Prevalence and prognostic significance of anemia in patients presenting for ST-elevation myocardial infarction in a Tunisian center

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Background: **Anemia on admission is a powerful predictor of major cardiovascular events in patients presenting for acute coronary syndromes. We sought to determine the prevalence and prognostic impact of anemia in patients presenting for ST-elevation myocardial infarction (STEMI).**

Methods: **We analyzed data from a Tunisian retrospective single center STEMI registry. Patients were enrolled between January 1998 and October 2014. Anemic and nonanemic patients were compared for clinical and prognostic features and according to four prespecified hemoglobin level subgroups. In patients with severe anemia, factors associated with in-hospital death were studied.**

Results: **A total of 1498 patients were enrolled. Mean age was 60.47 ± 12.7 years and prevalence of anemia was 36.6%. Anemic patients were more likely to be elderly, hypertensive, and diabetic in comparison to nonanemic patients. In-hospital mortality was significantly higher in anemic patients (14.9% vs. 5%, $p < 0.001$). Lower hemoglobin levels were significantly associated with a higher prevalence of heart failure on admission, cardiogenic shock, and in-hospital mortality ($p < 0.001$ for all). In univariate analysis, factors associated with in-hospital death in patients with severe anemia were hypertension ($p = 0.044$), heart failure on admission ($p < 0.001$), renal failure on admission ($p < 0.001$), and primary percutaneous coronary intervention (pPCI) use ($p = 0.016$). The absence of pPCI use was independently associated with in-hospital death in multivariate analysis (odds ratio = 2.22, 95% confidence interval: 1.07–4.76, $p = 0.033$).**

Conclusion: **According to this study, anemic patients presenting for STEMI have a higher in-hospital mortality rate. The absence of pPCI use was independently associated with in-hospital death.**

Keywords: Anemia, Mortality, Primary percutaneous coronary intervention, ST-elevation myocardial infarction

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1. Introduction

Anemia at presentation and during hospital stay is reported to be highly predictive of poor in-hospital and long-term outcomes in patients presenting with acute coronary syndromes (ACS) [1–4]. In several reports, baseline hemoglobin level was proven to be correlated to the incidence of in-hospital complications in patients treated for ST-elevation myocardial infarction (STEMI) [5–7]. Furthermore, blood transfusion is a frequently utilized therapeutic in this setting and was nevertheless proven to be another predictor of adverse events in patients hospitalized for ACS [8,9].

Aside from hemoglobinopathies in the younger demographic, iron-deficiency accounts for the majority of anemia cases in the adult population in the Middle East and North Africa [10–12]. In addition, it is also known that the epidemiology of STEMI with regards to patients risk profile and management strategies implemented are quite different in these parts of the world when compared to those in Western countries. In many of these countries, indeed, the implementation of primary percutaneous coronary intervention (pPCI) for the management of STEMI is still not the default strategy and an evaluation of the impact of anemia at presentation on outcomes, especially in relation to the management strategies adopted, is warranted. No data from the North African countries are available.

In this study, we sought to investigate the prevalence and the prognostic significance of anemia on admission in patients presenting with STEMI in a Tunisian tertiary care center, particularly in relation to therapeutic strategies utilized in this context.

Abbreviations

ACS	acute coronary syndrome
CCU	coronary care unit
CI	confidence interval
CKD	chronic kidney disease
HF	heart failure
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
MDRD	Modification of Diet in Renal Disease
OPTIMAAL	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
OR	odds ratio
pPCI	primary percutaneous coronary intervention
SPSS	statistical package for social sciences
STEMI	ST-elevation myocardial infarction

2. Materials and methods

2.1. Population and study design

The present study was led on data from the STEMI registry of Cardiology B Department, Fattouma Bourguiba University Hospital (Monastir, Tunisia). The registry enrolls in a yearly fashion all patients aged ⩾18 years presenting to our center for STEMI, regardless of the management strategy adopted. The study performed is a retrospective observational study on all consecutive patients admitted to our department between January 1998 and October 2014. Patients are referred to our department from the emergency ward or the local Emergent Medical Aid system. The diagnosis of STEMI was established in the presence of a significant ST-segment elevation (1 mm in frontal leads and 2 mm in precordial leads) in two adjacent leads, or a presumably new left bundle branch block concomitantly to a persistent (>20 minutes) chest discomfort. In our practice, the decision to perform pPCI, thrombolysis, or not to opt for a reperfusion therapy is undertaken as in accordance as possible with the European Society guidelines [13], while taking into account the ischemic-hemorrhagic balance for each reperfusion modality, implementation delays, and the patient clinical background. Reasons for managing patients conservatively (i.e., without reperfusion) were diverse (late presentation, advanced age, etc.). All patients received intravenously 100 UI/kg of weight unfractionated heparin upon diagnosis, 250 mg aspirin and a 300-mg or 600-mg loading dose of clopidogrel according to the reperfusion strategy chosen (thrombolysis or pPCI).

