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CLINICAL STUDY

Very early risk modeling in patients with chest pain based on the pattern on admission ECG

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ABSTRACT:
OBJECTIVES: The aim was to investigate the prognostic accuracy of admission ECG and its usefulness in determining the population at the highest risk of worse outcomes.
BACKGROUND: Fast and accurate assessment of chest pain patients remains a challenge for clinicians. Electrocardiogram (ECG) is performed in each case of suspicion of the cardiac origin of chest pain.
METHODS: Consecutive adult chest pain patients with suspicion of acute myocardial infarction (AMI) were enrolled in the study. The prognostic value of admission ECG changes alone and in combination with other clinical variables (cardiac troponin, diagnosis of AMI) were analyzed for the incidence of major adverse cardiac events (MACE) in a one-year observation.
RESULTS: The ischemic pattern on admission ECG was a single risk factor of MACE (HR 2.996 95% CI 1.31–6.86, p = 0.009), contrary to the single admission high-sensitivity cardiac troponin T assay (hs-cTnT) (HR 1.79 95% CI 0.695–4.61, p = 0.23). The highest risk of MACE was identified in case of the presence of both ischemic-ECG and positive hs-cTnT (HR 3.19 95% CI 1.496–6.81, p = 0.003).
CONCLUSIONS: The presence of ischemic changes in ECG in chest pain population with AMI suspicion increases the risk of MACE. The group at highest risk of MACE can by identified by the additional stratification with the admission single hs-TnT measurement *(Tab. 2, Fig. 4, Ref. 40)*. Text in PDF *www.elis.sk*
KEY WORDS: acute coronary syndromes, cardiac troponin, electrocardiogram, emergency department, chest pain.

Introduction

Chest pain remains a very frequent cause of Emergency Department (ED) admissions worldwide (1).Early identification of life-threatening medical conditions, such as acute myocardial infarction (AMI), is of utmost importance. It allows for the prompt implementation of effective treatments, which significantly contributes to reducing mortality rates. It is worth to highlight the fact that the chest pain group is heterogenous, and numerous medical disorders can mimic each other, which highly complicates the differential diagnosis and triage decisions. Among unselected ED patients with chest pain, up to 50 % suffer from the cardiac conditions (mostly acute coronary syndromes (ACS)) (2).

Despite many recent studies focusing on improvement in diagnosis and treatment, ACS cases place a substantial burden on the healthcare system (3–5). Implementation of high-sensitivity cardiac troponin (hs-cTn) assays in combination with rapid algorithms (0/1 h and 0/2 h) significantly shortened ACS diagnostic pathways (3–5). Regardless of hs-cTn assays` usefulness, consecutive guidelines recommend to set ACS diagnosis and perform the risk-stratification with the use of all available clinical data (such as symptoms, medical history, electrocardiogram (ECG) and other laboratory findings) (6).

For decades, electrocardiographic study remains to be regarded as one of the key parts of chest pain patients` differential diagnosis tools. A high proportion of ACS group (even over 30%) with normal ECG at the first medical contact, which may mislead clinicians and cause delay in the implementation of EBM therapy (2). The aim of this study was to investigate the prognostic accuracy of admission ECG and its usefulness in determining the population at the highest risk of poor outcomes.

Materials and methods

Study design

This prospective registry included consecutive adult patients admitted to the ED of the 2nd Department of Cardiology, Zabrze, Medical University of Silesia, Katowice, Poland, with chest pain and suspicion of AMI. Patients with the diagnosis of ST-Elevation Myocardial Infarction (STEMI) at admission were excluded from

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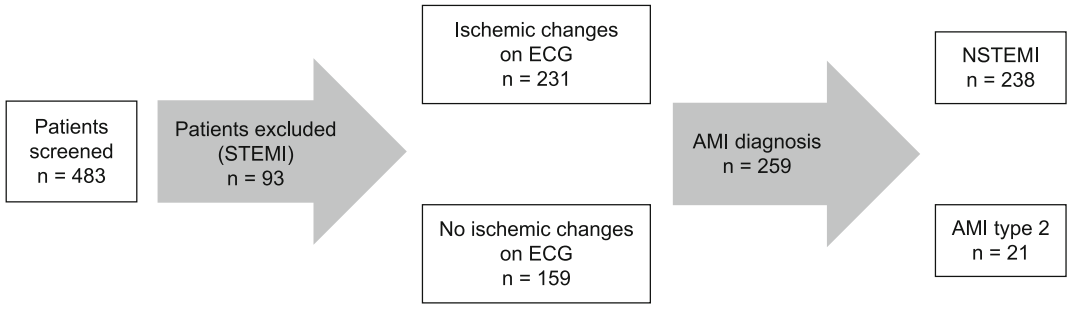

