

Hemoglobin, Leukocytosis and Clinical Outcomes of ST-Elevation Myocardial Infarction Treated With Primary Angioplasty

— Anin Myocardial Infarction Registry —

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Background Hemoglobin (Hb) levels may interact with inflammatory activation, but it is unknown whether the interaction has any impact on clinical outcomes in acute coronary syndromes. The aim of this study was to assess the relationship between admission Hb levels, leukocytosis and clinical outcomes of ST-elevation myocardial infarction (STEMI) treated with primary angioplasty.

Methods and Results The study group comprised 1,904 (1,380 men) patients with STEMI treated with primary percutaneous coronary intervention, enrolled in a prospective registry. The primary endpoint of in-hospital death occurred in 90 (4.7%) patients. According to univariate analysis, extreme values of Hb (for 1st and 5th vs mid quintiles respectively: hazard ratio (HR)=7.1, P<0.001 and HR=3.2, P=0.024) and leukocytosis above median (HR=2.09, P=0.001) significantly correlated with in-hospital death. After dividing patients into high and low white blood cell (WBC) count groups, a U-shaped relationship of Hb levels and mortality was observed for patients with higher leukocytosis (1st and 5th vs mid quintiles respectively: HR=8.1, P=0.001 and HR=4.4, P=0.022), whereas in patients with lower WBC count higher mortality was related solely to the lowest Hb quintile (HR=6.9, P=0.010 vs mid quintile).

Conclusion Higher mortality associated with higher Hb levels in STEMI patients treated with primary angioplasty is limited to patients with increased leukocytosis. (*Circ J* 2009; 73: 323–329)

Key Words: Hemoglobin; Inflammation; Leukocytes; Myocardial infarction; Primary angioplasty

The association of both low and high hemoglobin (Hb) concentrations with adverse outcomes of acute coronary syndromes (ACS) is recognized in prior literature, but no previous study has examined the relationship in patients with ST-elevation myocardial infarction (STEMI) treated with primary angioplasty.^{1–5} Likewise, inflammatory activation and, in particular, high white blood cell (WBC) count is related to increased risk in those patients.^{6,7} Links between anemia and inflammation, or similar, likely synergistic impact of leukocytosis or erythrocytosis on pathophysiological mechanisms associated with adverse clinical course of ACS suggest that there is a potential interaction between WBC count and Hb and outcomes of ACS.^{3–10} Despite this, the relationship of leukocytosis and Hb concentration has not been examined in the clinical setting.

Therefore, we assessed the association between admission Hb concentration, leukocytosis and clinical outcomes of STEMI patients treated with primary angioplasty.

Methods

Study Design and Patient Population

Our study group was derived from 1,995 unselected, consecutive, prospective registry patients with STEMI (ST-elevation ≥ 0.1 mV in >1 limb leads or ≥ 0.2 mV in contiguous chest leads or new left bundle branch block at presentation) and time from pain onset to admission less than 12 h, enrolled between February 2001 and December 2004. A predefined set of data recorded in the hospital registry for consecutive patients with STEMI who are admitted for primary angioplasty includes the following clinical and procedural data: gender, age >65 years, Killip class >1, known diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary artery disease (CAD), history of prior CAD, current smoking, time from onset to admission >3 h, culprit artery Thrombolysis In Myocardial Infarction (TIMI) flow >1 prior to and after coronary intervention, multivessel disease (>1 coronary vessel with >50% stenosis on coronary angiography), coronary stenting, glycoprotein IIb/IIIa use at the time of the primary procedure, systolic blood pressure

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Table 1 Baseline Characteristics According to Quintiles of Hb

