



Long-term predictors of death among Tunisian patients presenting for non ST-elevation acute coronary syndrome

Facteurs prédictifs de mortalité à long terme des patients Tunisiens se présentant pour syndrome coronarien aigu sans sus-décalage du segment ST

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RÉSUMÉ

Contexte. La maladie coronaire est une cause majeure de mortalité dans les pays émergents. Les données cliniques et pronostiques se rapportant aux patients Tunisiens se présentant pour syndrome coronarien aigu sans sus-décalage du segment ST (SCANST) manquent.

But. Nous nous sommes proposés d'étudier le profil de risque et les facteurs prédictifs de mortalité à 3 ans chez des patients Tunisiens se présentant pour SCANST dans le contexte actuel.

Méthodes. Dans cette étude monocentrique, les données de tous les patients consécutifs se présentant à notre centre pour SCANST entre avril 2014 et juillet 2016 ont été colligées. Le pronostic des patients a été déterminé de manière exhaustive et les prédicteurs de mortalité à 3 ans déterminés en analyse multivariée.

Resultats. Au total, 340 patients ont été inclus, parmi lesquels 204 (61,8%) étaient de sexe masculin. L'âge moyen était $63,6 \pm 10,3$ années. La prévalence du diabète, de l'hypertension artérielle et du tabagisme était 57,3%, 62,4% et 45,3%, respectivement. La mortalité hospitalière, à 6, à 12 et à 36 mois était de 2,3%, 3,2%, 7,1% and 15,2%, respectivement. En analyse multivariée, les facteurs prédictifs de décès étaient : l'âge >75 ans (HR=5,45, IC à 95% : 2,9-10,03, $p<0,001$), la déviation du segment ST (HR=1,86, IC à 95% : 1,04-3,33, $p=0,036$), l'anémie (HR=2,56, IC à 95% : 1,41-4,67, $p=0,002$), une fraction d'éjection du ventricule gauche (FEVG) <40% (HR=3,5, IC à 95% : 1,84-6,67, $p<0,001$) et un Global Registry of Acute Coronary Events (GRACE) score ≥ 140 (HR=2,38, IC à 95% : 1,02-5,57, $p=0,044$).

Conclusion. Chez les patients Tunisiens se présentant pour SCANST, la mortalité à long terme était élevée. L'âge avancé, une déviation du segment ST, l'anémie, une FEVG <40% et un GRACE score ≥ 140 étaient des facteurs prédictifs indépendants de mortalité à long terme.

Mots clés : syndrome coronarien aigu sans sus-décalage du segment ST, facteur de risque, revascularisation, mortalité

SUMMARY

Background. Coronary artery disease is the leading cause of death in emerging countries. Contemporary data about clinical profile and prognosis in Tunisian patients presenting for non ST-elevation acute coronary syndrome (NSTEMI-ACS) are lacking.

Aim. We sought to study the risk profile and 3-year mortality predictors in Tunisian patients presenting for NSTEMI-ACS in the contemporary setting.

Methods. In this single center study, data about all consecutive patients presenting to our center for NSTEMI-ACS from April 2014 to July 2016 were extracted and outcomes exhaustively updated. 3-year mortality predictors were determined by multivariable survival analysis.

Results. A total of 340 patients were included, of which 204 (61.8%) were male. Mean age was 63.6 ± 10.3 years. Prevalence of diabetes mellitus, hypertension and smoking was 57.3%, 62.4%, and 45.3%, respectively. In-hospital, 6, 12 and 36-month mortality rate was 2.3%, 3.2%, 7.1% and 15.2%, respectively. In multivariable survival analysis, independent predictors of death were age >75 (HR=5.45, 95% CI: 2.9-10.03, $p<0.001$), ST-segment deviation (HR=1.86, 95% CI: 1.04-3.33, $p=0.036$), anemia (HR=2.56, 95% CI: 1.41-4.67, $p=0.002$), left ventricular ejection fraction (LVEF) <40% (HR=3.5, 95% CI: 1.84-6.67, $p<0.001$) and a Global Registry of Acute Coronary Events (GRACE) score ≥ 140 (HR=2.38, 95% CI: 1.02-5.57, $p=0.044$).