Clinical history and cardiovascular risk factors were collected upon presentation and at 24 hours. Initial physical examination was reported. Blood samples were retrieved upon admission for blood cell count and other standard analyses. Anemia was defined according to the World Health Organization criteria (hemoglobin <13 g/dL in men and <12 g/dL in women) [14]. Severe anemia was defined by a hemoglobin rate <11 g/dL. Anemic and nonanemic patients were first compared regarding clinical characteristics, management, and in-hospital complications and mortality; the study population was then split into four prespecified subgroups according to baseline hemoglobin levels (⩾16 g/dL, 13.5–15.9 g/dL, 11–13.4 g/dL, and <11 g/dL) to better analyze trends in clinical and prognostic features according to the hemoglobin subgroup. Heart failure (HF) on admission was

defined by a Killip II or Killip III class. Killip IV class was referred to as cardiogenic shock. Renal failure on admission was defined as a creatinine clearance <45 mL/min using the Modification of Diet in Renal Disease formula in patients not previously known to suffer from chronic kidney disease (CKD); in patients known to have CKD, renal failure on admission was defined as an increase of ⩾30% of baseline serum creatinine rate. Bleeding complications were defined as any overt or nonovert bleeding with a drop of ⩾2 g/dL in hemoglobin or needing blood transfusion. In patients with severe anemia, relevant factors associated with in-hospital death were studied in univariate then in multivariate analysis.

2.2. Statistical analysis

Continuous variables were presented as means ± standard deviation. Categorical variables are presented as absolute values and percentages. When appropriate, the chi-square test was applied to compare proportions between anemic and nonanemic patients and between the four prespecified hemoglobin subgroups. It was also applied to determine factors associated with in-hospital death in univariate analysis. Mean values of continuous variables were compared between anemic and nonanemic patients using the Student *t* test. In the four subgroup analysis, the difference between means was evaluated using the one way analysis of variance test. Multivariate analysis on variables significantly associated with in-hospital death in univariate analysis was performed using binary logistic regression. Results are expressed as odds ratios (OR) with accompanying 95% confidence interval (95% CI). A p value <0.05 was considered significant. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA) version 17 for Windows.

3. Results

The overall study population included 1498 patients. Five hundred and forty-four (36.3%) patients were anemic. Prevalence of anemia was comparable between women and men (38.4% vs. 35.7%, $p = 0.36$) and significantly higher in elderly compared to younger patients (52.1% vs. 34.8%, $p < 0.001$). Compared to nonanemic patients, anemic patients were more likely to have a history of arterial hypertension ($p < 0.001$) and diabetes mellitus ($p = 0.007$) (Table 1). Conversely, they

Table 1. Clinical characteristics and in-hospital course in anemic patients versus nonanemic patients presenting for ST-elevation myocardial infarction (STEMI).

	Population (n = 1498)	Nonanemic (n = 954)	Anemic (n = 544)	p
Age (y)	60.47 ± 12.7	58 ± 12.5	64.71 ± 11.83	<0.001
Age > 75 y	211 (15%)	101 (11.5%)	110 (21%)	<0.001
Female gender	333 (22.2%)	205 (21.5%)	128 (23.5%)	0.361
Hypertension	451 (30.1%)	245 (25.7%)	206 (37.9%)	<0.001
Diabetes mellitus	534 (35.6%)	316 (33.1%)	218 (40.1%)	0.007
Current smoker	1000 (66.8%)	678 (71.1%)	322 (59.2%)	<0.001
Dyslipidemia	177 (12.1%)	115 (12.2%)	62 (11.9%)	0.869
Obesity	190 (12.7%)	132 (13.9%)	58 (10.7%)	0.071
History of HF	34 (2.3%)	18 (1.9%)	16 (2.9%)	0.188
History of PCI	122 (8.1%)	87 (9.1%)	35 (6.4%)	0.068
History of CABG	6 (0.4%)	5 (0.5%)	1 (0.2%)	0.316
HF on admission	331 (22.1%)	195 (20.4%)	136 (25%)	0.041
Cardiogenic shock on admission	35 (2.3%)	13 (1.4%)	22 (4%)	0.001
Renal failure on admission	116 (8.3%)	40 (4.6%)	76 (14.5%)	<0.001
Anterior infarction	696 (46.5%)	454 (47.6%)	242 (44.5%)	0.247
Primary PCI	424 (28.3%)	280 (29.4%)	144 (26.5%)	0.234
Symptoms to primary PCI delay (h)	4.88 ± 4.23	4.6 ± 3.85	5.39 ± 4.81	0.071
Thrombolysis	510 (34%)	348 (36.5%)	162 (29.8%)	0.009
Symptoms to thrombolysis delay (h)	3.79 ± 4	3.44 ± 3.35	4.5 ± 5.11	0.004
No reperfusion therapy	564 (37.6%)	326 (34.1%)	238 (43.7%)	0.001
New onset atrial fibrillation	100 (6.7%)	60 (6.3%)	40 (7.4%)	0.428
Inotropic agents use	216 (14.4%)	113 (11.8%)	103 (18.9%)	<0.001
Bleeding complication	41 (2.8%)	24 (2.5%)	17 (3.2%)	0.473
CCU length of stay (d)	4.74 ± 3.55	4.7 ± 3.1	4.79 ± 4.22	0.667
In-hospital mortality	129 (8.6%)	48 (5%)	81 (14.9%)	<0.001