	Hb on admission, g/dl					P value
	1 st quintile 4.45–12.50 (n=388)	2 nd quintile 12.60–13.40 (n=385)	3 rd quintile 13.50–14.20 (n=361)	4 th quintile 14.30–14.90 (n=399)	5 th quintile 15.00–19.90 (n=371)	
<i>Baseline data, n (%)</i>						
Men, 1,380 (72.4)	162 (41.8)	243 (63.1)	290 (80.3)	347 (87.0)	336 (90.6)	<0.001
Age >65 years, 675 (35.5)	227 (58.5)	175 (45.9)	101 (28.1)	89 (22.5)	83 (22.5)	<0.001
Heart rate >100 beats/min, 201 (10.6)	40 (10.3)	41 (10.6)	32 (8.9)	40 (10.1)	48 (13.0)	0.353
BP <100 mmHg, 177 (9.3)	46 (11.9)	42 (10.9)	29 (8.0)	34 (8.5)	26 (7.0)	0.011
Killip class >I, 181 (9.5)	54 (13.9)	29 (7.5)	27 (7.5)	38 (9.5)	33 (8.9)	0.086
Time from onset <3 h, 628 (33.0)	126 (32.4)	129 (33.6)	152 (42.2)	166 (41.6)	146 (39.3)	0.015
Hyperlipidemia, 501 (26.3)	88 (22.7)	98 (25.5)	97 (26.9)	108 (27.1)	110 (29.6)	0.029
Diabetes, 197 (10.3)	48 (12.4)	39 (10.1)	31 (8.6)	37 (9.3)	42 (11.3)	0.528
Hypertension, 837 (44.0)	172 (44.3)	168 (43.6)	146 (40.4)	168 (42.1)	183 (49.3)	0.312
Coronary disease, 616 (32.4)	125 (32.2)	136 (35.3)	120 (33.2)	111 (27.8)	124 (33.4)	0.484
Smoking, 594 (31.2)	108 (27.8)	110 (28.6)	120 (33.2)	147 (36.8)	109 (29.4)	0.117
WBC count >median, 947 (49.8)	144 (37.2)	175 (45.5)	186 (51.5)	233 (58.3)	209 (56.5)	<0.001
Serum creatinine >1.2 mg/dl, 564 (31.4)	120 (32.9)	103 (28.1)	91 (26.7)	124 (32.8)	126 (36.4)	0.136
hs-CRP, 1.03 (0.35) mmol/L	1.87 (4.28)	1.04 (2.68)	0.97 (4.91)	0.58 (1.42)	0.82 (2.37)	0.008*
Weight, 80 (15) kg	71 (14)	77 (13)	81 (14)	84 (16)	86 (16)	<0.001
<i>Angiography intervention, n (%)</i>						
Multivessel disease, 1,027 (53.9)	222 (57.2)	224 (58.2)	187 (51.8)	193 (48.4)	201 (54.2)	0.043
TIMI flow >1 pre PCI, 292 (15.4)	49 (12.6)	56 (14.5)	53 (14.7)	66 (16.6)	68 (18.4)	0.020
TIMI flow >1 post PCI, 1,604 (84.4)	312 (80.4)	329 (85.5)	312 (86.4)	343 (86.2)	308 (83.5)	0.227
Stent, 1,603 (84.4)	306 (78.9)	328 (85.2)	311 (86.2)	338 (84.7)	320 (86.3)	0.015
IABP, 33 (1.8)	8 (2.2)	9 (2.5)	5 (1.4)	6 (1.5)	5 (1.4)	0.257
Abciximab, 921 (48.4)	170 (43.8)	184 (47.8)	183 (50.7)	197 (49.5)	187 (50.7)	0.055
In-hospital transfusion, 62 (3.3)	40 (10.3)	7 (1.8)	3 (0.8)	7 (1.8)	5 (1.3)	<0.001
Peak CK/CK-MB (times upper limit of normal), 18.2 (62.0) IU	15.3 (31.6)	14.9 (18.1)	17.3 (30.5)	16.5 (17.6)	27.2 (130.6)	0.001

Frequency (%) for categorical variables, mean (standard deviation (SD)) for continuous variables; Comparisons between groups and P values derived from Spearman's correlation for categorical variables and Pearson's for continuous variables; *916 patients available for analysis.

Hb, hemoglobin; BP, blood pressure; WBC, white blood cell; hs, high-sensitivity; CRP, C-reactive protein; TIMI, Thrombolysis In Myocardial Infarction; PCI, index event percutaneous coronary intervention; IABP, intra-arterial balloon pump; CK/CK-MB, creatine kinase/creatinine-myocardial band.

<100 mmHg, and heart rate >100 beats/min. History data are obtained on admission from patient interview. Also, a pre-defined set of hematological and biochemistry parameters is collected for each patient on admission and prior to any coronary procedures or administration of contrast media, including blood morphology, serum creatinine, creatine kinase (CK) or myocardial band of CK (CK-MB), and since 2002 high-sensitivity C-reactive protein (hs-CRP). Moreover, CK or CK-MB are routinely assessed in all surviving patients on at least 1 consecutive day following the index infarction.

Standard methods were used for blood tests. Peripheral venous blood specimens were sampled in Vacutainer™ tubes containing K-ethylenediaminetetraacetic acid and applied immediately to an automated hematology analyzer, K-4500 (TOA Medical Electronics, Kobe, Japan) for Hb concentration and WBC count.

From among the study patients, in 91 (4.6%) cases no pre-intervention blood sample was available for either logistic reasons or because of sample hemolysis prior to testing. Those patients were excluded from further analysis because contrast agent used for coronary diagnostics, potential blood loss, or dehydration might affect the examined red blood cell (RBC) parameters.