Fig. 1. Study chart. Among patients in whom the final diagnosis of AMI was excluded (n = 131), 98 suffered from cardiovascular causes (unstable angina – 43, arterial hypertension – 11, acute myocarditis – 11, arrhythmia – 11, chronic coronary syndrome – 6, heart failure – 5, acute pulmonary embolism – 4, takotsubo cardiomyopathy – 3, postpartum cardiomyopathy – 1, aortic aneurysm – 1, acute pericarditis – 1, aortic stenosis – 1) and 33 from non–cardiovascular causes (musculoskeletal pain – 26, gastroesophageal reflux disease – 5, acute cholecystitis – 2). STEMI – ST-Elevation Myocardial Infarction, ECG – electrocardiogram, AMI – acute myocardial infarction, NSTEMI – Non-ST-Elevation Myocardial Infarction.

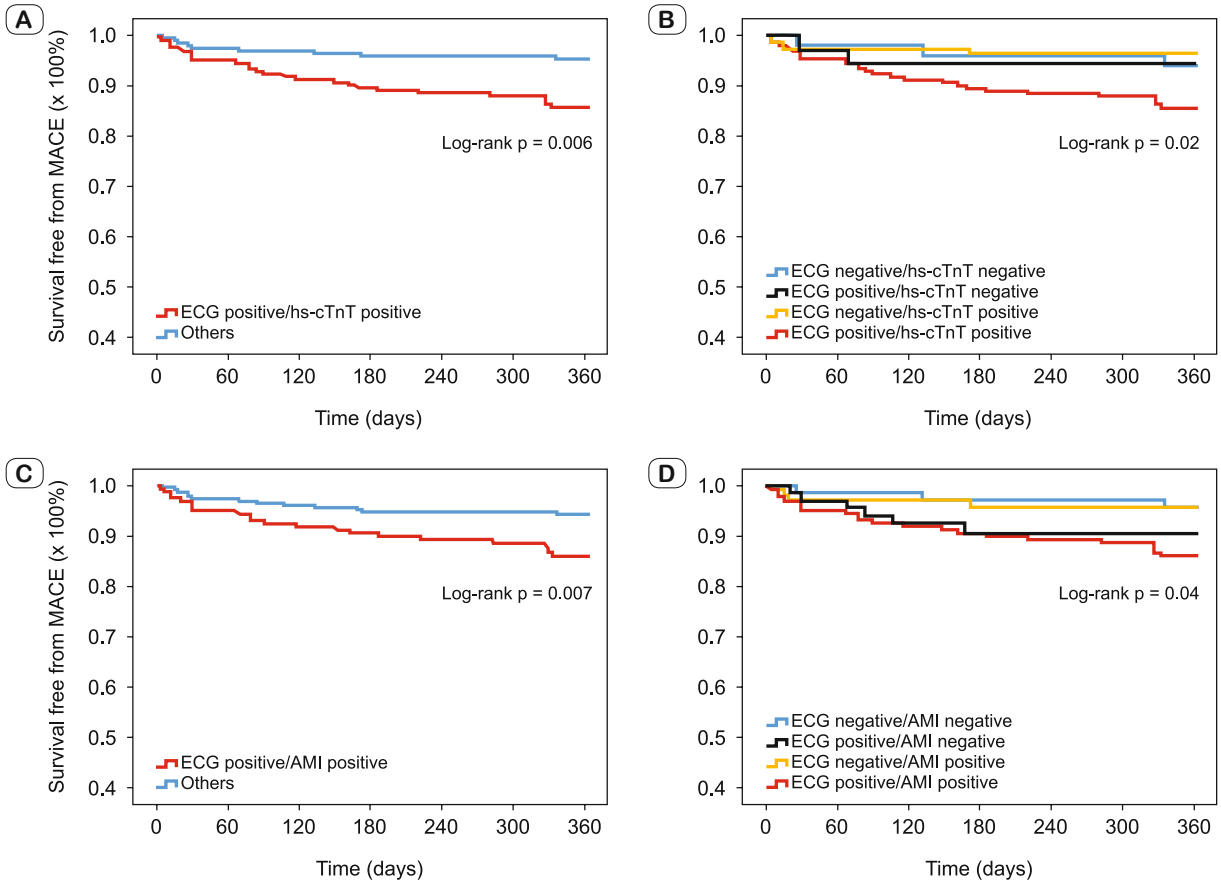

Fig. 2. Kaplan-Meier curves for one-year MACE-free survival for diverse combinations of patterns on admission ECG and high-sensitive cardiac troponin T concentration (A, B), pattern on admission ECG and the diagnosis of AMI (C, D). Positive ECG – presence of ischemic changes on admission ECG; negative ECG – no ischemic changes on admission ECG; AMI positive – final diagnosis of AMI; AMI negative – final diagnosis other than AMI.

the analysis due to particular diagnostic and therapeutic approaches (e.g. due to the need of urgent revascularization) and *a priori* poor outcomes, despite the significant management improvement in this population (1-year mortality of approximately 10 %) (7).

Written informed consent was signed by patients before inclusion. The study protocol is consistent with the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethical Committee (PCN/CBN/0022/KB/167/21). The design of the study,

Tab. 1. Baseline characteristics of patients, coronary angiogram findings, type of coronary intervention and one-year follow-up.