CABG = coronary artery bypass grafting; CCU = coronary care unit; HF = heart failure; PCI = percutaneous coronary intervention.

Table 2. Clinical presentation and in-hospital course in patients presenting for ST-elevation myocardial infarction (STEMI) according to four hemoglobin level subgroups.

	Group 1 Hb ⩾ 16 g/dL (n = 110)	Group 2 Hb 13.5–15.9 g/dL (n = 600)	Group 3 Hb 11–13.4 g/dL (n = 539)	Group 4 Hb < 11 g/dL (n = 249)	p
Age (y)	55.35 ± 11.05	56.88 ± 12.48	62.77 ± 12.15	66.52 ± 11.67	<0.001
Age > 75	5 (4.5%)	55 (9.2%)	90 (16.7%)	65 (26.1%)	<0.001
Female gender	11 (10%)	94 (15.7%)	135 (25%)	93 (37.3%)	<0.001
Hypertension	19 (17.3%)	139 (23.2%)	191 (35.4%)	102 (41%)	<0.001
Diabetes mellitus	35 (31.8%)	186 (31%)	201 (37.3%)	112 (45%)	0.001
Tobacco smoking	101 (91.8%)	454 (75.7%)	331 (61.4%)	114 (45.8%)	<0.001
HF on-admission	29 (26.4%)	106 (17.7%)	120 (22.3%)	76 (30.5%)	<0.001
Cardiogenic shock	2 (1.8%)	7 (1.2%)	11 (2%)	15 (6%)	<0.001
Renal failure on admission	3 (2.7%)	23 (3.8%)	40 (7.4%)	50 (20%)	<0.001
Primary PCI	31 (28.2%)	179 (29.8%)	154 (28.6%)	60 (24.1%)	0.41
Symptoms to primary PCI delay (h)	5.38 ± 6.09	4.53 ± 3.75	4.75 ± 4.11	5.97 ± 4.63	0.138
Thrombolysis	49 (44.5%)	210 (35%)	189 (35.1%)	62 (24.9%)	0.002
Symptoms to thrombolysis delay (h)	3.7 ± 3.94	3.21 ± 2.29	4.08 ± 4.76	4.98 ± 6.21	0.009
No reperfusion therapy	30 (27.3%)	211 (35.2%)	196 (36.3%)	127 (51%)	0.001
Bleeding complication	4 (3.7%)	12 (2%)	15 (2.8%)	10 (4.1%)	0.357
Inotropic agents use	16 (14.5%)	59 (9.8%)	74 (13.7%)	67 (26.9%)	<0.001
CCU Length of stay (d)	4.91 ± 2.76	4.62 ± 3.05	4.72 ± 3.4	4.98 ± 5.11	0.626
In-hospital mortality	7 (6.4%)	21 (3.5%)	46 (8.5%)	55 (22.1%)	<0.001

CCU = coronary care unit; Hb = hemoglobin; PCI = percutaneous coronary intervention.

were less likely to be current smokers ($p < 0.001$). Regarding clinical presentation, anemic patients were more likely to experience HF ($p = 0.041$), renal failure ($p < 0.001$), and cardiogenic shock ($p = 0.001$) on admission. No statistical difference could be reported regarding pPCI use as the reperfusion option for STEMI between anemic and nonanemic patients. By contrast, recourse to thrombolysis was significantly lower in the anemic group (29.8% vs. 36.5%, $p = 0.009$). Likewise, mean delay between symptoms onset and thrombolysis was significantly longer. Recourse to inotropic agents was more frequent in anemic patients, whereas no difference in the occurrence of bleeding complications was noticed between the two groups. Anemia was associated with a significantly higher in-hospital mortality rate (14.9% vs. 5% in nonanemic patients, $p < 0.001$).