In all the patients, angioplasty of the culprit lesion was attempted using standard techniques, following a loading dose of aspirin (300–500 mg) and clopidogrel (300 mg). Primary routine management also included 0.9% NaCl infusion. Abciximab administration was at the discretion of the physician performing the procedure; however, it was encouraged in cases of either diabetes or anterior location of the

infarction. Pre- and post-procedural angiograms were analyzed by 2 operators and the assessment of pre- and post-procedural TIMI flow grade in the infarct-related artery, and the number of significantly diseased vessels was determined by consensus. Based on the hospital records, in-hospital blood transfusions unrelated to coronary artery bypass grafting were recorded for all studied patients.

Study Endpoints

In-hospital mortality was regarded as the main study outcome. The mortality data were obtained for all subjects from their hospital records.

Secondary outcomes included heart failure (HF) and a composite of death or HF, as well as a composite of in-hospital death or HF or recurrent angina or reinfarction. The incidence of acute HF onset during hospitalization was ascertained by the treating physician or was predefined as the following events based on hospital charts: signs and symptoms of either pulmonary congestion on chest radiography in the absence of a noncardiac cause, or rales in more than one-third of the lung fields attributed to pulmonary congestion, or use of furosemide to treat presumed pulmonary congestion in a patient not previously treated with furosemide, or use of balloon counterpulsation, or use of positive inotropic agents. Recurrent angina was defined as symptoms of angina occurring after the primary procedure, necessitating repeat catheterization with or without subsequent percutaneous coronary intervention (PCI). Reinfarction was defined as a combination of at least 2 of typical symptoms of ischemia recurring after the index event, new Q-waves or re-elevation of ST segment on ECG or re-elevation of cardiac specific

Table 2 Baseline Characteristics According to Occurrence of the Primary Outcome (Death)

	Death (n=90)	No death (n=1,814)	P value
<i>Baseline data, %</i>			
Men, 72.4	61.1	72.9	0.015
Age >65 years, 35.5	59.6	34.5	<0.001
Heart rate >100 beats/min, 10.6	34.4	9.4	<0.001
BP <100 mmHg, 9.3	28.9	8.3	<0.001
Killip class >1, 9.5	50.0	7.5	<0.001
Time from onset <3 h, 33.0	26.7	33.3	0.192
Hyperlipidemia, 26.3	32.2	26.0	0.192
Diabetes, 10.3	13.3	10.2	0.341
Hypertension, 44.0	48.9	43.7	0.334
Coronary disease, 32.4	51.1	31.4	<0.001
Smoking, 31.2	17.8	31.9	0.005
WBC count >median, 49.8	66.7	49.0	0.001
Serum creatinine >1.2 mg/dl, 31.4	64.2	29.8	<0.001
hs-CRP, 1.03 (0.35) mmol/L	3.3 (6.4)	0.9 (3.1)	0.012*
Weight, 80 (15) kg	82 (18)	80 (15)	0.332
<i>Angiography intervention, %</i>			
Multivessel disease, 53.9	75.6	52.9	<0.001
TIMI flow >1 pre PCI, 292 (15.4)	6.7	15.8	0.019
TIMI flow >1 post PCI, 84.4	63.3	85.4	<0.001
Stent, 84.4	75.6	84.7	0.020
IABP, 1.8	22.7	0.8	<0.001
Abciximab, 48.4	51.1	48.3	0.604
In-hospital transfusion, 3.3	15.6	2.6	<0.001
Peak CK/CK-MB (times upper limit of normal), 18.2 (62.0) IU	38.2 (190.5)	17.3 (49.6)	0.342

Frequency (%) for categorical variables, mean (SD) for continuous variables; comparison between groups with chi-square or student t-test as appropriate; *916 patients available for analysis of CRP. Abbreviations see in Table 1.