	Ischemic changes on ECG (n=231)	No ischemic changes on ECG (n=159)	p
Age (years)	66 (59–75)	62 (56–69)	0.001
Male sex	146 (63)	113 (71)	0.1
History:			
Coronary artery disease	83 (36)	60 (38)	0.72
Myocardial infarction	62 (27)	36 (23)	0.35
PCI	70 (30)	47 (30)	0.88
CABG	17 (7)	19 (12)	0.12
Peripheral artery disease	28 (12)	9 (6)	0.03
Risk factors:			
Diabetes	66 (29)	35 (22)	0.15
Hypertension	181 (78)	125 (79)	0.95
Hypercholesterolemia	119 (52)	87 (55)	0.53
Active smokers	43 (19)	33 (21)	0.6
History of smoking	73 (32)	68 (43)	0.02
Laboratory and echocardiographic findings:			
Hs-TnT (ng/l)	113 (23–367)	51 (11–259)	0.003
LDL (mg/dL)	116 (86–157)	119 (97–163)	0.4
CRP (mg/L)	5.65 (1.76–24.13)	3.13 (1.13–8.8)	0.1
WBC (103/μl)	8.9 (7.02–10.9)	8.1 (6.9–10.1)	0.09
Baseline EF (%)	48 (40–55)	53 (43–60)	<0.001
Baseline EDD (mm)	50 (47–54)	49 (45–54)	0.17
Baseline GFR (ml/min/1.73m^2)	80 (66–90)	85 (69–94)	0.02
Chronic medication:			
Aspirin	125 (54)	78 (49)	0.31
Vitamin K antagonists	18 (8)	10 (6)	0.57
Beta blockers	113 (49)	83 (52)	0.54
Statins	108 (47)	76 (48)	0.86
ACEIs	150 (65)	96 (60)	0.34
ARBs	16 (7)	16 (10)	0.27
Calcium antagonists	45 (19)	26 (16)	0.42
Nitrates	6 (3)	3 (2)	0.64
Proton-Pump Inhibitors	37 (16)	25 (16)	0.93
Amiodarone	0 (0)	0 (0)	n/a
Digitalis	3 (1)	1 (1)	0.52
Coronary angiogram findings (lesion location)	n = 219	n = 144	
LM	26 (12)	15 (10)	0.67
LAD	142 (65)	77 (53)	0.03
LCx	105 (48)	68 (47)	0.89
RCA	117 (53)	71 (49)	0.44
Bypass	6 (3)	13 (9)	0.008
Location of coronary intervention (primary PCI)	n = 219	n = 144	
LM	6 (3)	8 (6)	0.17
LAD	78 (36)	42 (29)	0.2
LCx	45 (21)	38 (26)	0.2
RCA	47 (21)	38 (26)	0.28
Bypass	4 (2)	5 (3)	0.32
Follow up at one year	n = 228	n = 159	
Death	23 (10)	6 (4)	0.02
AMI	17 (7)	3 (2)	0.01
MACE	28 (12)	7 (4)	0.006
Revascularization	19 (8)	8 (5)	0.19

