Could an analysis of mean corpuscular volume help to improve risk stratification in non-anemic patients with acute myocardial infarction?

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Abstract

Background: Nowadays, when the majority of patients with acute myocardial infarction (AMI) are treated with primary percutaneous coronary intervention and modern pharmacotherapy, risk stratification becomes a challenge. Simple and easily accessible parameters that would help in a better determination of prognosis are needed. The aim of the study was to estimate the prevalence of high mean corpuscular volume (MCV, defined as MCV > 92 fL) and to establish its prognostic value in non-anemic patients with AMI.

Methods: We retrospectively analyzed the data of 248 consecutive non-anemic patients hospitalized due to AMI (median age: 65 [59–76] years, men: 63%, ST segment elevation myocardial infarction: 31%, and median left ventricular ejection fraction [LVEF]: 50%).

Results: The prevalence of high MCV was 39 ± 6% (± 95% confidence interval) in the entire AMI population. High MCV was more prevalent in males, patients with low body mass index, non-diabetics and cigarette smokers (all p < 0.05). During the 180-day follow-up, there were 38 (15%) events, defined as another AMI or death. In a multivariable Cox proportional hazard model, female gender (p < 0.01), low LVEF (p < 0.001), previous AMI (p < 0.05), arterial hypertension (p < 0.05), and high MCV (p < 0.001) were prognosticators of pre-defined events.

Conclusions: In non-anemic patients with AMI, high MCV is an independent prognostic factor of poor outcome defined as another AMI or death. (Cardiol J 2015; 22, 4: 421–427)

Key words: acute myocardial infarction, anemia, mean corpuscular volume, risk stratification
Introduction

The determination of prognosis in patients after acute myocardial infarction (AMI) has always been difficult. Nowadays, when the majority of these patients are treated with primary percutaneous coronary intervention (PCI) and modern pharmacotherapy, risk stratification has become even more challenging.

It is obvious that patients after AMI with anemia have greater cardiovascular risk [1–6], whereas in patients without anemia at admission the risk stratification remains equivocal. Easy and cheap parameters that would help in a better determination of prognosis are needed.

It is worth to mention that a complete blood count routinely performed in every patient admitted due to AMI includes a simple parameter, namely a red cell mean corpuscular volume (MCV), which potentially could be helpful in risk stratification. High MCV (macrocytosis) is known to be elevated in various conditions, regardless of concomitant anemia [7]. Several studies have addressed associations between high MCV and increased mortality, independently of anemia, in different pathologies, such as chronic kidney disease [8], acute heart failure [9], and in patients after PCI [10]. To the best of our knowledge, a prognostic value of high MCV among patients admitted due to AMI has not yet been analyzed.

Therefore, we performed the study in order to estimate the prevalence of high MCV in non-anemic patients admitted due to AMI and to establish its prognostic value.

Methods

Study population

The retrospective study was conducted among consecutive patients hospitalized due to AMI in Center for Heart Diseases, the 4th Military Hospital in Wroclaw, between May and November 2012. There were only two exclusion criteria for the purposes of this study: (1) lack of the patient’s written informed consent to participate in the study, and (2) anemia on admission. The diagnosis of AMI was established according to the third universal definition of myocardial infarction introduced by the European Society of Cardiology [11]. The study protocol was approved by the local Ethics Committee, and all subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Clinical and laboratory data

For the purposes of the following study, we analyzed the following variables in patients admitted due to AMI:

— demographic and anthropometric characteristics: sex, age, body mass index (BMI);
— characteristics of AMI: type of AMI — either ST segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI), peak troponin level, primary effective coronary revascularization;
— medical history and co-morbidities: history of previous AMI, stroke, transient ischemic attack, concomitant diabetes mellitus, arterial hypertension, nicotinism, alcohol consumption;
— left ventricular ejection fraction (LVEF) estimated visually with the use of echocardiography during first 48–72 h of hospitalization;
— standard laboratory parameters measured on admission: hemoglobin, estimated glomerular filtration rate (eGFR), gamma-glutamyl transpeptidase (GGTP), low density lipoprotein (LDL) cholesterol;
— medications administered prior to AMI: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), antiplatelet drugs, beta-blockers, metformin and statins;
— medications administered during the hospitalization and continued as post-discharge recommendations (post-AMI): ACE-I, ARB, antiplatelet drugs, beta-blockers, metformin and statins;
— MCV measured on admission.