Conclusion. In Tunisian patients presenting for NSTEMI-ACS, long-term mortality was high. Advanced age, ST-segment deviation, anemia, LVEF <40% and a GRACE score ≥ 140 were independent long-term predictors of death.

Keywords: Non ST-elevation acute coronary syndrome, risk factor, revascularization, mortality

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INTRODUCTION

Acute coronary syndromes (ACS) are a leading cause of death and disability worldwide and particularly in emergent countries [1, 2]. In Middle-Eastern and North African countries, where income per capita has improved over the last few decades, a concomitant metamorphosis in diet, lifestyle and social habits has occurred resulting in a substantial increase in the prevalence of coronary artery disease (CAD) risk factors [3, 4]. Alongside with these modifications in risk profile, antithrombotic therapies and coronary revascularization techniques have undergone dramatic improvements with notably the wide use of double antiplatelet therapy and percutaneous coronary intervention (PCI) with drug eluting stents (DES) [5]. In Tunisia, some recently published reports addressed management strategies and early prognosis in patients presenting for ST-elevation myocardial infarction (STEMI) in contemporary practice [6, 7]. However, data about risk profile, clinical course and long-term prognosis in patients presenting for non-ST elevation acute coronary syndrome (NSTEMI-ACS) are nearly absent. Thus, we performed the present study to establish the cardiovascular risk profile, early and long-term prognoses of patients presenting with NSTEMI-ACS and to determine long term predictive factors of death in this population.

METHODS

Study population and design. In this single center study, we retrospectively extracted data about all consecutive patients aged 18 and older admitted to our cardiology department in a major Tunisian tertiary care facility for NSTEMI-ACS suspicion, between April 2014 and July 2016. NSTEMI-ACS was suspected in the presence of any chest pain or discomfort at rest suggestive of myocardial ischemia during at least 10 minutes. Electrocardiogram (ECG) was performed in all patients in less than 10 minutes from first medical contact for NSTEMI-ACS characterization. Patients presenting with persistent ST-segment elevation on ECG were excluded. We also excluded from the analysis patients for whom transthoracic echocardiography (TTE), and/or when performed, cardiac resonance magnetic imaging eventually confirmed a specific non ischemic, pericardial or myocardial affection. Baseline characteristics and clinical data upon presentation and during hospital stay were extracted from medical files. Routine biology tests including at least two separate cardiac troponin I

assays withdrawn six hours apart, were performed in all patients. According to our local protocols, troponin assay was considered positive if one value at least was >0.06 $\mu\text{g/L}$. Creatinine clearance was calculated using the Modification of Diet in Renal Disease (MDRD) formula [8] and a value <30 mL/min designated severe chronic kidney disease (CKD). Anemia was defined as a blood hemoglobin rate <13 g/dL in men and <12 g/dL in women. The Global Registry of Acute Coronary Events (GRACE) risk score was calculated for risk stratification using the web calculator available on https://www.outcomes-umassmed.org/risk_models_grace_orig.aspx. TTE was performed in all patients and left ventricular ejection fraction (LVEF) was determined in two- and four-chamber views using the Simpson formula. All patients received upon presentation 300 or 600 mg clopidogrel, orally in loading dose, followed by 75 mg daily thereafter, and 250 mg aspirin followed by 125 mg daily thereafter. Anticoagulation with subcutaneous enoxaparin at the dose of 1000 IU/10 kg every 12 hours was administered for at least 6 days, or until invasive coronary angiography (ICA) was performed. Intravenous unfractionated heparin was used instead in patients with a creatinine clearance <30 mL/min. Other pharmacological treatments such as betablockers, angiotensin-converting enzyme inhibitors and statins were administered as guideline directed [9], and in the absence of contra-indications. During hospital course, patients presenting with recurrent symptoms, dynamic ST-segment changes on ECG, those presenting a rise or fall of cardiac troponin and patients with a calculated GRACE risk score ≥ 140 were referred in 24 to 48 hours to a so called *invasive strategy* with ICA and *ad hoc* PCI of the culprit vessel as assessed by the operator. Patients presenting multivessel disease on ICA did not undergo *ad hoc* PCI and were referred to heart team discussion for choosing the adequate revascularization option (i.e. PCI, surgical revascularization or conservative medical treatment). In the latter subgroup, patients referred to conservative medical treatment after heart team discussion were so due either to the absence of significant coronary stenosis or the presence of severe coronary disease non amenable to revascularization. On the other hand, patients with no ECG changes, negative ischemia biomarkers and no ischemic symptoms recurrence were referred to a so called *conservative strategy*. Treadmill ECG was therefore performed within 48 to 72 hours from admission and if positive, patient was referred to ICA. In case of inability