Data are presented as median (25th–75th percentile) or n (%). PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; Hs-TnT – high-sensitive cardiac troponin T; LDL – low density lipoprotein; CRP – c-reactive protein; WBC – white blood cell count; EF – ejection fraction; EDD – end-diastolic diameter; GFR – glomerular filtration rate; ACEIs – angiotensin-converting enzyme inhibitors; ARBs – angiotensin receptor blockers; LM – left main coronary artery; LAD – left anterior descending coronary artery, LCx – left circumflex coronary artery; RCA – right coronary artery; AMI – acute myocardial infarction; MACE – major adverse cardiac events

data gathering, and analysis were conducted according to the STARD guidelines for studies of diagnostic/prognostic accuracy.

Clinical assessment and diagnosis

All included patients underwent routine initial assessment according to local protocol (medical history, physical examination, 12-lead ECG, echocardiographic examination, and laboratory tests, including the measurement of hs-cTn), which was performed by the ED physician. After exclusion of patients diagnosed with STEMI, which were directly transferred to the cardiac catheterization laboratory according to current guidelines, the remaining patients were divided into two groups composed of those with and without ischemic changes on admission ECG. Ischemia on ECG was defined according to the electrocardiographic criteria of ST-segment elevation and/or depression and negative T-waves from the 4th Universal Definition of AMI, Sgarbossa Criteria were implemented in patients with left bundle branch block (LBBB) (6). After the initial diagnosis of AMI, all patients underwent the treatment according to the current ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (8). The final diagnosis of AMI and its type was adjudicated at discharge by two independent cardiologists based on all data gathered during the hospital stay. In case the diagnoses were inconsistent, an additional cardiologist was asked for their opinion.

Follow-up and clinical endpoints

The follow-up for the occurrence of endpoints was obtained by telephone call to the patient and/or relatives 12 months after discharge. In case patients/relatives could not be reached on telephone, a written form of contact was used. In case of contact failure, data on mortality were gathered from the National Health Fund. The primary endpoint was major adverse cardiac event (MACE), defined as death, non-fatal myocardial infarction and/or acute revascularization.

Statistical analysis

For quantitative variables, the data were checked for normality of distribution with Shapiro-Wilk test, and then compared between groups with Student's t-test or Mann-Whitney U test according to distribution. For qualitative variables, Chi square test was applied. Categorical variables are presented as n (%), continuous variables as median (25th–75th percentile). Univariate and then multivariate COX analyses were used for MACE prediction. Variables that reached statistical significance in univariate model were included in the multivariate analysis. Kaplan–Meier analysis for different risk models of MACE was assessed and compared with log-rank test. All tests were two-tailed. The p value of < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL) and GraphPad Prism, version 6.00 (GraphPad, La Jolla, California, USA).

Results

Out of the total of 483 consecutive ED patients who presented with chest pain, 93 with the diagnosis of STEMI were excluded. This left 390 cases available for analysis. After admission ECG assessment, 231 patients were assigned to the group with ischemic changes on ECG (59 %) (among them 3 with LBBB and 9 with RBBB) and 159 to the group with no ischemic changes on ECG (41 %, including 21 patients with history of LBBB and 2 with RBBB). The final diagnosis of AMI was adjudicated in 259 patients (65 %), among them 238 (92 %) with Non-ST-Elevation Myocardial Infarction (NSTEMI), and 21 patients (8 %) with AMI type 2 (Fig. 1). The median of duration of hospital stay was 6 (5–9) days.

Patients with ischemia on admission ECG were older (p = 0.001) and more frequently had the history of peripheral artery disease (p = 0.03); fewer cases of ex-smokers were reported in this group (p = 0.02). Regarding baseline laboratory and echocardiographic findings, they had a higher concentration of high-sensitivity troponin T (hs-TnT) (p = 0.003), lower glomerular filtration rate (GFR) (p = 0.02) and lower ejection fraction (EF) (p < 0.001). Considering the results of coronary angiogram, in the ischemic ECG group, the left anterior descending coronary artery was affected more frequently (p = 0.03). This group also had a higher one-year incidence of MACE driven by a higher rate of AMI and death. There was no statistically significant difference in chronic medication between the two groups (Tab. 1).

