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White blood cells count and its populations in patients with acute coronary syndromes and co-morbidities.

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ABSTRACT

INTRODUCTION: Acute coronary syndromes (ACS) and sudden death cause most ischemic heart disease (IHD)-related deaths, which represent 1.8 million deaths per year, with similar numbers of men and women dying from coronary artery disease (CAD). It's known that inflammation plays crucial role in atherosclerotic plaque formation and its destabilization. The purpose of this study is to evaluate of white blood cells count in its subpopulation in patients with ACS and modifiable cardiovascular risk factors – arterial hypertension and 2 type Diabetes Mellitus (DM).

MATERIAL AND METHODS: In this observational cohort trial we observed of 184 patients with ACS. All patients were randomized into four groups: 1st group - 42 patients with ACS without arterial hypertension (AH) or DM; 2nd group – 56 patients with ACS and previous AH; 3rd group – 42 patients with ACS and 2 type DM; and 4th group – 44 patients with ACS and AH and DM. We studied of leukocytes count and their subpopulations in blood.

RESULTS: The mean white blood cells count was significant higher in patients with ASC, compared with control group: 8.23 [6.50; 9.40] vs 5.49 [5.20; 5.70] ($p<0.001$). Similarly, ACS caused increase of leukocytes subpopulation count in blood. The significant higher count of white blood cells was observed in patients with ACS and co-morbidities: 2 type DM and its association with AH. In patients with ACS and previous AH we observed significant lower neutrophils count ($p<0.05$), but increased quantity of lymphocytes, compared with patients with ACS without co-morbidities ($p<0.001$). DM and its association with AH was characterized of neutrophils, lymphocytes and monocytes counts growth.

CONCLUSIONS: ACS is characterized of raised white blood cells count and its population, especially in cases of association with 2 type Diabetes Mellitus.

KEY WORDS: Acute coronary syndrome, white blood cells, hypertension, diabetes mellitus.

INTRODUCTION

Cardiovascular diseases (CVD) cause, approximately, one-third of all deaths in the world: nearly 7.5 million deaths are estimated to be due to ischemic heart diseases (IHD) or coronary artery diseases (CAD), more than twice that caused by cancer [1]. In Europe, cardiovascular deaths account for nearly 50% of all deaths, over 4 million each year [2]. Acute coronary syndromes (ACS) and sudden death cause most IHD-related deaths, which represent 1.8 million deaths per year, with similar numbers of men and women dying from CAD [1]. In the United States, it is estimated that each year approximately 660,000 individuals have a new coronary attack, over 300,000 persons have a recurrent attack, and that 160,000 silent myocardial infarctions occur [3].

Identification of the association between risk factors and CAD allowed the implementation of preventive strategies. Poor control of modifiable risk factors is responsible for a large proportion of mortality and morbidity worldwide. The impact of risk factor modification was highlighted in a population analysis of 6518 men from the Seven Countries Study, in which participants were assessed over a 50-year follow-up. Country cohorts showing long-term decreases in risk factors had a consistent decrease of coronary heart disease mortality during follow-up. In contrast, among participants whose risk factors increased, hazard rates also increased [4].

Arterial hypertension (AH) and type 2 diabetes (DM) are common comorbidities. AH is twice as frequent in patients with DM compared with those who do not have diabetes; and these modifiable cardiovascular factors are in high risk of ACS. It's known that inflammation plays crucial role in atherosclerotic plaque formation and its destabilization. Accumulating data demonstrate that in patients with ACS, elevated levels of circulating inflammatory markers predict an unfavorable cardiovascular outcome. A better knowledge of the molecular and cellular mechanisms of inflammation might not only further improve prognostic stratification but also allow us to identify novel therapeutic targets.

The purpose of this study is to evaluate of white blood cells count in its subpopulation in patients with ACS and modifiable cardiovascular risk factors – arterial hypertension and 2 type Diabetes Mellitus.