Anemia was defined according to the World Health Organization criteria as hemoglobin < 12 g/dL and < 13 g/dL in women and men, respectively [12]. MCV was assessed with the use of Sysmex XT-4000i and Sysmex XS-1000i Hematology Analyzers (Sysmex Inc., Kobe, Japan) and calculated according to the formula: [HCT(%) / RBC (×10⁹/µL)] × 10 [13]. High MCV was defined as MCV > 92 fL (the upper limit of reference ranges in our laboratory, which is also a commonly accepted cut-off for the diagnosis of macrocytosis) [14]. Renal function was assessed using eGFR, calculated from the Modification of Diet in Renal Disease equation [15].

Survival analysis

The follow-up period of event-free survivors was 180 days. The study endpoint was considered...
another AMI or death. The follow-up information was complete in all cases and was obtained from medical records.

**Statistical analyses**

Hemoglobin, eGFR and LDL cholesterol (as continuous variables with a normal distribution) were expressed as means ± standard deviations. The intergroup differences were tested using the Student’s t-test. Age, BMI, peak troponin level, LVEF and GGTP (being continuous variables with a skewed distribution) were expressed as medians with lower and upper quartiles. The intergroup differences were tested using the Mann–Whitney U-test. Categorical variables were expressed as numbers with percentages. The intergroup differences were tested using the $\chi^2$ test.

Clinical determinants of high MCV were established using univariate logistic regression models. Univariate and multivariable Cox proportional hazard regression models were used to calculate the predictive value of high MCV and other clinical prognosticators for AMI and death. The multivariable model included all variables that had been shown to be significant ($p < 0.05$) prognosticators of another AMI and death in univariate models.

Kaplan–Meier event-free survival curves were constructed to demonstrate the effect of high MCV on cumulative survival. Differences in event-free survival rates were examined using the log-rank test.

A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistica 10 data analysis software system (StatSoft Inc., Tulsa, Oklahoma, United States).

**Results**

**Baseline characteristics of non-anemic patients admitted due to AMI**

After exclusion of 48 patients with anemia on admission, the study population consisted of 248 patients (Table 1). The median age was 65 (59–76) years, 63% of patients were men, and NSTEMI was the most common type of AMI (69%). The mean hemoglobin level was 14.0 ± 1.3 g/dL. The mean MCV was 91.4 ± 5.0 fL.

**Determinants of high MCV**

MCV > 92 fL was diagnosed in 96 non-anemic patients admitted due to AMI, which corresponds to a prevalence of 39 ± 6% (± 95% confidence interval [CI]). None of the studied subjects had MCV < 80 fL, MCV ≤ 86 fL was found in 37 subjects, MCV > 86 fL and ≤ 92 fL in 115, MCV > 92 fL and ≤ 98 fL in 76 and MCV > 98 fL in 20.

Men, patients with low BMI, those without diabetes and cigarette smokers were characterized by greater prevalence of high MCV (Table 1). High MCV was not related to alcohol consumption (Table 1).

**Survival analysis**

The proportion of patients surviving the 180-day follow-up free from another AMI or death was 85% (95% CI 80–89%).

In univariate Cox proportional hazard regression models (Table 2), the following variables were related with the increased risk of another AMI or death: female gender, advanced age, low LVEF, previous AMI, arterial hypertension, high LDL cholesterol and high MCV (all $p < 0.05$).

Female gender, low LVEF, previous MI, arterial hypertension and high MCV (all $p < 0.05$) remained significant predictors of another AMI or death in patients hospitalized due to AMI also in the multivariable model (Table 2).

The 180-day event-free survival rates were 76% (95% CI 68–85%) vs. 90% (95% CI 85–95%) in non-anemic patients admitted with AMI with high vs. normal MCV ($\chi^2 = 9.56$, $p = 0.002$) (Fig. 1). The 180-day free of death survival rates were 86% (95% CI 78–93%) vs. 95% (95% CI 91–98%) in patients with high vs. normal MCV ($\chi^2 = 5.50$, $p = 0.02$). The difference in 180-day event-free survival rates 86% (95% CI 75–97%) vs. 91% (95% CI 86–96%) in patients with MCV ≤ 86 fL vs. MCV > 86 fL and ≤ 92 fL, respectively, was not significant ($\chi^2 = 0.64$, $p = 0.41$). Neither was the difference 75% (95% CI 65–85%) vs. 80% (95% CI 62–98%) in patients with MCV > 92 fL and ≤ 98 fL vs. MCV > 98 fL ($\chi^2 = 0.16$, $p = 0.69$), respectively.

