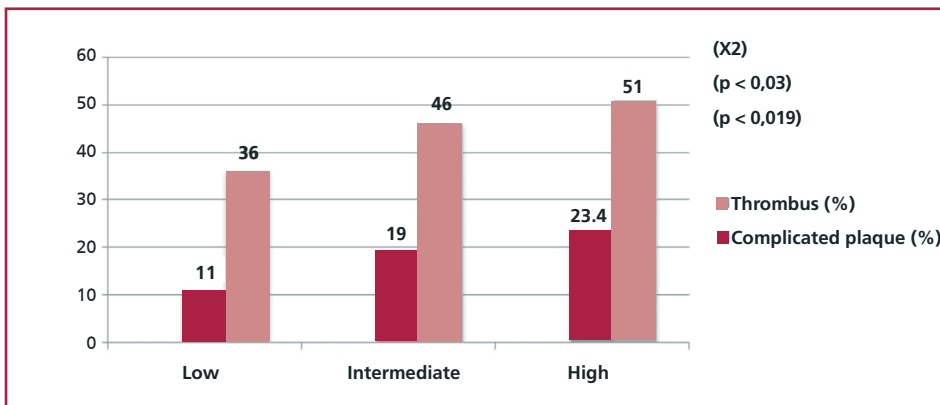


Fig. 1. Angiographic findings of thrombus and complicated plaque according to leukocyte count.

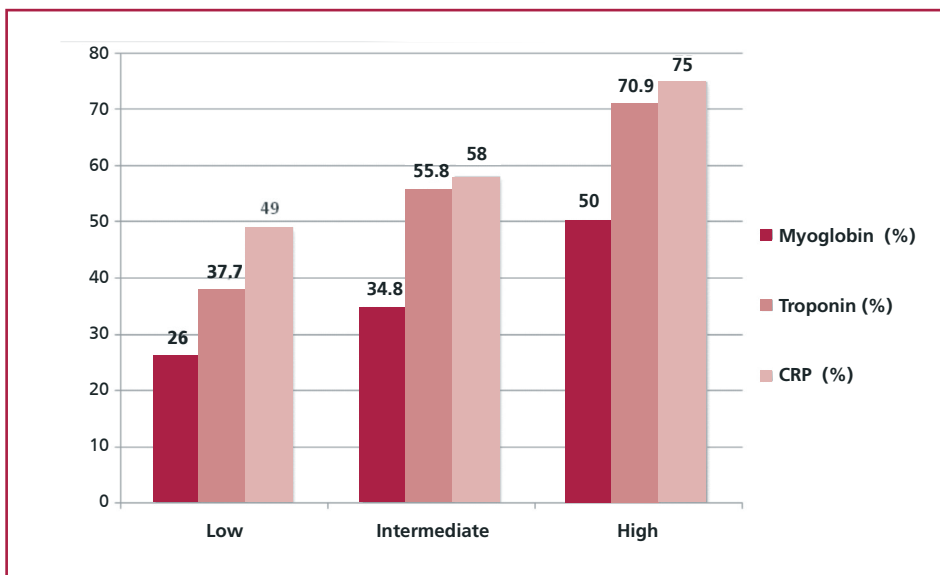


Fig. 2. Relationship between serum markers and leukocyte count

	OR	95% CI	p
Clinical variables / AMI / 6-month mortality			
Age	3.68	2-6.7	0.001
Diabetes	3.81	2-7	0.001
Leukocytes	2.07	1.11-3.8	0.02

Table 3. Multivariate analysis

	OR	95% CI	p
Clinical variables / AMI / 6-month mortality			
Age	3.29	1.8-6	0.0001
Diabetes	3.78	2-7	0.0001
Troponin 0.03	3.08	1.5-6.2	0.002
CRP > 3	2.2	1.1-4.8	0.05

Table 4. Multivariate analysis

with elevated CRP. This is an interesting finding as CRP (as inflammation marker) in previous studies on this same population was not significantly associated to anatomical findings and prognostic value. (10)

Inflammation is part of the atherogenic process described more than thirty years ago, (14, 15) but the prognostic value of multiple serologic markers has only been recently mentioned in NSTEMACS. (1, 6, 7, 11, 12, 16-19)

