White blood cell count on admission and mortality in patients treated with primary percutaneous coronary intervention (ANIN Myocardial Infarction Registry)

Leukocytoza przy przyjęciu a śmiertelność chorych leczonych pierwotną angioplastyką wieńcową (Rejestr Zawałów Serca ANIN)

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Abstract

Aim: To determine the relationship between baseline white blood cell (WBC) count, clinical characteristics and mid-, and long-term clinical outcomes in patients with ST-elevation myocardial infarction (STEMI) treated with primary mechanical reperfusion (PCI) in real-life conditions.

Methods and results: 958 consecutive prospective registry patients addmitted for primary PCI to a tertiary cardiological center followed-up clinically for one year.

One-year and 2.6-year mortality rate were 7.6 and 9.4%, respectively. A higher baseline WBC count was independent predictor of both 1-year (OR 1.09; 95% CI 1.02-1.17) and 2.6-year mortality (OR 1.06; 95% CI 1.01-1.11), as was final TIMI <3 and age >70 years. Higher baseline WBC counts were independently associated with adverse clinical characteristics reflecting patients' status on admision including Killip class >1 (p=0.033), heart rate >100/minute (p=0.015), and systolic blood pressure <100 mmHg (p=0.027).

Conclusions: WBC count independently predicts mid-term mortality in patients with STEMI treated with contemporary mechanical reperfusion. Increased WBC count on admission seem at least partly reflect patients' adverse clinical condition on admission. Our findings may support a role of WBC count in risk prediction following myocardial infarction.

Key words: myocardial infarction, percutaneous coronary intervention, leukocytes, inflammation

Streszczenie

Cel badania: Ocena związku między leukocytozą przy przyjęciu i średnio- oraz długookresowym rokowaniem u chorych ostrym zawałem serca z uniesieniem odcinka ST (STEMI) leczonych pierwotną angioplastyką wieńcową.

Metody i wyniki: Do badania włączono 958 kolejnych chorych ze STEMI przyjętych do ośrodka referencyjnego w celu leczenia metodą bezpośredniej angioplastyki wieńcowej.

Jednoroczna i średnio 2,6-letnia śmiertelność w grupie badanej wyniosła odpowiednio 7,6% i 9,4%. Wzrastające wartości leukocytozy były niezależnie powiązane ze śmiertelnością zarówno w okresie jednorocznej (OR 1,09; 95% CI 1,02–1,17), jak i 2,6-letniej obserwacji (OR 1,06; 95% CI 1,01–1,11), podobnie jak przepływ w tętnicy dozawałowej TIMI <3, wiek <70 lat, klasa Killipa >1, ciśnienie skurczowe <100 mmHg lub czynność serca >100/min.

Wyższe wartości leukocytozy były niezależnie powiązane ze zmiennymi klinicznymi wskazującymi na wyższe ryzyko, takimi jak klasa Killipa >1 (p=0,033), czynność serca >100/min (p=0,015) lub ciśnienie skurczowe <100 mmHg (p=0,027).

Wnioski: Leukocytoza jest niezależnym czynnikiem rokowniczym u chorych ze STEMI leczonych pierwotną angioplastyką wieńcową. Zwiększona leukocytoza koreluje z parametrami klinicznymi opisującymi cięższy stan pacjenta przy przyjęciu. Nasze obserwacje mogą potwierdzić rolę leukocytozy w przewidywaniu ryzyka po zawale serca.

Słowa kluczowe: zawał serca, przezskórna angioplastyka wieńcowa, leukocytoza, zapalenie

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Introduction

Baseline values of white blood cell (WBC) count have been shown to independently predict mortality of patients presenting with acute coronary syndromes (ACS), including ST elevation myocardial infarction (STEMI) [1-7]. According to our previous analysis, WBC count may predict short-term mortality in patients treated with mechanical reperfusion for STEMI [8]. However, the longer-term relation of leukocytosis and mortality is challenged by findings from Stent PAMI Trial, which suggested that the association of leukocytosis and mortality might not be present in STEMI patients treated with primary coronary revascularisation [9]. Moreover, a previous study of non-STEMI acute coronary syndromes suggested that the excess risk due to an elevated WBC count indeed might be relieved by interventional treatment [1].