Investigating population clinical characteristics and outcomes according to baseline hemoglobin levels (Table 2) revealed a gradual increase in mean age with lower hemoglobin levels. Prevalence of elderly, female gender, hypertension, and diabetes was significantly higher in the lower hemoglobin subgroups. A progressive increase in the occurrence of HF and cardiogenic shock upon presentation was noted in lower hemoglobin subgroups and so was the recourse to inotropic agents use. No significant ascending or descending trend for bleeding complications occurrence or in the mean coronary care unit length of stay could be seen across the hemoglobin level spectrum. In-hospital mortality was by far the highest (22.1%) in the severe anemia subgroup (hemoglobin <11 g/dL) compared to 6.4% (in the hemoglobin ⩾16 g/dL subgroup), 3.5% (in the hemoglobin

Table 3. Relevant factors associated with in-hospital death in patients with severe anemia presenting for ST-elevation myocardial infarction (STEMI) in univariate analysis.

	Surviving	Dead	p
Female gender	69 (35.6%)	24 (43.6%)	0.275
Age < 75 y	49 (25.3%)	16 (29.1%)	0.568
Hypertension	73 (37.6%)	29 (52.7%)	0.044
Diabetes mellitus	83 (42.8%)	29 (52.7%)	0.191
HF on admission	47 (24.2%)	29 (52.7%)	<0.001
Renal failure on admission	27 (14.8%)	23 (41.8%)	<0.001
Primary PCI	40 (20.6%)	20 (36.4%)	0.016
New onset atrial fibrillation	15 (7.7%)	10 (18.2%)	0.023

HF = heart failure; PCI = percutaneous coronary intervention.

Table 4. Factors independently associated with in-hospital death in patients with severe anemia presenting for ST-elevation myocardial infarction (STEMI) in multivariate analysis.

Variable	Odds ratio	95% CI	*p*
Hypertension	1.66	0.83–3.29	0.148
Diabetes mellitus	1.3	0.64–2.60	0.458
HF on admission	3.42	1.73–6.74	<0.001
Renal failure on admission	3.82	1.83–7.96	<0.001
Primary PCI	0.45	0.21–0.93	0.033
New onset atrial fibrillation	0.44	0.16–1.2	0.112

CI = confidence interval; HF = heart failure; PCI = percutaneous coronary intervention.

13.5–15.9 g/dL subgroup), and 8.5% (in the hemoglobin 11–13.4 g/dL subgroup). In the severe anemia subgroup, 34 (61.8%) patients died from cardiogenic shock or refractory pulmonary edema, seven (12.8%) from refractory ventricular arrhythmia, three (5.4%) from mechanical complications, and the remaining from noncardiac causes.

In the severe anemia subgroup, clinical and prognostic factors relevant to in-hospital mortality were studied (Table 3). In univariate analysis, factors significantly associated with in-hospital mortality in patients with severe anemia were hypertension ($p = 0.044$), HF on admission ($p < 0.001$), renal failure on admission ($p < 0.001$), new onset atrial fibrillation ($p = 0.023$), and pPCI as a reperfusion strategy ($p = 0.016$). Multivariate analysis performed on this model showed that factors independently associated with in-hospital death were HF on admission (OR = 3.42, 95% CI: 1.73–6.74, $p < 0.001$), and renal failure on admission (OR = 3.82, 95% CI: 1.83–7.96, $p < 0.001$). The absence of pPCI use as the reperfusion option was independently associated with in-hospital death in multivariate analysis (OR = 2.22, 95% CI: 1.07–4.76, $p = 0.033$) (Table 4).

4. Discussion

This is an original study performed in a North African country that clearly highlights the prognostic impact of baseline anemia in patients presenting for ACS and in particular acute STEMI. Furthermore, the study emphasizes the heavy prognostic impact of clinical presentation in severely anemic patients and the beneficial effect of pPCI in these critically ill patients.

In the present study, prevalence of anemia in patients presenting for STEMI was 36.3%. This rate is considerably higher than those reported in western series. Al Falluji et al. [1] reported a prevalence of 10.2% in a large American database from New Jersey and Tsujita et al. [4] found similar rates in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial [4]. In the Middle Eastern Gulf RACE II registry [15], this prevalence rose to 28% in patients presenting for ACS but remained lower than that reported in our study.

