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Prognostic value of inflammatory markers in acute coronary syndrome in a population with premature cardiovascular disease (RCD code: VIII)

Agnieszka Pura[1]*, Marta Wilk[1], Maria Olszowska[2]

[1] Student's Scientific Group at the Department of Social Cardiology, Jagiellonian University Medical College; [2] Department of Social Cardiology, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College

Abstract

Introduction: Inflammation plays a significant role in the development of atherosclerosis, and inflammatory markers could be used in risk assessment of patients with ischaemic heart disease. The use of such markers could be beneficial in younger patients, since in this group, prevention is more effective than treatment of myocardial infarctions, as long-term prognoses are often unfavourable. Aim: Our goal was to examine the value of inflammatory biomarkers as an assessment tool for cardiovascular risk in a population with a premature ischaemic heart disease. Materials and Methods: We analysed laboratory test results of 100 consecutive patients hospitalized in the John Paul II Hospital in Krakow, Poland between 2014–2017. Inclusion criteria was cardiovascular disease diagnosed in coronarography under the age of 55 years for women and 45 years for men. We excluded patients with incomplete data and acute infections. The remaining 90 patients were divided into groups based on the reason of admission (myocardial infarction or elective diagnostics). Results: White blood cell count (median of 6.990×10^3 per/µl in comparison to $8.535 \times 10_3$/µl) and absolute neutrophil count (median of 4060×10^3/µl and 5360×10^3/µl) were lower in the group admitted for diagnostics. Although inflammatory biomarkers (platelet distribution width, white blood cells) were within normal ranges, we observed higher values (above the medians for studied population) in the group admitted to hospital due to acute coronary syndrome. Conclusion: Inflammatory biomarkers could be useful in the assessment of cardiovascular risk in patients with a premature ischaemic heart disease. Since the measured values of the inflammatory biomarkers were within normal range in the examined population, further studies should be conducted to determine appropriate cut-off values. JRCD 2019; 4 (2): 37–41

Key words: risk assessment; inflammatory markers; premature cardiovascular disease; acute coronary syndrome

Background

Pathogenesis of atherosclerosis is a complex multifactorial process. Well-known risk factors such as hyperlipidaemia, diabetes mellitus (DM), arterial hypertension (AH), and smoking can all lead to endothelial damage with a subsequent inflammatory response. This chronic inflammatory process plays a major role in the development of atherogenic lesions by promoting recruitment and infiltration of leukocytes. Metalloproteinases, reactive oxygen species and various cytokines secreted by activated macrophages or neutrophils can weaken the atherosclerotic plaque and make it more liable to rupture. The ensuing platelet activation and thrombogenesis induced by the exposed core of the atheroma plays a central role in atherosclerosis-related conditions such as myocardial infarction or stroke [1–4].

For this reason, in addition to conventional cardiovascular risk factors such as changes in lipid profile [5], inflammatory biomarkers are also considered as a risk stratification tool [6]. These markers vary from more specific ones, such as proinflammatory cytokines or adhesion molecules, to those which could be obtained from basic laboratory tests, such as a full blood count [7].

White blood cell count (WBC) and the neutrophil-lymphocyte ratio (NLR) (a ratio of absolute value of neutrophils to lymphocytes) are markers which could indicate an inflammatory response

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* Corresponding author: Department of Social Cardiology, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College and John Paul II Hospital, ul. Prądnicka 80, 31-202 Krakow, Poland; tel. +48 12 614 22 87; fax. +48 12 614 33 32 e-mail: agnieszkapura@poczta.fm