Presumably, divergent inflammation related pathomechanisms may prevail with respect of short- and long-term outcomes of patients with STEMI treated with primary PCI. The pathophysiological interaction of inflammation and coronary disease is extensive, however, more specific background of association between inflammation and clinical outcome in ACS remains unclear. It is often interpreted in terms of causal relationship, in which excessive baseline inflammatory activaton may impair patient adaptation to acute heart failure associating myocardial injury [10]. However, in a case of acute coronary syndrome it is also plausible to expect that WBC count may be secondarily increased in response to severity of the acute event, or may be elevated in patients with more extesive coronary atherosclerosis or more comorbidities, therefore constituting only a marker of worse patient condition [8].

It is not known whether WBC count may be significantly associated with longer term results of STEMI patients treated with mechanical reperfusion and the relationship has not been investigated previously in unselected population of patients.

Therefore, we examined the relationship between the admission WBC count, clinical data, and mid-term mortality in STEMI patients treated with primary percutaneous intervention.

Methods

Study design and patient population

The prospective registry of 1064 consecutive patients with STEMI (ST-elevation of ≥0.1 mV in >1 limb leads or of ≥0.2 mV in contiguous chest leads or LBBB at presentation) and time from the pain onset to admission ≤12 h who were admitted between February 2001 and October 2002 for primary angioplasty was screened for patients who had their WBC count assessed on admission. In all patients primary angioplasty of the culprit lesion was attempted according to the standard techniques, following loading dose of ASA (300-500 mg) and clopidogrel (300 mg). Abciximab administration was at the discretion of physician performing the procedure, however encouraged in case of either diabetes or anterior location of the infarction. Pre- and post-procedural angiograms were analyzed by two operators and the assessment of pre- and post-procedural Thrombolysis in Myocardial Infarction flow grade in the infarction related artery, and number of diseased vessels was made by consensus. Clinical and angiographic data, including: Killip class above 1, anterior myocardial infarction location or left bundle branch block (LBBB), culprit artery TIMI 3 flow prior to coronary intervention, final TIMI 3 flow, coronary stenting, systolic blood pressure below 100 mmHg, heart rate above 100 per minute, glycoprotein IIb/IIIa use, age over 70 years, male gender, known diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary disease, previous myocardial infarction, current smoking and time from onset to admision were prospectively determined at the time of the primary procedure. Blood was drawn for WBC count after sheath insertion and prior to any coronary procedures.

The study protocol was approved by the local Ethics Commitee.

Study end point was defined as mortality at one-year follow-up.

Follow-up: Based on the files of outpatient clinic and phone calls to the examined patients or the national registry death database one-year and a mean 2.6 years follow-up information was obtained for all subjects.

Statistics

Baseline WBC count values were analysed as a continuous variable ($\times 10^9$/l). To assess the relation between WBC count and baseline clinical data multivariable linear regression was applied incorporating all baseline data with significance of $p \leq 0.10$ in univariable analysis.

Study end points were defined as mortality at one-year and a mean of 2.6 year follow-up (minimum 1 year for all subjects). Continuous data are presented as mean values with standard deviation and compared by use of Student's t-test or Mann-Whitney U test depending on the data distribution. Categorical data are presented as frequencies and analyzed with χ^2 tests. The relation between one-year mortality and clinical factors including WBC count is examined with stepwise, multivariable logistic regression incorporating all baseline data with significance of $p \leq 0.10$ in univariable analysis. Risk ratios are reported with regression model that adjust for factors that are independently associated with the outcome variable.

Estimation curve of mortality as a function of WBC count is presented graphically with Kaplan-Meier method.

Table 1. Baseline categorical characteristics and mean WBC count

Tabela 1. *Charakterystyka kliniczna badanej grupy w zależności od poziomu leukocytozy*