or contraindication to treadmill ECG, coronary computed tomography (CCT) was performed.

Outcomes. For the purpose of the present study, in-hospital events reported were bleeding, heart failure, and death. Bleeding was defined as any overt digestive or urinary bleeding or access related bleeding in patients treated invasively. Long term follow-up was completed in all patients and included rehospitalization for ischemic recurrence or heart failure, ischemia driven revascularization at any delay and death at 6, 12 and 36 months. Follow-up data were extracted from medical files and systematically confirmed or completed by phone calls in all patients. Additionally, crude in-hospital and long-term mortality rates were reported according to the GRACE risk score category (≥ 140 or < 140) on-admission. Long-term survival trends were established according to relevant clinical variables collected upon admission. 3-year independent predictors of death in the overall population were determined.

Statistical analysis. Categorical variables were presented as absolute values and percentages and continuous variables as means \pm standard deviation (SD). Baseline characteristics and outcomes were compared between genders. Proportions were compared using Pearson chi-square test or Fisher exact test when appropriate. Means were compared using Student t-test for independent samples. Kaplan-Meier survival curves over the 3-year follow-up period were established and survival function tested for a set of categorical variables using the log-rank test. Variables that led a $p < 0.25$ on log-rank test were included in a Cox regression multivariate survival model. Variables tested comprised age > 75 , hypertension, diabetes mellitus, anemia, severe CKD, heart failure on-presentation, ST segment deviation, positive troponin assay, LVEF $< 40\%$ and a GRACE score ≥ 140 . Multivariable adjusted hazard ratio (HR) with accompanying 95% confidence intervals were reported. A value of $p < 0.05$ was set for statistical significance. All analyses were performed using Statistical Package for Social Sciences (SPSS) V. 21 for Windows.

RESULTS

A total of 340 patients were included in the current study. Baseline characteristics of the study population are reported in table 1. Mean age was 63.6 ± 10.3 years and

204 (61.8%) patients were male. Prevalence of diabetes mellitus was 57.3% in the overall population and was significantly higher in women compared to men (72.5% vs. 53.9%, $p = 0.001$). Prevalence of hypertension was also higher in women (80.9% vs. 50%, $p < 0.001$) whereas tobacco smoking was significantly higher in men (74.5% vs. 1.5%, $p < 0.001$). Upon presentation, angina pectoris was present in 327 (96.4%) patients and heart failure in 46 (13.5%) patients. Cardiogenic shock was reported in only two (0.6%) patients. ECG was normal in 128 (37.6%) patients and showed an ST-segment depression in 102 (30%) patients. Troponin assay was positive in 194 (57.1%) patients. Mean calculated GRACE score was 102 ± 30 in the overall population and 46 (13.5%) patients had a GRACE score ≥ 140 with no significant difference between genders.

Regarding management, 276 (81.1%) patients underwent an *invasive strategy* whereas 64 (18.8%) were part of the *conservative strategy* group (table 2). Compared to female gender, prevalence of male gender was significantly higher in the *invasive strategy* group (85.2% vs. 75%, $p = 0.017$). One hundred ninety six (57.6%) patients underwent myocardial revascularization either by PCI (45%) or CABG (12.6%) with no significant difference between genders regarding revascularization modality.