Table 1a. Clinical characteristics of patients

Factor	All patients		Diagnostics		ACS		p-value
	Number	Percent	Number	Percent	Number	Percent	
Males	37	41%	16	33.33%	21	52.5%	0.0215
AH	65	72%	34	68%	31	77.5%	0.1463
DM	21	23%	16	32%	5	12.5%	0.0124
Smoking	58	64%	29	58%	29	72.5%	0.0707
Alcohol	6	7%	3	6%	3	7.5%	0.2966
BMI ≥ 25*	64	76%	38	77,55%	26	74.29%	0.1002
IMC > Norm	64	71%	35	70%	29	72.5%	0.2998
Neoplasms	9	10%	4	8%	5	12.5%	0.2123
Chronic inflammatory diseases	8	9%	5	10%	3	7,5%	0.2752

AH – arterial hypertension; DM – diabetes mellitus type 2; BMI – body mass index (kg/m^2); IMC – intima media complex
*percentages calculated for population with complete data (total: 84, Diagnostics: 49, ACS: 35)

Table 1b. Clinical characteristics of patients – Laboratory tests results

Factor	All patients		Diagnostics		ACS		p-value
	Number	Percent	Number	Percent	Number	Percent	
hsCRP > 3	40	44%	19	38%	21	52.5%	0.0782
LDL > 1,8	76	84%	40	80%	36	90%	0.0897
HDL < 1 for Males < 1,3 for Females	32	36%	11	22%	21	52.5%	0.0009
TG > 1,7	24	27%	12	24%	12	30%	0.2278
Total cholesterol > 4,9	30	33%	14	28%	16	40%	0.1069

hsCRP – high sensitivity C-reactive protein (mg/l,); LDL – low density lipoprotein (mmol/l); HDL – high density lipoprotein (mmol/l); TG – triglycerides (mmol/l); Total cholesterol (mmol/l); IMC – intima media complex

and imbalance in leukocyte subpopulations [8]. C-reactive protein, a protein produced in the liver in response to inflammation is another marker which has been well-studied in this regard [9]. To estimate the platelet activation and thrombogenic potential, mean platelet volume (MPV) and platelet distribution width (PDW) could be used. A larger platelet size suggests that they are more active, while greater PDW implicates a faster rate of myeloid production and replacement of used platelets [10].

Ischaemic heart disease is rare among younger patients (only 6–10% of myocardial infarctions concern population under the age of 45 [11]), however, in Europe, it is a leading cause of death in adults as young as 30 years old [12]. Developing an easily-accessible risk stratification tool could be especially beneficial for younger patients with coronary artery disease, as in this group, long-term prognoses are particularly unfavourable [13]. Such method could potentially make prevention and early reaction easier.

Methods

We included in our study 100 patients hospitalized between 2014 and 2017 in the John Paul II Hospital in Krakow, Poland. Inclusion criteria were coronary artery disease diagnosed and confirmed in coronary angiography and age under 55 years for women and 45 years for men. We performed retrospective analysis of the collected data from medical records, focusing on basic laboratory test results which were made on admission. Our exclusion criteria were incomplete medical data (those missing high-sensi-

Table 2. Laboratory tests results

Factor	All patients	Diagnostics	ACS	p-value
	median (Q1; Q3)	median (Q1; Q3)	median (Q1; Q3)	
WBC (per µl)	7.92 (6.34; 9.43)	6.99 (6.15; 8.42)	8.54 (7.72; 10.35)	0.0026
NEU (per µl)	4.69 (3.64; 6.19)	4.06 (3.18; 5.4)	5.36 (4.02; 6.91)	0.0029
LYMP (per µl)	2.06 (1.63; 2.71)	2.03 (1.54; 2.48)	2.17 (1.72; 2.84)	0.1925
PLT (per µl)	230 (205; 275)	241.5 (214; 283)	219 (179; 274.5)	0.1299
MPV (fl)	10.5 (10.1; 11.2)	10.3 (10; 11)	10.7 (10.35; 11.2)	0.1777
PDW (%)	12.4 (11.1; 13.5)	11.9 (10.9; 13.5)	12.8 (11.75; 13.6)	0.1044
NLR	2 (1.56; 3.24)	1.96 (1.56; 2.77)	2.5 (1.54; 3.62)	0.2856
hsCRP (mmol/l)	2.03 (1; 6.62)	1.76 (0.95; 4.86)	4 (1.8; 7.68)	0.0944
LDL (mmol/l)	2.73 (2.17; 3.52)	2.48 (2; 3.14)	3.06 (2.42; 3.85)	0.0384
HDL (mmol/l)	1.25 (0.99; 1.6)	1.41 (1.17; 1.74)	1.07 (0.87; 1.33)	0.0001
TG (mmol/l)	1.26 (0.93; 1.74)	1.27 (0.89; 1.69)	1.26 (1.02; 1.78)	0.4001
Total cholesterol (mmol/l)	4.47 (3.71; 5.22)	4.41 (3.54; 5.11)	4.68 (3.82; 5.32)	0.4477
Crea (µmol/l)	75 (64.8; 86)	76 (66; 87)	73 (64.4; 84)	0.3462
eGFR (ml/min/1,73m^2)	93.5 (81; 104)	90.5 (73; 99)	97 (89.5; 107)	0.0033