**Discussion**

Our study for the first time provides evidence on links between elevated MCV and cardiovascular risk in patients admitted due to AMI. Increased MCV (> 92 fL) has been associated with a higher incidence of subsequent cardiovascular event or death in these patients during a relatively short follow-up. Most importantly, this relationship has been demonstrated in non-anemic subjects.

MCV is one of standard blood morphology parameters assessed routinely, however, surpris-
Table 1. Baseline characteristics of non-anemic patients admitted due to acute myocardial infarction, also a comparison of those with high vs. normal mean corpuscular volume (MCV).

<table>
<thead>
<tr>
<th>Variables, units</th>
<th>All studied patients (n = 248)</th>
<th>Patients with MCV &gt; 92 fL (n = 96)</th>
<th>Patients with MCV ≤ 92 fL (n = 152)</th>
<th>Units (OR)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, yes</td>
<td>63%</td>
<td>74%</td>
<td>56%</td>
<td>Yes vs. no</td>
<td>2.23</td>
<td>1.28–3.92</td>
<td>8.04</td>
<td>0.005</td>
</tr>
<tr>
<td>Age [year]</td>
<td>65 (59–76)</td>
<td>65 (59–78)</td>
<td>66 (59–76)</td>
<td>1 ln year</td>
<td>1.04</td>
<td>0.22–4.83</td>
<td>0.002</td>
<td>0.96</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>27.6 (24.2–31.5)</td>
<td>25.8 (23.7–29.8)</td>
<td>28.4 (25.0–35.0)</td>
<td>1 ln kg/m²</td>
<td>0.10</td>
<td>0.02–0.45</td>
<td>9.00</td>
<td>0.03</td>
</tr>
<tr>
<td>STEMI, yes</td>
<td>31%</td>
<td>33%</td>
<td>30%</td>
<td>Yes vs. no</td>
<td>1.19</td>
<td>0.68–2.07</td>
<td>0.38</td>
<td>0.54</td>
</tr>
<tr>
<td>Peak troponin level [µg/L]</td>
<td>4.4 (0.9–25.3)</td>
<td>5.3 (1.4–18.6)</td>
<td>4.2 (0.7–28.0)</td>
<td>1 ln µg/L</td>
<td>1.04</td>
<td>0.92–1.17</td>
<td>0.36</td>
<td>0.55</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>50 (40–55)</td>
<td>50 (40–55)</td>
<td>50 (40–55)</td>
<td>1 ln %</td>
<td>0.59</td>
<td>0.22–1.55</td>
<td>1.17</td>
<td>0.28</td>
</tr>
<tr>
<td>Primary effective coronary revascularization, yes</td>
<td>74%</td>
<td>76%</td>
<td>73%</td>
<td>Yes vs. No</td>
<td>1.17</td>
<td>0.65–2.12</td>
<td>0.28</td>
<td>0.60</td>
</tr>
<tr>
<td>Previous AMI, yes</td>
<td>34%</td>
<td>41%</td>
<td>30%</td>
<td>Yes vs. No</td>
<td>1.58</td>
<td>0.92–2.70</td>
<td>2.79</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous stroke or/and TIA, yes</td>
<td>7%</td>
<td>4%</td>
<td>9%</td>
<td>Yes vs. No</td>
<td>0.46</td>
<td>0.17–1.48</td>
<td>1.70</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>24%</td>
<td>17%</td>
<td>28%</td>
<td>Yes vs. No</td>
<td>0.51</td>
<td>0.27–0.97</td>
<td>4.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Arterial hypertension, yes</td>
<td>81%</td>
<td>79%</td>
<td>82%</td>
<td>Yes vs. No</td>
<td>0.86</td>
<td>0.45–1.63</td>
<td>0.22</td>
<td>0.64</td>
</tr>
<tr>
<td>Nicotinism, yes</td>
<td>28%</td>
<td>42%</td>
<td>19%</td>
<td>Yes vs. No</td>
<td>3.03</td>
<td>1.70–5.39</td>
<td>14.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol consumption ≥ 2 times per week, yes</td>
<td>63%</td>
<td>68%</td>
<td>59%</td>
<td>Yes vs. No</td>
<td>3.31</td>
<td>0.80–13.66</td>
<td>2.77</td>
<td>0.10</td>
</tr>
<tr>
<td>Hemoglobin [g/dL]</td>
<td>14.0 ± 1.3</td>
<td>14.1 ± 1.4</td>
<td>14.0 ± 1.3</td>
<td>1 g/dL</td>
<td>1.05</td>
<td>0.86–1.27</td>
<td>0.21</td>
<td>0.65</td>
</tr>
<tr>
<td>eGFR [mL/min/1.73 m²]</td>
<td>76.4 ± 25.0</td>
<td>79.6 ± 22.9</td>
<td>74.4 ± 26.1</td>
<td>1 mL/min/1.73 m²</td>
<td>1.00</td>
<td>1.00–1.02</td>
<td>2.48</td>
<td>0.11</td>
</tr>
<tr>
<td>GGTP [IU/L]</td>
<td>36 (27–61)</td>
<td>40 (27–76)</td>
<td>35.0 (27–57)</td>
<td>1 ln IU/L</td>
<td>1.17</td>
<td>0.79–1.73</td>
<td>0.62</td>
<td>0.43</td>
</tr>
<tr>
<td>LDL cholesterol [mg/dL]</td>
<td>105 ± 43</td>
<td>102±38</td>
<td>107 ± 46</td>
<td>1 mg/dL</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.75</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Treatment prior to AMI:

- ACE-I and/or ARB, yes: 52%
- Antiplatelet drug, yes: 35%
- Beta-blocker, yes: 46%
- Metformin, yes: 11%
- Statin, yes: 40%

Treatment during the hospitalization and continued as post-discharge recommendations:

- ACE-I and/or ARB, yes: 97%
- Antiplatelet drug, yes: 99%
- Beta-blocker, yes: 91%
- Metformin, yes: 19%
- Statin, yes: 98%

*Data are presented as means ± standard deviations, medians (with lower and upper quartiles), or numbers (with percentages) where appropriate. Conversion factors to SI units are as follows: for hemoglobin — 10, for LDL cholesterol — 0.0259. CI — confidence interval; ln — natural logarithm; STEMI — ST elevation myocardial infarction; LVEF — left ventricle ejection fraction; AMI — acute myocardial infarction; TIA — transient ischemic attack; eGFR — estimated glomerular filtration rate; GGTP — gamma-glutamyl transpeptidase; LDL — low density lipoprotein; ACE-I — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker.
Table 2. Prognosticators of another acute myocardial infarction or death in non-anemic patients hospitalized due to acute myocardial infarction during the 180-day follow-up (Cox proportional hazard regression models).

<table>
<thead>
<tr>
<th>Prognosticators, units</th>
<th>Univariate models</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Gender, men vs. women</td>
<td>0.45</td>
<td>0.24–0.85</td>
</tr>
<tr>
<td>Age, 1 ln year</td>
<td>8.42</td>
<td>1.09–64.98</td>
</tr>
<tr>
<td>BMI, 1 ln kg/m(^2)</td>
<td>0.22</td>
<td>0.04–1.37</td>
</tr>
<tr>
<td>STEMI, yes vs. no</td>
<td>0.82</td>
<td>0.40–1.69</td>
</tr>
<tr>
<td>Peak troponin level, 1 ln (\mu)g/L</td>
<td>0.92</td>
<td>0.80–1.07</td>
</tr>
<tr>
<td>LVEF, 1 ln %</td>
<td>0.14</td>
<td>0.05–0.36</td>
</tr>
<tr>
<td>Primary effective coronary revascularization, yes vs. no</td>
<td>1.14</td>
<td>0.54–2.41</td>
</tr>
<tr>
<td>Previous AMI, yes vs. no</td>
<td>2.47</td>
<td>1.31–4.69</td>
</tr>
<tr>
<td>Previous stroke or/and TIA, yes vs. no</td>
<td>1.14</td>
<td>0.35–3.70</td>
</tr>
<tr>
<td>Diabetes mellitus, yes vs. no</td>
<td>1.76</td>
<td>0.90–3.44</td>
</tr>
<tr>
<td>Arterial hypertension, yes vs. no</td>
<td>4.70</td>
<td>1.13–19.51</td>
</tr>
<tr>
<td>Nicotinism, yes vs. no</td>
<td>0.67</td>
<td>0.31–1.47</td>
</tr>
<tr>
<td>Alcohol consumption ≥ 2 times per week, yes</td>
<td>0.69</td>
<td>0.10–5.06</td>
</tr>
<tr>
<td>Hemoglobin level, 1 g/dL</td>
<td>0.77</td>
<td>0.60–1.01</td>
</tr>
<tr>
<td>eGFR, 1 mL/min/1.73 m(^2)</td>
<td>0.99</td>
<td>0.98–1.00</td>
</tr>
<tr>
<td>GGTP, 1 ln IU/L</td>
<td>1.46</td>
<td>0.93–2.29</td>
</tr>
<tr>
<td>LDL cholesterol, 1 mg/dL</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>ACE-I and/or ARB post-AMI, yes vs. no</td>
<td>0.47</td>
<td>0.11–1.95</td>
</tr>
<tr>
<td>Antiplatelet drug post-AMI, yes vs. no</td>
<td>0.45</td>
<td>0.06–3.28</td>
</tr>
<tr>
<td>Beta-blocker post-AMI, yes vs. no</td>
<td>0.76</td>
<td>0.27–2.15</td>
</tr>
<tr>
<td>Metformin post-AMI, yes vs. no</td>
<td>0.67</td>
<td>0.26–1.71</td>
</tr>
<tr>
<td>Statin post-AMI, yes vs. no</td>
<td>0.74</td>
<td>0.10–5.41</td>
</tr>
<tr>
<td>High MCV, yes vs. no</td>
<td>2.63</td>
<td>1.37–5.03</td>
</tr>
<tr>
<td>Multivariable model corrected ( \chi^2 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conversion factors to SI units are as follows: for hemoglobin — 10, for LDL cholesterol — 0.0259.