Although some of the results have been reported in previous studies showing the importance of leukocytes after a coronary event, few studies have analyzed angiographic findings and their correlation with clinical events. Nuñez et al. (20) established correlation between WBC count and clinical events; yet, they did not analyze anatomical findings. Conversely, Brunetti

et al (19) showed significant correlation between CRP and major cardiovascular events similarly to Ray's group (5), but were unable to demonstrate correlation with anatomical complexity, comparable to Navarro Estrada et al's findings. (10)

Recently, Brunetti et al., (4) using sophisticated inflammatory markers (IL-2, IL-8, TNF- α and interferon), found significant correlation between anatomical findings and clinical events in the acute phase of NSTEMACS.

Ultrasensitive CRP is a well-known marker of inflammatory activity in the acute and chronic phase of coronary disease. (3, 7, 15, 16, 21) Some limitations as cost, availability and complex assessment prompted leukocyte analysis, as its determination is very accessible, reproducible and low cost. (22)

A limitation of leukocytes as acute phase reactant is their low specificity and lack of systematic studies of WBC (9) in NSTEMACS to define cut-off points, kinetics and application to daily life. On the other hand, this is an observational, multicentric analysis without randomized sampling. In addition, the present substudy was not designed to evaluate the end points analyzed here (11, 12) (post hoc analyses with the limitations these observations have).

It is possible that the widespread availability, low cost and feasibility will turn leukocyte count into a tool (8) that would add prognostic information to clinical variables and well-known markers. (12)

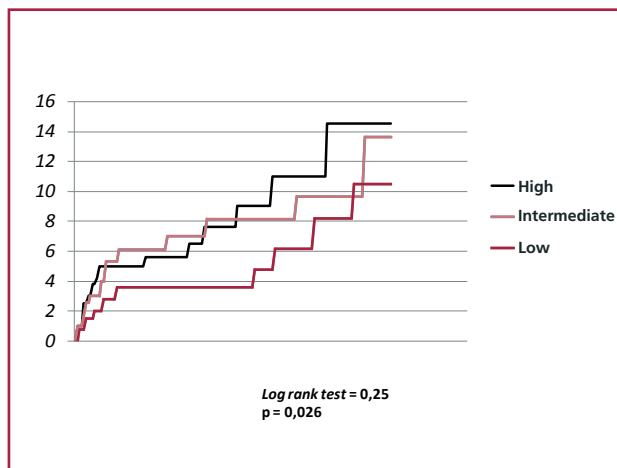


Fig. 3. Relationship between cumulative incidence of death/myocardial infarction at 180 days and leukocyte count. Patients in the higher percentile doubled the risk of infarction or death at 180 days compared with the lower percentile (14.2% vs. 7.5%; $p = 0.026$).

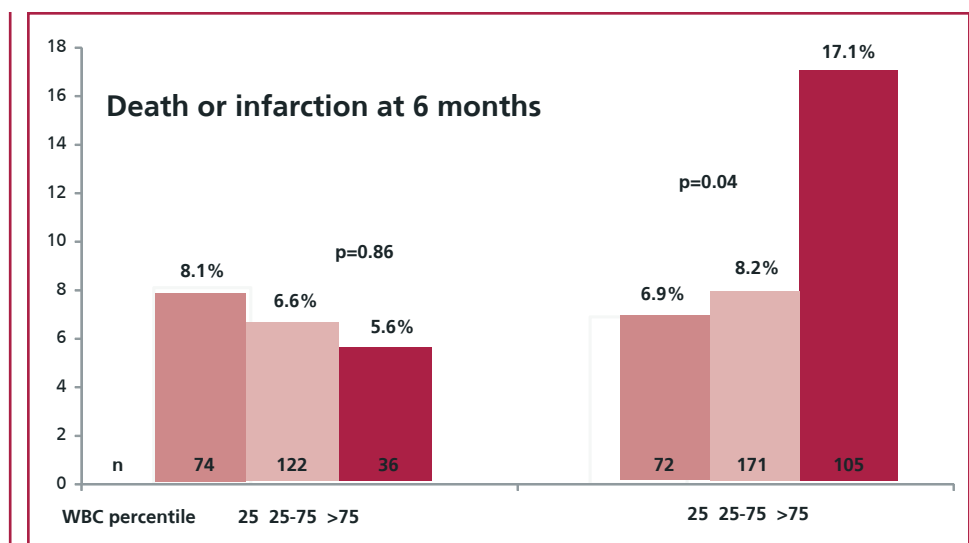
CONCLUSION

Elevated leukocytes at admission in patients with NSTEMACS were associated with more complex coronary lesions (greater presence of thrombi and complicated plaques) and worse clinical prognosis at 180 days.