BASELINE CHARACTERISTICS	Mean±SD WBC count	p (multivariate analysis)
Male, 703 (73.4%) Female, 255 (26.6%)	11.68±3.60 11.68±3.89	NS
Anterior MI or LBBB, 394 (41.1%) No Anterior MI or LBBB, 564 (57.3%)	11.76±3.75 11.63±3.62	NS
Smoke current, 483 (50.4%) Non smoking, 475 (49.6%)	12.23±3.65 11.83±3.70**	0.001
Killip class >1, 113 (11.8%) Killip class 1, 845 (98.2%)	12.50±4.67 11.58±3.51**	0.033
Age >70 years, 233 (24.3%) Age up to 70 years, 725 (75.7%)	10.94±3.53 11.92±3.69*	0.029
HR >100 per minute, 91 (9.5%) HR up to 100 per minute, 867 (90.5%)	12.6±4.7 11.6±3.5**	0.015
SBP <100 mmHg, 103 (10.8%) SBP up to 100 mmHg, 855 (89.2%)	12.7±4.4 11.6±3.6**	0.027
Time of pain onset to admission<3 h, 446 (46.6%) Time of pain onset to admission above 3 h, 512 (53.4%)	12.00±3.6 11.4±3.7**	0.10
HISTORY		
Diabetes mellitus, 123 (12.8%) No diabetes mellitus, 835 (87.2%)	11.72±3.72 11.68±3.67	NS
Hypertension, 452 (47.2%) No hypertension, 506 (52.8%)	11.62±3.74 11.74±3.62	NS
Family history of coronary disease, 293 (30.6%) No family history of coronary disease, 665 (69.4%)	12.08±3.76 11.51±3.63**	0.128
Myocardial infarction, 193 (20.2%) No myocardial infarction, 765 (79.8%)	11.13±3.52 11.81±3.64	0.044
Hypercholesterolemia, 309 (32.3%) No hypercholesterolemia, 649 (67.7%)	11.43±3.75 11.13±3.61*	NS
PERI-PROCEDURAL DATA		
Glycoprotein IIb/IIIa use, 451 (47.1%) No glycoprotein IIb/IIIa use, 507 (52.9%)	11.9±3.8 11.5±3.6	NS
Baseline culprit artery TIMI 3 flow, 86 (9.0%) Baseline culprit artery TIMI <3 flow, 872 (91.0%)	11.3±4.2 11.7±3.6	NS
Final TIMI 3 flow in the culprit artery, 797 (83.2%) Final TIMI <3 flow in the culprit artery, 161 (16.8%)	11.7±3.6 11.7±4.0	NS
Coronary stenting, 733 (76.5%) No coronary stenting, 225 (23.5%)	11.8±3.6 11.4±3.8	NS
Multivessel disease, 500 (52.2%) Single vessel disease, 458 (47.8%)	11.5 ±3.6 11.9±3.8	NS

Abbreviations: MI – myocardial infarction, LBBB – left bundle branch block, HR – heart rate, SBP – systolic blood pressure
for univariate analysis: *p <0.0001, **p <0.05
Skróty: MI – zawał serca, LBBB blok lewej odnogi pęcka Hisa, HR – częstotliwość akcji serca, SBP – skurczowe ciśnienie krwi
*Dla analizy jednoczynnikowej *p<0.0001, **p<0.05*

Significance is assumed at the two-tailed p value of ≤0.05. Data analysis is performed using SPSS 9.0.

Results

Baseline characteristics

Baseline WBC counts were available in 958 (90%) of the 1064 consecutive patients in the registry. The patients with known WBC count and without known WBC count did not differ with respect to mortality (log rank p=0.8).

The baseline WBC count ranged from 3.8 to 30.7. The mean WBC count was 11.7±3.7). Higher WBC count values were observed in younger patients (<70 years old), currently smoking, with known family history of coronary disease, previous myocardial infarction, with time of pain onset to admision <3 hours, and with

adverse characteristics reflecting clinical status on admision including: Killip class >1, heart rate >100/min, and systolic blood pressure <100 mmHg (tab. 1). After adjustment for multiple variables all of the above except for family history of coronary disease and time of onset to admission were found to be independently associated with WBC count (tab. 1).

WBC count and mortality

The overall rate of mortality was 7.6 and 9.4% for one-year, and a mean of 2.6 years of follow-up respectively. WBC count was higher in patients who died up to one-year than in patients who survived (13.1±5.3 vs. 11.6±3.5; p=0.017 respectively). WBC count tended to be higher in patients who died than in patients who survived the mean of 2.6 year observational period (12.6±5.0 vs. 11.6±3.5; p=0.056).

Predictors of mortality at univariate analysis are shown in fig. 1. Independent predictors of both one-year and 2.6-year mortality at multivariate analysis included WBC count, Killip class >1, final TIMI <3, SBP <100 mmHg, HR >100/min and age over 70 years old (tab. 2).