The impact that anemia has on in-hospital course in patients presenting for STEMI has been confirmed in several studies and irrespectively of the antithrombotic regimens and reperfusion modalities used [4,16,17]. Results from the present study regarding the harmful effect of anemia in these patients are in accordance with those reported elsewhere. Such an effect could be due to anemia itself, but also to other comorbid conditions classically associated with it that could aggravate the former effect or be a confounding factor such as renal failure. Likewise, the prognostic significance of low baseline hemoglobin levels was consistent in a variety of demographic groups and clinical settings. Kitai et al. [18] demonstrated an impact of low hemoglobin levels on mortality in patients undergoing pPCI that was maintained even for those with mild anemia. In the same study, a concomitant CKD was associated with significantly higher incidence of major cardiovascular events. In our study, the relationship between baseline hemoglobin level and the occurrence of HF or cardiogenic shock upon presentation was obvious. Recourse to inotropic agents had also the same trend. In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), anemia was associated with HF on presentation and there was a clear trend to higher Killip classes in STEMI with lower hemoglobin levels [19]. In a study carried out in 2310 patients presenting for ACS in the United Kingdom, Archbold et al. [6] identified anemia as a powerful determinant of clinically diagnosed left ventricular dysfunction occurrence with the highest rates in STEMI and for the lowest hemoglobin categories. In another report, on top of being predictive of overall mortality, anemia was also predictive of mortality from noncardiac causes in young patients [20].

In-hospital mortality rate was significantly higher in anemic patients in comparison to nonanemic ones and was particularly high in patients with severe anemia (22.1%). This fact could be demonstrated in several reports, but in our study, the in-hospital mortality rate in anemic patients is generally higher. In our context, these patients have a higher prevalence of traditional

cardiovascular risk factors and other comorbidities when compared to Western populations, which could partly explain such a disparity in outcomes.

There are several pathophysiological explanations to the worse clinical outcome and mortality in patients suffering from coronary artery disease and anemia. In anemic patients, there is a significant reduction of oxygen supply to the myocardium in addition to the impaired coronary blood flow. Other mechanisms include tachycardia and decrease in blood viscosity [21]. Eventually, recourse to blood transfusion in anemic patients with or without hemorrhagic complications was proven to be a powerful predictor of worse outcome in the whole ACS spectrum [9].

In our current practice, reperfusion strategies (i.e., thrombolysis and pPCI) were not equally utilized according to hemoglobin subgroups. While there was a significant trend to less thrombolysis use in patients with lower baseline hemoglobin levels, pPCI was equally used in the different subgroups. This propensity to a lesser recourse to reperfusion therapies in anemic patients was frequently reported in the literature [22,23]. Operators often prefer not to opt for an invasive procedure or hemorrhage-inducing pharmacological therapeutic in patients at risk of bleeding. In our study, in patients with severe anemia, the use of pPCI as the reperfusion option was associated with a worse in-hospital outcome in univariate analysis. In our context, the decision to perform (or not) a pPCI is left to the discretion of the operator, and in all likelihood this led to a subpopulation with a critical clinical presentation and outcome. Nonetheless and interestingly, this observation was reversed when pPCI was included in a multivariate model where its effect on in-hospital mortality was adjusted to main variables associated with the latter outcome. This is a highly informative result given that it emphasizes the beneficial effect of pPCI in STEMI even for patients suffering from severe anemia for whom such a procedure could be considered hazardous at a first glance.

4.1. Study limitations

Although very informative about our current practice, the present study was performed on data that were collected retrospectively in a periodical manner and the results have to be interpreted very cautiously. No randomization was carried out and compared subgroups cannot perfectly match regarding all variables linked with risk profile and prognosis. Results certainly cannot be extrapolated to the whole Tunisian population given that the study was performed on a near exclusively urban population. Another study limitation is the absence of relation between the hemoglobin levels and the occurrence of hemorrhagic events during hospital stay. Indeed, prevalence of bleeding complications was low and statistical significance precisely in this topic could probably be reached in a larger study population.

5. Conclusion

The present study issued from a single center registry confirms the high prevalence of anemia in patients presenting for STEMI in the Tunisian context. In these patients, low baseline hemoglobin levels were significantly associated with worse in-hospital outcomes. In patients with severe anemia, initial clinical presentation was very impactful on in-hospital outcomes and the absence of pPCI use as a reperfusion therapy was independently associated with in-hospital death.

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