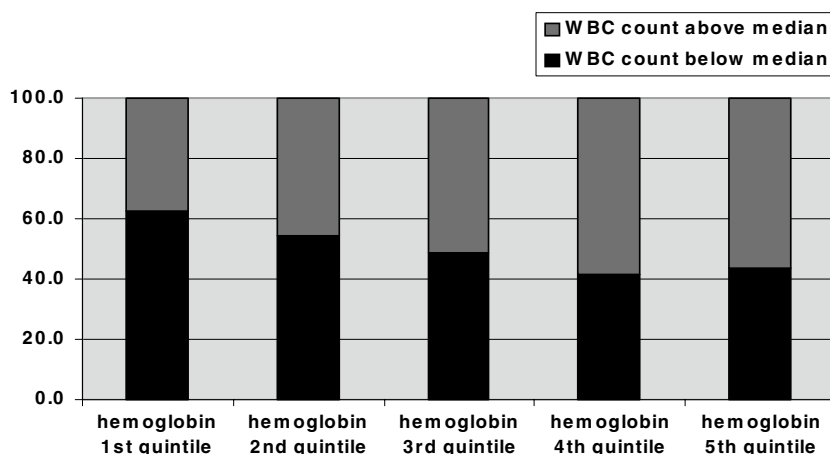


Fig 1. Hemoglobin quintiles and the proportion of patients with leukocytosis above median. Linear to linear association $P < 0.001$. WBC, white blood cell.

(CK-MB or troponin I) enzymes after confirmed initial downslope. Based on the hospital files, secondary outcomes were assessed in all patients.

The study protocol was approved by the local Ethics Committee.

Statistical Analysis

Categorical variables were summarized as percentages and compared with the chi-square test; continuous variables were compared by ANOVA or Student's t-test. Hb levels were analyzed as quintiles, whereas WBC count was dichotomized into low vs high leukocytosis about a median. Such an approach was based on previous literature suggesting a U-shaped relationship for Hb and outcomes of ACS, whereas for WBC count worse outcomes were shown to correlate with increased values. Separate univariate logistic regression analyses were performed for Hb and WBC count. Other

potential independent predictors of death were established by means of step-down modeling in a multivariate model adjusting for baseline variables (**Tables 1, 2**). Alpha was set at 0.05. Statistical analyses were performed with the SPSS (version 9.0) software package (Chicago, IL, USA).

Results

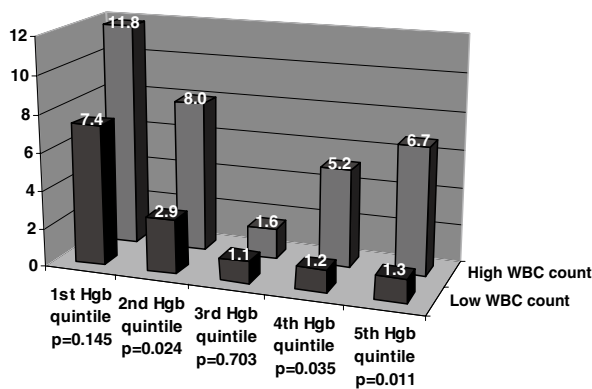
Baseline Characteristics

The study population comprised 1,904 registry patients. In-hospital death occurred in 90 patients with baseline hematological parameters available, and its frequency did not differ from the 5/91 patients without the baseline parameters available (4.7% vs 5.5%; $P = 0.774$). HF occurred in 278 (14.6%) cases, and the composite of death or HF occurred in 368 (19.4%) of the registry patients. The composite outcome of in-hospital death or HF or recurrent angina or

Table 3 Unadjusted and Adjusted HR for Respective Endpoints for Hb Quintiles: the Mid Quintile Used as the Reference

Endpoint	Hb			
	1 st quintile	2 nd quintile	4 th quintile	5 th quintile
Death				
Unadjusted HR, 95% CI	7.06 (2.73–18.23)	3.90 (1.45–10.51)	2.60 (0.93–7.28)	3.23 (1.17–8.90)
Adjusted HR, 95% CI	4.73 (1.73–12.93)	2.73 (0.94–7.92)	2.01 (0.68–5.96)	1.58 (0.51–4.84)
Heart failure				
Unadjusted HR, 95% CI	1.70 (1.14–2.53)	1.00 (0.65–1.54)	0.91 (0.59–1.41)	1.33 (0.88–2.01)
Adjusted HR, 95% CI	1.23 (0.75–2.01)	0.94 (0.57–1.57)	0.87 (0.52–1.44)	1.42 (0.87–2.31)
Death or heart failure				
Unadjusted HR, 95% CI	2.47 (1.71–3.56)	1.33 (0.89–1.97)	1.10 (0.73–1.64)	1.57 (1.06–2.31)
Adjusted HR, 95% CI	1.87 (1.20–2.90)	1.14 (0.72–1.81)	1.01 (0.64–1.61)	1.64 (1.05–2.57)
Death or heart failure or recurrent angina or reinfarction				
Unadjusted HR, 95% CI	2.13 (1.50–3.03)	1.29 (0.89–1.87)	1.12 (0.77–1.63)	1.49 (1.03–2.15)
Adjusted HR, 95% CI	1.56 (1.00–2.45)	1.18 (0.74–1.86)	1.04 (0.66–1.65)	1.39 (0.88–2.19)

HR, hazard ratios; CI, confidence interval. Other abbreviation see in Table 1.