In-hospital and long-term outcomes are presented in table 3. Overall in-hospital mortality rate was 2.3% with no significant difference between men and women. Rehospitalization for ischemic recurrence or heart failure occurred in 74 (21.7%) patients at a mean delay of 225 ± 214 days from index episode. Ischemia driven revascularization occurred in 41 (12%) patients at a mean delay of 182 ± 180 days. Mortality at 6, 12 and 36 months was 3.2%, 7.1% and 15.2%, respectively (table 3). In comparison to patients with a GRACE score < 140 , in-hospital, 6-, 12- and 36-month mortality rates were significantly higher in those with a GRACE score ≥ 140 (table 4). Results of log-rank test for survival according to these variables are depicted in table 5. In multivariable survival analysis over 3-year follow-up period, independent predictors of death were an age > 75 (HR=5.45, 95% CI: 2.9-10.03, $p < 0.001$), ST-segment deviation (HR=1.86, 95% CI: 1.04-3.33, $p = 0.036$), anemia (HR=2.56, 95% CI: 1.41-4.67, $p = 0.002$), LVEF $< 40\%$ (HR=3.5, CI: 1.84-6.67, $p < 0.001$) and a GRACE score ≥ 140 (HR=2.38, 95% CI: 1.02-5.57, $p = 0.044$) (table 5).

Table 1. Baseline characteristics

	Total population N=340	Male N= 204	Female N=136	P
Age	63.69 ± 10.37	62.14 ± 11.18	66.03 ± 9.67	0.084
NSTE-ACS diagnosis				
NSTEMI	194 (57.1%)	122 (59.8%)	72 (52.9%)	0.21
Unstable angina	146 (42.9%)	82 (40.2%)	64 (47.1%)	0.21
Medical history				
Hypertension	212 (62.4%)	102 (50%)	110 (80.9%)	<0.001
Diabetes mellitus	195 (57.3%)	110 (53.9%)	98 (72.5%)	0.001
Smoker	154 (45.3%)	152 (74.5%)	2 (1.5%)	<0.001
Dyslipidemia	68 (20%)	26 (12.7%)	42 (30.04%)	0.01
Percutaneous coronary intervention	78 (22.9%)	50(24.5%)	28 (20.5%)	0.129
Coronary artery bypass graft	6 (1.7%)	4(1.9%)	2 (1.47%)	0.73
CKD	22 (6.4%)	10 (4.9%)	12 (8.8%)	0.01
TIA/Stroke	14 (4.1%)	6 (2.1%)	8 (5.8 %)	0.18
Atrial fibrillation	10 (2.9%)	4 (1.96%)	6 (4.4%)	0.19
Peripheral arterial disease	30 (8.9%)	21 (10.29%)	9 (6.6%)	0.02
Clinical presentation				
Angina	327 (96.4%)	199 (97.5%)	128 (94.1%)	0.03
Heart rate	78.82 ± 18.04	77.92 ±16.76	80.18 ± 19.8	0.7
Heart failure on-presentation	46 (13.5%)	34 (16.7%)	12 (8.8%)	0.038
ST segment deviation	102 (30%)	46 (22.54%)	56 (41.17%)	<0.001
Anemia	80 (23.5%)	25 (12.2%)	55 (40.4%)	<0.001
Serum glucose (mmol/l)	10.9 ± 2.55	10.6 ± 2,6	11.37 ± 2.76	0.13
Serum creatinine (µmol/l)	109.68 ± 109	84.35 ± 38.8	147.67 ± 159.6	<0.001
Positive troponin assay	194 (57.1%)	122 (59.8%)	72 (52.9%)	0.21
LVEF <40%	44 (12.9%)	39 (19.1%)	5 (3.67%)	0.01
GRACE score	102 ± 30.27	99.65 ± 30.72	106.67 ± 29.14	0.55
GRACE score >140	46 (13.5%)	24 (10.7%)	22 (16.17%)	0.24

CKD: chronic kidney disease, GRACE: Global Registry of Acute Coronary Events, LVEF: left ventricular ejection fraction, NSTE-ACS: non ST-elevation acute coronary syndrome, NSTEMI: non ST-elevation myocardial infarction, TIA: transient ischemic attack.