Ischemia on admission ECG was a single risk factor of MACE at year one (hazard ratio (HR) 2.996 95% confidence interval (CI) 1.31–6.86, p = 0.009), whereas the single admission hs-TnT concentration and final diagnosis of AMI were not (HR 1.79 95% CI 0.695–4.61, p = 0.23 and HR 1.53 95% CI 0.72–3.27, p = 0.27, respectively) (Tab. 2). Ischemia on ECG remained significant in the multivariate model (HR 2.35, 95% CI 1.01–5.49, p = 0.048) along with admission hs-TnT (HR 1.0, 95% CI 1.00–1.001, p = 0.002) and EF (HR 0.95, 95% CI 0.93–0.98, p < 0.001). The combination of ischemic ECG with the final diagnosis of AMI increased the predictive value of AMI alone (HR 2.48, 95% CI 1.25–4.93, p = 0.009). The patients with ischemic pattern on ECG and final diagnosis of AMI had a worse prognosis than others (log rank p = 0.007) (Fig. 2 C,D). The analysis of the prognostic value of particular ischemic changes on admission ECG revealed that the pattern of ST-segment depression was a single risk factor of MACE (HR 2.12, 95% CI 1.08–4.17, p = 0.03). The pattern of

Tab. 2. Univariate Cox regression model for MACE at one year.

Characteristic	HR	95% CI	p
Hs-cTnT concentration (admission)	1.79	0.695–4.61	0.23
Final diagnosis of AMI	1.53	0.72–3.27	0.27
Ischemia on admission ECG	2.996	1.31–6.86	**0.009**
ST–segment depression	2.12	1.08–4.17	**0.03**
Negative T-wave	1.37	0.7–2.66	0.36
Age	1.045	1.014–1.078	**0.004**
Sex	1.473	0.69–3.143	0.32
Diabetes mellitus	2.657	1.366–5.167	**0.004**
GFR	0.986	0.972–1.001	0.06
EF	0.945	0.923–0.967	**<0.001**

HR – hazard ratio; CI – confidence interval; Hs-cTnT – high-sensitive cardiac troponin T; AMI – acute myocardial infarction; ECG – electrocardiogram; GFR – glomerular filtration rate; EF – ejection fraction

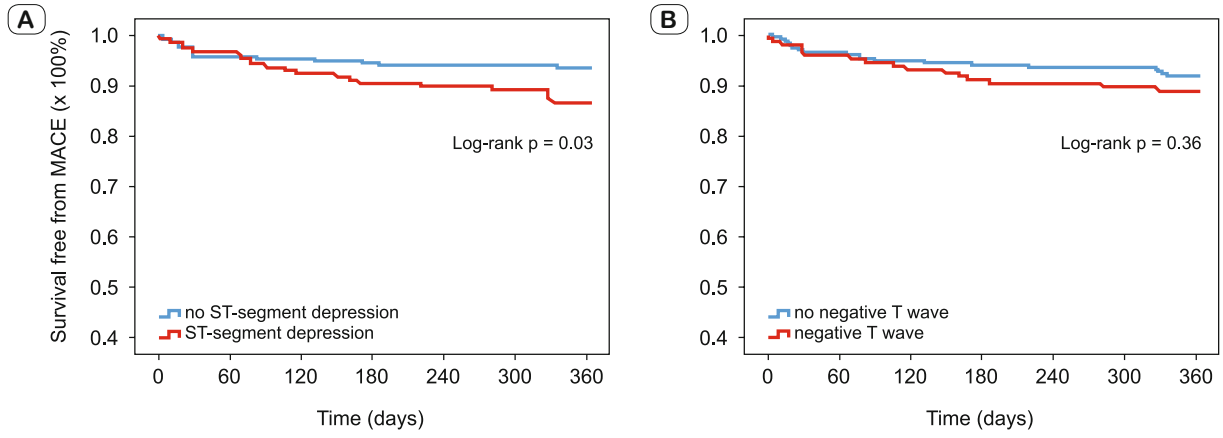

Fig. 3. Kaplan-Meier curves for one-year MACE-free survival between groups with/without the ST-segment depression (A) and presence/absence of negative T-wave on admission ECG (B).