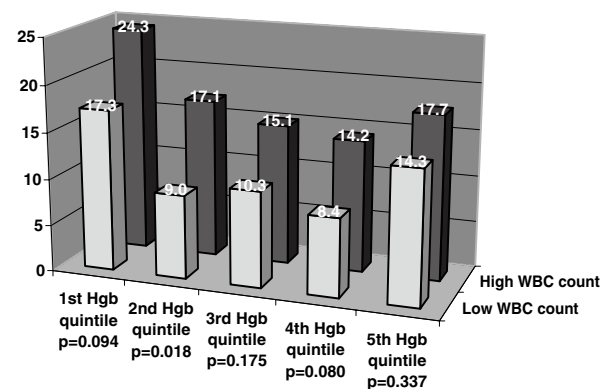


High WBC count	Hazard ratio for death vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	8.14, 2.34-28.29
2 nd quintile of hemoglobin	5.29, 1.50-18.69
4 th quintile of hemoglobin	3.32, 0.92-11.91
5 th quintile of hemoglobin	4.39, 1.24-15.48
Low WBC count	
1 st quintile of hemoglobin	6.92, 1.58-30.22
2 nd quintile of hemoglobin	2.54, 0.51-12.77
4 th quintile of hemoglobin	1.06, 0.15-7.58
5 th quintile of hemoglobin	1.10, 0.15-7.87

Fig 2. Incidence (%) of in-hospital mortality within respective quintiles of hemoglobin for patients with lower and higher white blood cell (WBC) count. Comparisons with chi-square between lower and higher WBC count within quintiles of hemoglobin. Below the chart, hazard risk and 95% confidence intervals for hemoglobin quintiles and mortality within lower and higher WBC count. Mid (3rd) hemoglobin quintile is the reference.

reinfarction occurred in 418 (22.0%) patients.

Increasing quintiles of Hb were significantly associated with male gender, lower age, higher blood pressure, shorter time from pain onset to admission, more hyperlipidemia, and less multivessel disease. Regarding the procedural variables, increasing Hb was associated with better TIMI flow in the culprit artery prior to PCI, but not afterward, more stents, less transfusions, but higher peak CK/CK-MB, suggesting more extensive infarction. Levels of hs-CRP also varied significantly according to Hb quintiles. The hs-CRP levels for lowest Hb were significantly higher than that for 4th and 5th Hb quintiles (P=0.003 and P=0.032, Bonferroni corrected



High WBC count	Hazard ratio for heart failure vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	1.81, 1.04-3.15
2 nd quintile of hemoglobin	1.17, 0.67-2.05
4 th quintile of hemoglobin	0.93, 0.54-1.61
5 th quintile of hemoglobin	1.21, 0.71-2.08
Low WBC count	
1 st quintile of hemoglobin	1.82, 1.01-3.29
2 nd quintile of hemoglobin	0.87, 0.44-1.71
4 th quintile of hemoglobin	0.80, 0.39-1.67
5 th quintile of hemoglobin	1.45, 0.75-2.81

Fig 3. Incidence (%) of in-hospital heart failure within respective quintiles of hemoglobin for patients with lower and higher white blood cell (WBC) count. Comparisons with chi-square between lower and higher WBC count within quintiles of hemoglobin. Below the chart, hazard risk and 95% confidence intervals for hemoglobin quintiles and the outcome within lower and higher WBC count. Mid (3rd) hemoglobin quintile is the reference.

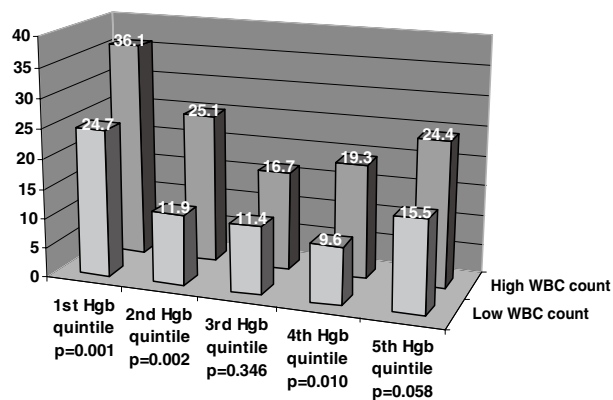
pairwise comparison) (Table 1).

The baseline WBC count ranged from 3.3 to 41.9×10³/μl. The median WBC count was 11.2×10³/μl (interquartile range 9.0–13.5×10³/μl).