MATERIAL AND METHODS

In this observational cohort trial we observed of 184 patients with ACS in period from 1 January 2020 to 30 December 2020, which were hospitalized at Ivano-Frankivsk Regional Cardiology Center or Ivano-Frankivsk Central City Hospital (Ukraine). The diagnosis was verified by laboratory and instrumental methods according to European Society of Cardiology guidelines (2017, 2020) [5,6]. All patients were randomized into four groups: 1st group - 42 patients with ACS without AH or DM; 2nd group – 56 patients with ACS and previous AH; 3rd group – 42 patients with ACS and 2 type DM; and 4th group – 44 patients with ACS and AH and DM. 30 apparently healthy persons were included into control group. We studied of leukocytes count and their subpopulations in blood at admission. The mean duration of time interval from the onset of heart attack symptoms to admission in emergency unit was 02:23'(02:07') (h:m [SD]).

The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline. The study was approved by the local ethics committee (decision from 20 December 2020) and written informed consent was obtained from all patients. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standart error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ^2 test and continuous variables by the t test or the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with Statistica system software, version 12.0.

RESULTS

The mean age of all observed patients with ACS was 64.6±11.9 years; 93 (50.5%) were males and 91 (49.5%) females among them (Table 1). ACS without persistent ST segment elevation was diagnosed in 44 (23.9%) cases; instead ACS with persistent ST segment elevation – in 140 (76.1%) cases. 63 (34.2%) patients were identified as current smokers.

Table 1. Baseline characteristic of observed patients with ACS.

Patients	Total (n=184)
Average age, years	64.6±11.9
Male sex, n (%)	93 (50.5%)
Female sex, n (%)	91 (49.5%)
Average age in males, years	70.3±11.3
Average age in females, years	62.5±11.5
Current smoker, n (%)	63 (34.2%)
nSTE-ACS, n (%)	44 (23.9%)
STE-ACS, n (%)	140 (76.1%)
Inferior STEMI	39 (27.9%)
Inferior-lateral STEMI	10 (7.1%)
Anterior STEMI	21 (15.0%)
Anterior-lateral STEMI	70 (50.0%)

Females with ACS were younger than males: 62.5±11.5 years vs 70.3±11.3 years (p<0.001), but these syndromes more often occurred in males aged before 50 years old: in 21 (22.6%) cases vs 2 (2.2%), respectively (χ^2= 17.471; p<0.001).

ACS with persistent ST segment elevation more often was presented as anterior-lateral myocardial infarction with persistent ST segment elevation (STEMI) – in 70 (50.0%) cases. Other walls of left ventricle were injured in 39 (27.9%) cases – inferior wall, in 21 (15.0%) cases – anterior wall, and in 10 (7.1%) cases necrosis was localized on anterior and lateral parts of left ventricle.

The mean white blood cells count was significant higher in patients with ASC, compared with control group: 8.23 [6.50; 9.40] vs 5.49 [5.20; 5.70] ($p<0.001$). Similarly, ACS caused increase of leukocytes subpopulation count in blood (Table 2).

Table 2. White blood cells and their subpopulation count in blood.

Parameters	Observed persons	
	Patients with ACS, n=184	**Control group, n=30**
Leukocytes, x 10^9 per liter	8.23 [6.50; 9.40]	5.49 [5.20; 5.70] **p<0.001**
Neutrophils, x 10^9 per liter	5.31 [3.91; 6.22]	3.64 [3.55; 3.86] **p<0.001**
Lymphocytes, x 10^9 per liter	1.85 [1.40; 2.31]	1.41 [1.27; 1.57] **p<0.05**
Monocytes, x 10^9 per liter	0.44 [0.29; 0.56]	0.34 [0.29; 0.37] **p<0.05**

The significant higher count of white blood cells was observed in patients with ACS and co-morbidities: 2 type DM and its association with AH (Table 3).

Table 3. White blood cells and their subpopulation count in patients with ACS.