WBC – White blood cells count; NEU – neutrophils; LYMP – lymphocytes; PLT – platelets; MPV – mean platelet volume; PDW – platelet distribution width; NLR – neutrophils to lymphocytes ratio; hsCRP – high sensitivity C-reactive protein; LDL – low density lipoprotein; HDL – high density lipoprotein; Crea – serum creatinine; eGFR – estimated glomerular filtration rate

tivity c-reactive protein (hsCRP) and lipid panel results) and presence of acute infectious disease on admission. We divided the remaining 90 patients into 2 groups based on reason for admission to the hospital (40 with emergency admission due to treatment of acute coronary syndrome (ACS) and 50 with elective coronary artery disease diagnostics). We compared the groups in terms of sex, incidence of AH, DM, smoking status, body mass (body mass index (BMI) over > 25 kgm^{-1}), occurrence of neoplasms in past medical history, and values of hsCRP over 3mg/l and incidence of abnormalities in lipid profile.

We counted medians and quartiles of the chosen parameters obtained from a complete blood count (CBC): WBC, neutrophils (NEU), lymphocytes (LYMP), platelets (PLT), MPV, PDW and from the following biochemical laboratory test results: hsCRP, total cholesterol ratio, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), serum creatinine, and estimated glomerular filtration rate (eGFR) which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Numbers of patients with values of WBC, NLR, PDW, and MPV above the median for the studied population (for WBC 7.92×10^3/µl, NLR 2, PDW 12.4% and MPV 10.5 fl) were compared.

All statistical calculations were performed using Statistica StatSoft and Microsoft Excel. The Shapiro-Wilk test was used to assess the normality of distribution (none of the studied parameters were distributed normally). Comparative statistical analysis was performed using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Spearman's rank correlation coefficient was performed. The data are presented as median (Q1, Q3) or number and percentage when appropriate.

Results

Of the patients admitted to hospital due to ACS, 19 were women and 21 were men whereas for elective diagnostics, 34 were women and 16 were men. The median age for patients was 45 years (42; 53), for patients with ACS median age was 43.5 years (41.5; 49.5), and median age was 51 years (43; 53;) for the group admitted for elective coronary artery disease diagnostics (p=0.0018).

Only 5 patients with ACS had DM compared to 16 in the other group. Twenty-one patients with ACS had HDL level under the normal range, while only 11 patients in the group admitted for diagnostics had HDL level under the normal range. Baseline characteristics of the studied population are shown in Table 1a and Table 1b.

Analysis of laboratory test results are shown in Table 2.