Hb, WBC and In-Hospital Outcomes

Increasing Hb quintiles correlated significantly with an increasing proportion of patients with higher leukocytosis (linear to linear association P<0.001) (Fig 1).

In the univariate analysis, an increased hazard ratio (HR) of death was associated with the highest and 2 lower quintiles of Hb as compared with the mid quintile (a reverse



High WBC count	Hazard ratio for death or heart failure vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	2.83, 1.69-4.73
2 nd quintile of hemoglobin	1.68, 1.00-2.81
4 th quintile of hemoglobin	1.20, 0.72-1.98
5 th quintile of hemoglobin	1.61, 0.98-2.66

Low WBC count	Hazard ratio for death or heart failure vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	2.54, 1.47-4.40
2 nd quintile of hemoglobin	1.05, 0.56-1.96
4 th quintile of hemoglobin	0.83, 0.41-1.66
5 th quintile of hemoglobin	1.43, 0.76-2.68

Fig 4. Incidence (%) of the composite outcome (in-hospital death or heart failure) within respective quintiles of hemoglobin for patients with lower and higher white blood cell (WBC) count. Comparisons with chi-square between lower and higher WBC count within quintiles of hemoglobin. Below the chart, hazard risk and 95% confidence intervals for hemoglobin quintiles and the composite outcome within lower and higher WBC count. Mid (3rd) hemoglobin quintile is the reference.

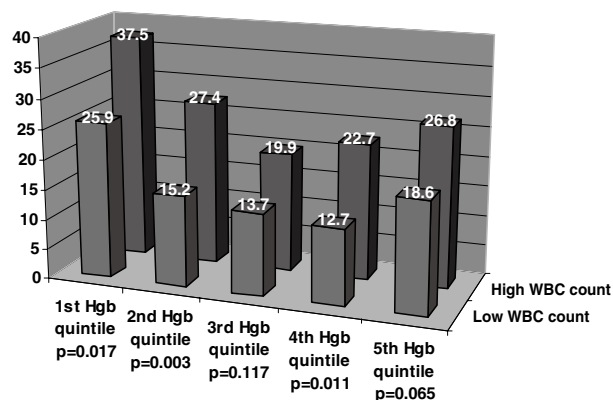
J-shaped relationship). Patients with lowest Hb more likely also had HF. Regarding the composite outcomes, patients with extreme values (1st and 5th quintiles) of Hb more likely experienced both composite outcomes as compared with patients from within the mid quintile (Table 2).

Regarding WBC count, its values above the median were associated with increased incidence of in-hospital death (HR 2.09; 95% confidence interval (CI): 1.33–3.26, P=0.001) and the incidence of HF (HR 1.50; 95%CI: 1.16–1.95, P=0.002). With respect to the composite outcomes, higher WBC count was significantly related to death or HF (HR 1.70; 95%CI: 1.35–2.14, P<0.001), and death or HF or recurrent angina or reinfarction (HR 1.64; 95%CI: 1.31–2.04, P<0.001).

Multivariate Models

The multivariate model incorporated all baseline data including Hb (quintiles), and WBC count (below/above median).

According to the multivariate model, higher in-hospital mortality was independently associated with WBC count (HR 2.01; 95%CI: 1.17–3.47, P=0.011 for values above median) and with 1st Hb quintile (P=0.008) (Q1 vs Q3–HR 4.73; 95%CI: 1.73–12.93) (Table 3). Other independent predictors of in-hospital death included Killip class >1 (HR 5.85; 95%CI: 3.39–10.07, P<0.001), heart rate >100 beats/min (HR 4.20; 95%CI: 2.37–7.42, P<0.001), systolic blood pressure <100 mmHg (HR 2.15; 95%CI: 1.16–3.99, P=0.15), TIMI >1 post procedure (HR 0.29; 95%CI: 0.17–0.51, P<



High WBC count	Hazard ratio for death or heart failure or recurrent angina or reinfarction vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	2.42, 1.48-3.96
2 nd quintile of hemoglobin	1.52, 0.93-2.48
4 th quintile of hemoglobin	1.19, 0.74-1.90
5 th quintile of hemoglobin	1.47, 0.92-2.36

Low WBC count	Hazard ratio for death or heart failure or recurrent angina or reinfarction vs medium quintile, 95% confidence intervals
1 st quintile of hemoglobin	2.20, 1.31-3.70
2 nd quintile of hemoglobin	1.13, 0.64-2.00
4 th quintile of hemoglobin	0.91, 0.49-1.71
5 th quintile of hemoglobin	1.44, 0.80-2.59

Fig 5. Incidence (%) of the composite outcome (in-hospital death or heart failure or recurrent angina or reinfarction) within respective quintiles of hemoglobin for patients with lower and higher white blood cell (WBC) count. Comparisons with chi-square between lower and higher WBC count within quintiles of hemoglobin. Below the chart, hazard risk and 95% confidence intervals for hemoglobin quintiles and the composite outcome within lower and higher WBC count. Mid (3rd) hemoglobin quintile is the reference.