Parameters	Patients with ACS, n=184			
	ACS, n=42	**ACS+AH, n=56**	**ACS+DM, n=42**	**ACS+AH+DM, n=44**
Leukocytes, x 10^9 per liter	8.78 [6.70; 10.85]	8.47 [6.8; 10.0] p_1-p_2 >0.05	10.85 [9.72; 11.51] p_1-p_3 **<0.001**	10.51 [9.69; 11.43] p_1-p_4 **<0.001**
Neutrophils, x 10^9 per liter	6.51 [4.66; 8.36]	5.48 [4.37; 6.22] p_1-p_2 **<0.05**	8.36 [7.35; 8.57] p_1-p_3 **<0.001**	8.29 [7.21; 8.13] p_1-p_4 **<0.001**
Lymphocytes, x 10^9 per liter	1.35 [1.21; 1.49]	1.88 [1.43; 2.31] p_1-p_2 **<0.001**	1.47 [1.28; 1.65] p_1-p_3 **<0.01**	1.49 [1.30; 1.63] p_1-p_4 **<0.01**
Monocytes, x 10^9 per liter	0.31 [0.17; 0.44]	0.47 [0.32; 0.61] p_1-p_2 **<0.01**	0.41 [0.31; 0.57] p_1-p_3 >0.05	0.39 [0.29; 0.56] p_1-p_4 >0.05

In patients with ACS and previous AH we observed significant lower neutrophils count ($p<0.05$), but increased quantity of lymphocytes, compared with patients with ACS without co-morbidities ($p<0.001$). DM and its association with AH was characterized of neutrophils, lymphocytes and monocytes counts growth.

DISCUSSION

The significant increase of white blood cells count in patients with ACS at admission was detected in our study, especially in co-morbidities cases (ACS and DM, ACS, DM and AH). It's known that the elevated leukocytes count is as part of healing response following myocardial infarction as well as a predictor of adverse cardiovascular events. Several trials report that increased white blood cells count predicted increased MACE and mortality risk independently (approximately 2.5 times risk increase) [7,8].

Results of multinational, observational Global Registry of Acute Coronary Events (GRACE) trial with 8269 patients presenting of ACS showed, that increasing leukocyte count was significantly associated with hospital death (adjusted odds ratio [OR] 2.8, 95% CI 2.1-3.6 for Q4 compared to Q2 [normal range]) and heart failure (OR 2.7, 95% CI 2.2-3.4) for patients presenting with ACS. This association was seen in patients with ST-segment elevation AMI (OR for hospital death 3.2, 95% CI 2.1-4.7; OR for heart failure 2.4, 95% CI 1.8-3.3), non-ST-segment elevation AMI (OR for hospital death 1.9, 95% CI 1.2-3.0; OR for heart failure 1.7, 95% CI 1.1-2.5), or unstable angina (OR for hospital death 2.8, 95% CI 1.4-5.5; OR for heart failure 2.0, 95% CI 0.9-4.4) [9].

We identified of neutrophil count increase in patients with ACS and DM, and its association with AH. Different studies have described that elevated neutrophil counts in patient with ACS associate with worse outcome in short- and long-term perspectives [9]. In addition, neutrophils can induce vascular plugging, thereby extending infarct size associated with endothelial disruption as a consequence of released reactive oxygen species [10]. For our opinion, the higher counts of white blood cells and neutrophils in patients with concomitant DM could be indicator of high level of chronic low-grade inflammation in this cohort and predictor of worse outcome. Recent trials showed that more total leukocytes and neutrophils in diabetic patients is significantly correlated with diabetic ketoacidosis and diabetic ketosis [11], and with macroalbuminuria [12]. The increased count of lymphocytes was present in all patients with ACS and co-morbidities (with AH, with DM and their association) in our trial. Lymphocyte count, and particularly the CD4+ number, represent the regulatory arm of the immune system and have a pivotal role in modulating the inflammatory response at various stages of the atherosclerotic process [13]. On the other hand, several trials showed the low level of lymphocytes in patient with ACS and it impact to poor prognosis [14,15]. Thus, the information on the prognostic value of lymphocytes and specific lymphocyte subtypes in patient with ACS is limited and need of future investigation.

This study has some limitations. Besides the sample size, this was a double-center study, thus its results can't be fully extended to other populations. Moreover, this is an observational study and therapeutic strategies were not randomized, which could lead to a selection bias.

CONCLUSIONS

ACS is characterized of raised white blood cells count and its population (neutrophils, lymphocytes), especially in cases of association with 2 type Diabetes Mellitus.

SUPPLEMENTARY INFORMATION

Funding: *This research received no external funding.*
Institutional Review Statement: *The study was conducted according to the guidelines of the Declaration of Helsinki.*
Informed Consent Statement: *Informed consent was obtained from all subjects involved in the study.*
Data Availability Statement: *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
Conflicts of Interest: *The authors declare no conflicts of interest.*

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