Discussion

The primary finding of our study is the presence of significant relationship between baseline WBC count and mid-term mortality in unselected patients treated with primary PCI, which extends previous observations on STEMI patients treated with mechanical reperfusion [8, 9]. Importantly, the relationship persists after adjustment for other potential confounders. Moreover, the present study offers insight into possible relation of history or baseline clinical variables and WBC count. In our dataset higher WBC count was ascertained in younger patients, however simultaneously, already on admision presenting with more severe clinical status.

WBC count and mortality

According to our data WBC count is significantly related to mid-term mortality in patients treated with primary PCI. The current analysis constitutes extension of previously reported short-term observation, in which WBC count independently of TIMI risk score predicted 30-day mortality in STEMI treated with mechanical reperfusion [8].

Obviously short-term (acute) mortality following MI is dependent on the severity of clinical status on admission and success of reperfusion. Whereas the longer term mortality is considered, the more events may be subscribed to progression of atherosclerosis.

The relation of leukocytosis and mortality following acute coronary syndromes has been disputed since 1980's, when an elevated WBC count as a predictor of mortality post-MI was primarily observed by Schlant et al. [2]. More recently, Barron et al. have demonstrated that in the clinical trial setting of STEMI treated with thrombolysis, an elevated WBC count was associated with worse 30-day clinical outcomes [3], which was further supported by short- [4-6] and mid-term [7] mortality data covering full spectrum of ACS treated with various modes of reperfusion. However, with time, standard of reperfusion for STEMI evolved, which conceivably influenced outcome determinants. Indeed, a report of Bhatt et al. shows in the

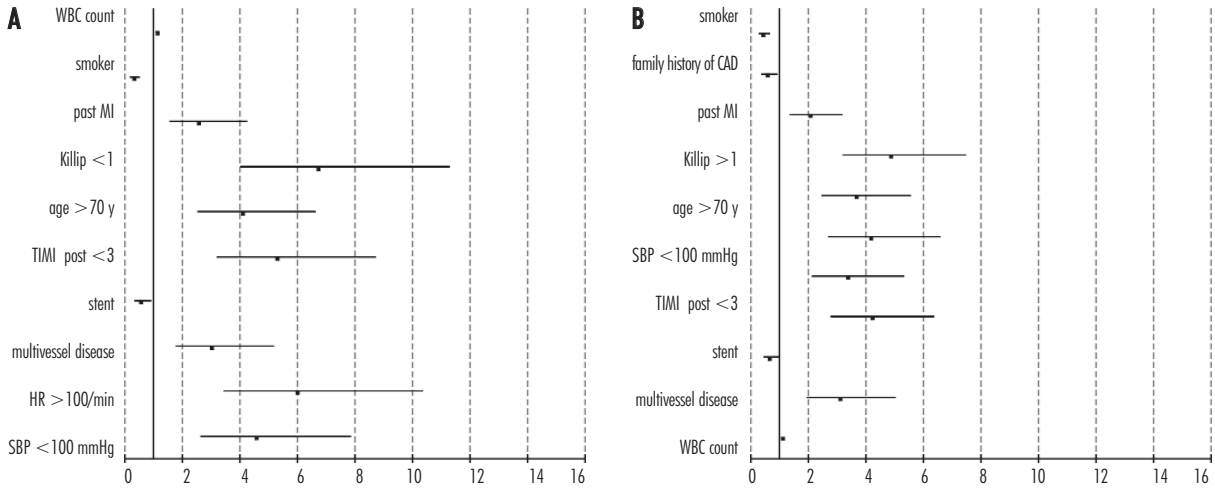

Fig. 1. Factors predictive of **(A)** one-year, and **(B)** 2.6-year death, in univariate analysis. Risk ratio plots: point estimates and 95% confidence intervals
MI – myocardial infarction, HR – heart rate, SBP – systolic blood pressure, CAD – coronary artery disease

Ryc. 1. *Czynniki związane z* ***(A)*** *jednoroczną i* ***(B)*** *2,6-letnią śmiertelnością w analizie jednoczynnikowej. Na wykresie przedstawiono iloraz ryzyka i 95% przedziały ufności*
MI – zawał serca, HR – częstotliwość akcji serca, SBP – skurczowe ciśnienie krwi, CAD – choroba wieńcowa

setting of acute coronary syndrome (non-STEMI) that the excess risk due to an elevated WBC count might be attenuated by interventional treatment [1]. Consequently, the data derived from the Stent PAMI trial failed to show any relation of WBC count and mortality in STEMI patients treated with primary angioplasty.