Table 2. Management strategy in study population.

	Total population N=340	Male N= 204	Female N=136	P
Invasive strategy	276 (81.1%)	174 (85.2%)	102 (75%)	0.017
PCI	153 (45%)	99 (48.5%)	54 (39.7%)	0.52
CABG	43 (12.6%)	31 (15.1%)	12 (8.8%)	0.18
Conservative medical treatment	80 (23.5%)	44 (21.5%)	36 (26.4%)	0.07
Conservative strategy	64 (18.7%)	30 (14.6%)	34 (24.9%)	0.017
Treadmill ECG	44 (12.9%)	15 (7.3%)	29 (21.3%)	0.03
CCT	20 (5.8%)	15 (7.3%)	5 (3.6%)	0.01

CABG : Coronary artery bypass grafting, CCT : Coronary computed tomography, ECG : electrocardiogram, PCI: percutaneous coronary intervention.

Table 3. In-hospital and long-term outcomes.

	Total population N=340	Male N= 204	Female N=136	P
In-hospital outcomes				
Heart failure	46 (13.5%)	34 (16.7%)	12 (8.8%)	0.026
Bleeding	30 (8.8%)	14 (6.8%)	16 (11.7%)	0.11
Death	8 (2.3%)	6 (2.9%)	2 (1.4%)	0.38
Follow-up				
Rehospitalisation	74 (21.7%)	54 (26.5%)	22 (16.1%)	0.04
Revascularisation	41 (12%)	22 (10.7%)	19 (13.9%)	0.9
6-month mortality	11 (3.2%)	7 (3.4%)	4 (2.9%)	0.8
12-month mortality	24 (7.1%)	11 (5.3%)	13 (9.5%)	0.14
3-year mortality	52 (15.2%)	26 (12.7%)	26 (19.1%)	0.11

Table 4. In-hospital and long-term mortality according to GRACE Score

	GRACE score ≥ 140	GRACE score < 140	p
In-hospital mortality	4 (8.7%)	4 (1.4%)	0.02
6-months mortality	5 (10.9%)	6 (2%)	0.002
12-months mortality	12 (26.1%)	12 (4.1%)	<0.001
36-months mortality	25 (54.3%)	27 (9.2%)	<0.001

Table 5. Independent predictors of death at 3 years in multivariable Cox regression.

	Log rank analysis		Cox regression		
	Log rank	P	HR	95% CI	P
Age >75	95.51	<0.001	5.45	2.9-10.03	<0.001
Hypertension	3.26	0.071	1.63	0.83-3.18	0.15
Diabetes mellitus	1.46	0.225	1.27	0.61-2.65	0.52
Heart failure on-presentation	35.54	<0.001	1.18	0.49-2.85	0.7
ST-segment deviation	5.25	0.022	1.86	1.04-3.33	0.036
Positive troponin assay	13.82	<0.001	0.52	0.23-1.14	0.52
Anemia	28.08	<0.001	2.56	1.41-4.67	0.002
Severe CKD	2.67	0.1	0.71	0.16-3.07	0.71
LVEF <40%	31.25	<0.001	3.5	1.84-6.67	<0.001
GRACE score ≥ 140	74.11	<0.001	2.38	1.02-5.57	0.044

DISCUSSION

In the present study, we aimed at depicting the clinical and risk profile of patients presenting for NSTEMI-ACS in the current Tunisian healthcare context. We also presented therapeutic strategies implemented, early and long-term prognoses in this particular setting and independent predictors of death over a 3-year follow-up period. Major findings yielded by the present analysis could be summarized as follows: (a) we reported a strikingly high prevalence of classic atherosclerosis risk factors in Tunisian patients presenting for NSTEMI-ACS, (b) although short-term mortality rates were fairly low in the study population, 3-year mortality rate was quite high, and (c) as in other settings, ECG signs, anemia on-admission, low

LVEF and a high GRACE risk score have been confirmed as long-term predictors of adverse prognosis in our context.