0.001), serum creatinine >1.2 mg/dl (HR 2.42; 95%CI: 1.43–4.08, P=0.001), history of CAD (HR 1.78; 95%CI: 1.05–3.03, P=0.03), and age >65 years (HR 1.81; 95%CI: 1.04–3.15, P=0.037).

Occurrence of HF was associated with higher leukocytosis (HR 1.57; 95%CI: 1.15–2.15, P=0.005), but not with Hb quintiles in the multivariate model (Table 3). Other independent predictors of HF were: serum creatinine >1.2 mg/dl (HR 1.79; 95%CI: 1.30–2.46, P<0.001), age >65 years (HR 1.64; 95%CI: 1.18–2.27, P=0.003), systolic blood pressure <100 mmHg (HR 2.41; 95%CI: 1.60–3.65, P<0.001), Killip class >1 (HR 3.10; 95%CI: 2.05–4.69, P<0.001).

An increased HR of death or HF was associated with extreme values (1st and 5th quintiles) of Hb as compared with the 3rd quintile (respectively HR 1.87; 95%CI: 1.20–2.90, P=0.006 and HR 1.64; 95%CI: 1.05–2.57, P=0.031) (Table 3), higher leukocytosis (HR 1.87; 95%CI: 1.41–2.47, P<0.001), TIMI >1 post procedure (HR 0.67; 95%CI: 0.47–0.95, P=0.023), heart rate >100 beats/min (HR 1.94; 95%CI: 1.32–2.84, P<0.001), systolic blood pressure <100 mmHg (HR 3.25; 95%CI: 2.18–4.86, P<0.001), age >65 years (HR 1.91; 95%CI: 1.43–2.57, P<0.001), admission serum creatinine >1.2 mg/dl (HR 2.36; 95%CI: 1.79–3.12, P<0.001), female gender (HR 1.38; 95%CI: 1.00–1.91, P=0.050), Killip class >1 (HR 6.38; 95%CI: 4.35–9.37, P<0.001).

The composite outcome of death or HF or recurrent angina or reinfarction was independently predicted by leukocytosis (HR 1.77; 95%CI: 1.33–2.36, P<0.001), but not Hb level

(**Table 3**). Other independent predictors of the outcome included serum creatinine >1.2 mg/dl (HR 2.04; 95%CI: 1.52–2.73, $P<0.001$), Killip class >1 (HR 5.09; 95%CI: 3.41–7.59, $P<0.001$), age >65 years (HR 1.74; 95%CI: 1.29–2.36, $P<0.001$), heart rate >100 beats/min (HR 1.93; 95%CI: 1.31–2.84, $P<0.001$), systolic blood pressure <100 mmHg (HR 3.04; 95%CI: 2.03–4.54, $P<0.001$) and multivessel disease (HR 1.63; 95%CI: 1.22–2.19, $P=0.001$).

Interaction of WBC Count With Hb Level

After stratification of the study patients into groups based on median WBC count, a reverse J-shaped relationship between in-hospital death and Hb quintile was present in patients with higher WBC count, whereas in patients with lower WBC count an increased risk of events was associated only with the lower quintiles of Hb. Accordingly, patients within all but the mid Hb quintiles, with higher leukocytosis had or tended to have significantly higher mortality than respective patients with lower WBC count (**Fig 2**).

Regarding HF alone or both composite outcomes, the U-shaped relationship with the Hb quintiles was not maintained in either subgroup with low or high WBC count (event rates for 5th quintiles vs the mid quintiles did not differ significantly). However, in all subgroups there was a significant relationship between the lowest Hb quintile and the examined outcome (**Figs 2–5**).

Discussion

The main findings of our study are that both high and low Hb levels are significantly related to the prognosis of STEMI patients treated with primary angioplasty, and that the excess mortality associated with high Hb concentration is limited to those with increased baseline leukocytosis. The resulting hypothesis that leukocytosis may condition increased risk of adverse cardiovascular outcomes associated with higher Hb concentration or possibly with blood transfusion is unprecedented in the previous literature and has important therapeutic implications.