Clinical implication

As seen in this subanalysis, given their special availability and feasibility, leukocytes could become a tool

Fig. 4. Incidence of death or myocardial infarction at 6 months according to CRP level ($> 0 < 3$ mg/dL) and leukocyte (WBC) percentile.



providing additional prognostic information in subgroups of patients with NSTEMI who are at greater risk, though a larger number of studies in randomized patients is required.

RESUMEN

Recuento de glóbulos blancos como predictor de hallazgos angiográficos y eventos clínicos en los síndromes coronarios agudos sin supradesnivel del segmento ST. Subanálisis del estudio PACS angiográfico

Introducción

La relación entre los marcadores inflamatorios y los síndromes coronarios agudos se ha estudiado previamente. PACS (Prognosis in Acute Coronary Syndromes) es un estudio prospectivo multicéntrico que se desarrolló entre enero de 2000 y mayo de 2002 en 11 unidades coronarias de la Argentina e incluyó pacientes con síndrome coronario agudo sin elevación del segmento ST (SCASEST) con el objetivo de determinar el valor pronóstico de los diferentes biomarcadores, solos o en combinación en la estratificación de riesgo. Sin embargo, la relación de la elevación de leucocitos con los hallazgos angiográficos y los eventos a mediano plazo se ha estudiado escasamente.

Objetivo

Determinar si el nivel de leucocitos al ingreso se relaciona con lesiones coronarias complejas y pronóstico adverso a los 6 meses en pacientes internados con SCASEST.

Material y métodos

El subestudio PACS angiográfico comprendió un subgrupo de 1.253 pacientes de la cohorte del estudio PACS central (cuya población total fue de 1.500 pacientes) e incluyó centros con disponibilidad de cinecoronariografía (CCG). De los 1.253 pacientes del subestudio, se realizó una CCG (media de tiempo 48 horas del ingreso, percentiles 25-75, 24-72 horas) en 633 (50,5%).

Para el presente subanálisis se obtuvieron datos completos de 580 pacientes (46,2%). En estos, además de lo establecido en el protocolo PACS de biomarcadores, se analizó el recuento de leucocitos en sangre dentro de las 24 horas de la admisión. La población se dividió en percentiles según el recuento leucocitario al ingreso. En el percentil inferior se incluyeron los pacientes con un recuento inicial de glóbulos blancos < 7.700/mm³, en el percentil intermedio los pacientes con un recuento de entre 7.700 y 11.500/mm³ y en el percentil superior aquellos con > 11.500/mm³.

Resultados

De los 580 pacientes, la mayoría eran hombres (72,9%), edad media de 66 años (\pm 12). Tenían antecedentes de hipertensión el 64,4%, de diabetes el 17,9%, historia de infarto previo el 22,2%, riesgo clínico alto (ACC/AHA) el 60% y el electrocardiograma de ingreso mostró alteración del segmento ST o T en el 61,1%. El recuento de leucocitos superior a 11.500/mm³ se asoció con una tasa mayor de trombo visible, presencia de placa complicada y mayor extensión de enfermedad coronaria ($p = 0,019$, $0,033$ y $0,07$, respectivamente). En el seguimiento a 6 meses, los pacientes del percentil superior tuvieron mayor tendencia a muerte o infarto que los pacientes del percentil inferior (14,2% vs. 7,5%; $p = 0,026$).

Conclusión

En los pacientes con SCASEST, un recuento elevado de leucocitos al ingreso se asocia con lesiones coronarias complejas y peor pronóstico a los 6 meses.

Palabras clave > Síndromes coronarios agudos - Leucocitos - Enfermedad coronaria

Conflicts of interest

None declared.

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APPENDIX

PACS study

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