As for several developing countries worldwide, the Tunisian population is witnessing an epidemiological transition characterized by a marked decline over the last decades, of infectious diseases as a cause of death in the adult, and the rise of non-communicable diseases such as cardiovascular diseases and neoplasms [4, 10, 11]. Such occurring changes are generally imputed to a so-called "lifestyle westernization" characterized by a substantial increase in carbohydrates and fat diet intake, a sedentary lifestyle, and an alarmingly high prevalence of tobacco smoking across age spectrum. Similar findings have already been reported in Middle-Eastern studies [12, 13]. Data about coronary artery disease from North African countries are nonetheless lacking and the impact of the implementation of contemporary therapeutic strategies such as aggressive novel anti-thrombotic regimens and revascularization in the acute setting has not so far been adequately assessed. Previous data from our local and national ST-elevation myocardial infarction (STEMI) registries are in accordance with the results from the present study with regard to the high prevalence of classic risk factors of coronary atherosclerosis [6, 14]. Nevertheless, prevalence of such risk factors in the NSTEMI-ACS setting reported herein is higher. Another peculiar finding brought by the present study is the relatively young age of patients presenting for NSTEMI-ACS, comparable with that reported in some Middle-Eastern reports, but younger than in western studies [15-17] denoting a more aggressive course of the atherosclerotic disease in our North-African population. Prevalence of cardiovascular risk factors was higher in female patients and distribution according to gender was the same as in previous reports from European cohorts [18]. Yet, that did not translate into a significant difference in mortality between the two genders.

Another interesting finding yielded by the current study is the relatively low early mortality rates in patients presenting for NSTEMI-ACS. In-hospital and 6-month outcomes remain comparable to those from other studies [19] and lower than early mortality reported in Tunisian patients presenting for STEMI [6]. Nevertheless, overall 3-year mortality was remarkably high (15.2%) and could be attributed to the importance of comorbidities in patients with CAD as a whole, but also in many instances, by an

insufficient patient adherence to secondary prevention measures and medical therapies in the Tunisian context. An additional follow-up effort needs to be implemented in healthcare facilities to better quantify and remedy this issue. Another determining factor related to the dire long-term prognosis reported could be the absence of coronary revascularization in many cases due to severe and diffuse CAD.

In the current study, 3-year follow-up was reported in all patients. This allowed us to obtain accurate survival trends according to several relevant prognostic factors. Advanced age was independently associated to worse long-term outcomes in survival analysis. These findings are in line with those from major reports but also with results in the STEMI setting [7, 20]. ST segment deviation on ECG, anemia and impaired LVEF appeared to be very potent predictors of death at 3-years. ST segment depression, especially when affecting several leads was proved to be well correlated to short and long-term survival in patients with NSTEMI-ACS [9]. Anemia and impaired LVEF were proved to be potent predictors of adverse outcomes across all the ACS spectrum [21, 22]. Interestingly, a high GRACE risk score (≥ 140) was also an independent predictor of death in our multivariate 3-year survival model. The GRACE risk score is a well validated tool for in-hospital and 6-month mortality prediction in patients presenting for ACS [23]. Despite not being a validation for longer term death prediction, our findings hint at a possible value of the GRACE score in predicting long-term mortality that needs to be confirmed. In the same vein, in a 10-year follow-up analysis of the Third Randomized Intervention Treatment of Angina (RITA-3) trial [24], the modified post-discharge GRACE score was shown to reliably discriminate patients presenting for NSTEMI-ACS at higher or lower risk of 10-year mortality.

Study limitations. Limitations of the present study are inherent to its retrospective and observational character. As a consequence, it did not take into account all potential confounders. Important variables other than studied might not be included in the current survival prediction model. For some variables, statistical significance could not be reached due to the relatively small study population. Finally, we did not perform any comparison according to invasive treatment delays so that we determine what might be the optimal strategy in NSTEMI-ACS management in our context.

CONCLUSION

According to the present study, patients presenting for NSTEMI-ACS in our Tunisian context have a high cardiovascular risk profile. Long-term mortality is high and advanced age, ST segment deviation, anemia, impaired LVEF and high GRACE risk score are independent predictors of death in multivariate survival analysis.

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