HR — hazard ratio; CI — confidence interval; ln — natural logarithm; BMI — body mass index; STEMI — ST elevation myocardial infarction; LVEF — left ventricle ejection fraction; ACE-I — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; AMI — acute myocardial infarction; TIA — transient ischemic attack; eGFR — estimated glomerular filtration rate; GGTP — gamma-glutamyl transpeptidase; LDL — low density lipoprotein others; ACE-I — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; MCV — mean corpuscular volume.
Macrocytosis is defined as an enlargement of erythrocyte volume, commonly identified as an increase in MCV above 100 fL [16]. However, some studies have demonstrated that lesser deviations in the erythrocyte volume may also indicate pathology and lower cut-off values for high MCV are also used (92 fL) [14, 17].

Changes in MCV reflect aberrations on various steps of erythrocyte’s life cycle. Depending on the etiology of macrocytosis in non-anemic patients, we may distinguish its megaloblastic and non-megaloblastic forms [16]. Megaloblastic process is caused by impaired DNA synthesis that may be linked to certain drug administration (e.g. metformin, methotrexate, trimethoprim, nitrous oxide), folate or vitamin B\textsubscript{12} deficiency [18, 19], for instance due to their insufficient supply in food [20, 21]. Non-megaloblastic macrocytes occur when a damaging factor acts after a completed erythropoiesis. Then, it can be caused e.g. by an increased deposition of lipids on the cell membranes in the course of hepatobiliary diseases [19]. Other causes of non-megaloblastic macrocytosis in patients without anemia could be alcoholism [22] or familial macrocytosis [19]. The identification of high MCV does not allow to distinguish these two types of macrocytosis, and we need to acknowledge that the causes of high MCV found in almost 40% of non-anemic patients admitted due to AMI have not been investigated in our study, which might be considered as a study limitation.

The important and intriguing question is which pathophysiological processes are responsible for the demonstrated relationship between high MCV and increased cardiovascular risk in subjects without concomitant anemia. Our study was not designed to investigate these pathomechanisms, however some other studies may provide some potential explanations. Possible pathomechanisms can be more or less direct. A direct mechanism would be associated with a hindered flow of larger, less flexible erythrocytes through microcirculation, which is a phenomenon that might contribute to myocardial ischemia [23, 24]. Patients with high MCV commonly develop hyperhomocysteinemia [25], which is known to augment cardiovascular risk [26–28]. Moreover, high MCV is an independent prognosticator of impaired endothelial function measured via flow-mediated dilatation [8], which may be explained by disrupted erythrocyte antioxidative potential in macrocytes and an associated imbalance in global redox homeostasis of the organism [8]. Finally, macrocytosis may reflect a malnutrition, as associations between high MCV, and lower LDL cholesterol levels and lower BMI were reported [9, 10].

Conclusions

In summary, high MCV contributes to cardiovascular risk stratification in non-anemic patients with AMI. After verification of our observations in bigger cohorts and in other clinical contexts, commonly used scales for cardiovascular risk assessment might potentially consider to include MCV to improve the preciseness of risk estimation, which seems to be easily attainable and probably economically advantageous.

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Conflict of interest: None declared

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