The second condition limiting comparability of ours with previous data concerns disparate inclusion criteria between registry versus randomised trial patients [11]. For example, in otherwise comparable to ours analysis [9], patients with known renal impairment, cardiogenic shock, lesions not eligible for stenting, or target lesion located not in the native coronary artery were excluded. The inclusion differences likely account for the discrepant results of the study, as according to our data, baseline parameters reflecting detrimental patient condition such as heart rate above 100/min, systolic blood pressure below 100 mmHg, or Killip class above 1 were all significantly realted to both WBC count and mortality.

The third difference concerns the moment blood for assessment of WBC count was collected. In a study of Kojima et al. the blood was collected within 48 hours of the AMI onset [6]. It implies a role for further confounders secondarily influencing WBC count such as worsening clinical status or no success of reperfusion, and also might preclude inclusion of some patients dying within 48 hours.

Other clinical variables independently predictive of clinical outcome in our analysis included age above 70 years, postprocedural TIMI flow below 3 in the target artery or smoking status. Those findings remain consistent with previous studies [12-17].

Clinical characteristics on admission and WBC count

Inflammatory activation is a factor imprinted into development, progression, and thrombotic complications of atherosclerosis and associated mortality. Leucocytes may be regarded as both a reflection of inflammation and probably also as a causative factor influencing clinical course of atherosclerosis [18-24]. Importantly, in the context of acute coronary syndromes a role of acute stress merits consideration, as it has been shown to augment peripheral leukocytosis [25]. However, it remains to be elucidated due to which pathomechanism leukocytosis is predominantly linked to adverse clinical outcomes follwing STEMI; specifically, whether elevated leucocytosis may be related to the causes of or merely reflect detrimental patient condition. According to our data, higher admission WBC count was observed in patients presenting with higher Killip class, heart rate above 100/min or systolic blood pressure less than 100 mmHg – factors shown previously to determine acute mortality risk following STEMI [17].

Therefore, as WBC count may be acutely increased by stress, given our data it is plausible to speculate that higher admission WBC count is to a certain extent secondary to patients' severe clinical status on admision. This relation may partly explain the association of leukocytosis and mortality, and WBC count might be simply regarded as another marker of clinical status on admision, however such an assumption requires further studies.

Consistently with some of previous studies, significantly higher WBC count values were found also in smokers and in younger patients [9, 26], however in general population higher leukocytosis is related to older age.

Table 2. Odds and hazard ratios and respective 95% confidence intervals for independent predictors of death

Tabela 2. *Iloraz szans oraz 95% przedział ufności dla zmiennych niezależnie związanych z punktem końcowym*

Variable	Odds (one-year) and hazard (for mean of 2.6 years) ratios (95% confidence interval) for mortality	
	one-year	mean of 2.6 years
WBC count	1.09 (1.02-1.17)	1.06 (1.01-1.12)
Killip class >1	3.69 (1.94-7.04)	2.57 (1.59-4.16)
Final TIMI <3	3.85 (2.15-6.91)	2.87 (1.83-4.53)
SBP <100 mmHg	2.67 (1.33-5.36)	2.18 (1.31-3.63)
HR >100 per minute	4.46 (2.30-8.65)	2.43 (1.48-3.99)
Current smoker	0.49 (0.25-0.97)	NS
Age >70 years	3.05 (1.65-5.62)	2.32 (1.42-3.80)
Multivessel disease	NS	2.04 (1.22-3.42)

Abbreviations: HR – heart rate, SBP – systolic blood pressure

Skróty: HR – częstotliwość akcji serca, SBP – skurczowe ciśnienie krwi

Limitations

There are several limitations to the present study. It is an observational investigation, and therefore can identify associations and not causality. No information on WBC differential was collected, which might be important. Moreover, more specific markers of inflammation were not measured, such as C-reactive protein. Although the association of WBC count and either mortality or other clinical variables was assessed with multivariable model, other potential significant confounders may exist that were not accounted for.

Conclusions

WBC count independently predicts mid-term mortality in patients with STEMI treated with contemporary mechanical reperfusion. Increased WBC count on admission seems at least to partly reflect patients' adverse clinical condition on admission. Our findings may support a role of WBC in risk prediction following myocardial infarction. However, the pathophysiological basis of the relationship between leucocytosis and mortality remains to be elucidated.

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