CBC parameters were within normal ranges in both groups, yet we noticed that WBC and NEU levels were higher in the group with emergency admission. The calculated NLR was comparable in both groups. The level of hsCRP in the group with emergency admission was slightly above the norm for patients with high cardiovascular risk but within the normal range in the group with planned ad-

Table 3. Inflammatory biomarkers above median value for the population

Factor	All patients		Diagnostics		ACS		p-value
	Number	Percent	Number	Percent	Number	Percent	
WBC >median	44	49%	18	36%	26	65%	0.0023
NLR >median	44	49%	21	42%	23	57.5%	0.0662
MPV >median	43	48%	20	40%	23	57.5%	0.0447
PDW >median	41	46%	18	36%	23	57.5%	0.0179

mission, however this parameter did not vary significantly between groups.

Calculated medians of inflammatory indicators obtained from CBC were within normal ranges in both groups. Significantly more patients with ACS had values of PDW, MPV, and WBC above the median calculated for the studied population (23 and 18 patients for PDW; 20 and 23 for MPV; 26 and 18 for WBC) (Table 3.)

In lipid profile analysis, significant differences were observed in LDL and HDL levels. LDL values were higher in the group admitted with ACS. HDL level was lower in the group admitted for treatment of ACS with medians of 1.07 mmol/l and 1.41 mmol/l.

In Spearman's rank correlation coefficient (Rs), the only inflammatory biomarkers demonstrating a significant positive correlation to the reason of admission were WBC and NEU (Rs = 0.32 for both factors). Other correlated factors included abnormalities in the lipid profile – HDL and LDL levels (Rs = -0.42 and 0.22 respectively). Out of all the studied inflammatory markers, only hsCRP demonstrated a weak positive correlation to other coexisting factors, such as incidence of chronic inflammatory diseases, AH, or BMI (Rs = 0.24; 0.21; 0.36, respectively).

Discussion

Two of the studied inflammatory biomarkers (WBC, NEU) demonstrated a positive correlation to the occurrence of ACS at admission, which could be a result of the immunological response to myocardial infarction, as well as chronic inflammation connected with atherosclerosis. Although other tested factors did not show such a dependence, we observed an increase in their values in the group with ACS, especially that of PDW. The relatively low number of patients included in our study, while easily explained by the low incidence of premature cardiovascular disease [14], could impact some of the results. It is possible that the NLR, which showed an upward trend with p-value close to the desired range, would reach the level of significance in a larger group.

Correlation of hsCRP levels to conditions such as chronic inflammatory diseases may indicate the low specificity of this marker, which has been discussed in many previous studies [15]. Taking this fact into consideration, we decided to focus mainly on other biomarkers. Furthermore, we decided to exclude patients with acute infections to eliminate it as a cause of elevated inflammatory markers, with hsCRP being among them.

Since more women were admitted for planned diagnostics, the inclusion age criteria could explain the significant difference in the median age between groups. Such differences in patient sex distribution may be due to the protective features of oestrogens against the occurrence of ACS [16].

Surprisingly, DM appeared more often in patients admitted for planned diagnostics rather than those with emergency admission. This could be due to the relatively young age of the studied population and thus, a shorter duration of this disease, which usually begins in the fifth decade of life. Complications of DM need approximately 10 years to develop [17–18], so at an early stage of disease other factors may play a greater role in development in of ischaemic heart disease. It is also possible that in those patients, ACS was the first manifestation of previously undiagnosed DM.

Both LDL and HDL demonstrated differences in values between groups, but it was the latter which was more frequently statistically below the recommended normal range in the group with ACS. This indicates that in young patients, HDL level seems to be more important as a risk factor when compared to other lipid levels and should be considered more closely in patient risk management [19].

Conclusion

Inflammatory markers investigated in this study (NLR, WBC, NEU, LYMP, MPV, PDW) appeared to have higher values in patients with ACS. Since no NLR cut-off value for assessing cardiovascular risk is established and the assumed normal ranges vary from study to study, further research in this field is required [20–23]. In addition, inflammatory biomarkers acquired from CBC should be of interest, because even though they were within normal ranges in the studied population, they showed a positive correlation with incidence of ACS. This could be useful to identify patients at high risk for ACS, which would allow for early and appropriate patient management.

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