Literature Comparisons: Clinical Studies

In a broad range of ACS patients enrolled in clinical trials and treated medically for ACS, both lower and higher Hb levels have been shown to predict worse clinical outcomes! A post-hoc analysis of 2,027 patients from the CADILLAC trial showed that anemia diagnosis based on hematocrit predicted death in MI patients treated with primary angioplasty.² However, because the previously examined groups comprised selected populations, derived from clinical trials, the relationship in real life patients remains uncertain.^{2,11} According to data from 30,341 patients registered in the Myocardial Infarction Data Acquisition System database, anemia has no significant effect on 1-year mortality following MI treated medically!² A series of other studies indicate that higher RBC indices may correlate with cardiovascular outcomes; however, none of the studies reported the relationship in STEMI!³

The basic explanation of the relationship between low erythrocyte mass and worse outcomes of ACS pinpoints a possible direct impact of lower myocardial tissue oxygen delivery combined with increased myocardial oxygen demand. On the other hand, higher Hb concentrations are related to increased blood viscosity and a prothrombotic state, which in turn may affect myocardial perfusion and workload, parameters particularly critical in the setting of

ACS.^{3,6,7} Accordingly, our data indicate a positive correlation between higher Hb levels and increasing peak CK/CK-MB, which suggests increasing infarct size!⁴ Anemia or erythrocytosis may also be linked with other conditions that limit survival, such as like inflammatory, pulmonary or bone marrow diseases. However, despite its importance and possible therapeutic implications, the exact underlying pathomechanisms are not well recognized. The causal impact of low and high hematologic parameters on clinical outcomes in ACS and other critical care conditions is challenged by data showing that routine blood transfusions in anemic patients with ACS may be related to increased death rate!^{5–17}

WBC and Hb

In the present study, patients with lower leukocytosis were less likely to experience death or HF. This fact concurs with previous data correlating leukocytosis with adverse prognosis in STEMI patients treated with primary angioplasty.^{6,9,10,18,19} Interestingly, in the current study we observed that the relationship between Hb level and in-hospital mortality was significantly divergent for patients with high and low WBC counts. The adverse impact of high Hb concentration on in-hospital death was restricted to patients with high baseline leukocytosis; interestingly, there was not any trend observed for an increase in death rate in patients with higher Hb levels within the lower leukocytosis stratum.

Postulated pathomechanisms by which leukocytosis likely affects clinical course of ACS include enhancement of acute thrombosis, microvascular obstruction, increase of reperfusion injury, or facilitation of development of the systemic inflammatory response syndrome in ACS.^{9,10} Among other links of leukocytosis with STEMI outcomes, it is hypothesized that higher WBC count may reflect a more severe condition or an association with other comorbidities that convey increased risk of adverse outcomes, such as infection, malignancy, trauma, or other inflammatory disorders commonly linked to anemia. Actually, we did not find an association between higher inflammatory activation as measured by WBC count and lower Hb. On the contrary, the prevalence of higher leukocytosis was positively correlated with increasing quintiles of Hb.

Our data provide no causal relationship; however, the plausible hypothesis is that high leukocytosis may be a condition necessary for high Hb levels to affect mortality in STEMI patients treated with primary angioplasty. Such an explanation concurs with the underlying synergistic role of leuko- and erythrocytosis in cardiovascular pathology and, in particular, their role in acute thrombosis, reperfusion injury or microvascular plugging.

A possible untoward synergy of leukocytosis and erythrocytosis may have important clinical implications for several yet unresolved issues related to the acute care of patients with ACS. First, it may help to understand the mechanisms contributing to unfavorable outcomes of patients with higher RBC indices or blood transfusion, which is a problem concerning many critical care patients. If the relationship observed in our study proves to be causal, it may provide stimulus for studies of anti-leukocyte intervention, so far yielding unsatisfactory results in the clinical setting.^{9,20}

Study Limitations

First, it is an observational investigation and its construction based on prospective registry allows generation of hypothesis, but not identification of causality. Although the association of Hb level and leukocytosis and the examined

endpoints was assessed with a multivariate model, other potential significant confounders may exist that were not accounted for. To avoid the known potential impact of contrast media or course of angioplasty procedure on hematologic parameters, patients without an available baseline sample were not investigated; however, this group was relatively small (<5%) and the mortality rate was not different from the examined cohort. Importantly, our results relate to patients with STEMI diagnosis on admission, who are treated with primary PCI as the routine strategy, therefore the reference of our results to other types of ACS or those treated conservatively for the index event should be made with caution.

Conclusions

Our data indicate that higher Hb level is related to increased risk of cardiac events in STEMI patients treated with primary angioplasty. Moreover, the risk of in-hospital death associated with high Hb is limited to patients with increased leukocytosis and is not observed in those with lower WBC counts.

The authors declare that they have no competing interests.

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