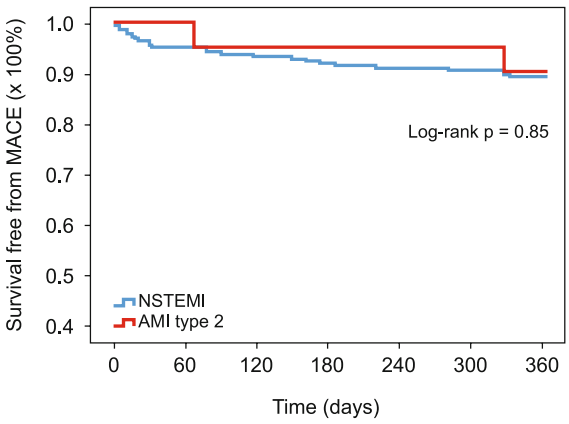

Fig. 4. Kaplan-Meier curves for-one year MACE-free survival depending on the type of AMI.

negative T-wave did not reach statistical significance (HR 1.37, 95% CI 0.7–2.66, p = 0.36). These results were also confirmed in Kaplan–Meier analysis (Fig. 3).

There was no difference in MACE-free survival between patients diagnosed finally with NSTEMI (89%) or AMI type 2 (91 %) (log rank p = 0.85) (Fig. 4). Among patients diagnosed with AMI type 2, all reported cases of MACE occurred in the ECG-ischemic group. A tendency to a worse clinical outcome in patients with ischemic changes on admission ECG as compared to those without ischemic changes was shown, but did not reach statistical significance (log rank p = 0.31).

There was a significant but weak correlation between the presence of ischemia on admission ECG and hs-TnT concentration (r = 0.175, p = 0.001) with 194/231 (84 %) positive admission hs-TnT cases in ischemic ECG group and 110/159 (69 %) in patients with no ischemia on ECG. The combination of ischemic ECG and positive hs-TnT at admission identified the group of patients at the highest risk of MACE at year one in Cox analysis (HR 3.19 95% CI 1.496–6.81, p = 0.003). Kaplan-Meier survival analysis confirmed that the combination of ischemic ECG and positive admission hs-TnT is a more valuable predictor of MACE than any other combination of those two variables (Fig. 2 A,B).

Discussion

The aim of this study was to investigate the prognostic accuracy of the admission ECG and assess its utility in identifying the population at the highest risk of adverse outcomes. As a result of the analysis, four major factors have been identified.

Firstly, ischemic pattern on admission ECG was present in 60 % of patients admitted with chest pain and it was a strong risk factor of one-year MACE in this population. Ischemic changes on admission ECG also worsened the prognosis in patients finally diagnosed with AMI.

Secondly, the mid-term risk prediction with ischemic ECG was driven by ST-segment depression, while single negative T-waves did not increase the risk.

Thirdly, incorporating an early single hs-TnT meaurement upon admission in addition to evaluating the ischemic ECG, proved to be superior in identifying the highest risk group for adverse events. This combined approach yielded a higher hazard ratio compared to relying solely on the ischemic ECG or hs-TnT alone. It also outperformed the risk stratification based on the final diagnosis of AMI, which was conducted at a later stage.

Fourthly, considering equal one-year rates of MACE in patients with NSTEMI and AMI type 2, ischemic changes on admission ECG in patients diagnosed finally with AMI type 2 tend to increase the mid-term risk in this group which results in equal one-year MACE-free survival as in patients diagnosed finally with NSTEMI.

It is a well-known fact that ischemic changes in ECG help to identify the group with the highest risk of adverse events. Our study corroborates numerous previous publications that revealed the utility of ECG as a tool for risk stratification (9–22). The most useful prognostic ECG change is the ST-segment depression. In general, the prognosis in the group of patients with any significant ST-segment depression is worse than in the group without pathological findings (11, 14, 16). It serves as a marker of poor income, encompassing both qualitative and a quantitative aspects (11, 14, 18). Contrary to the latter ECG change, transient ST-segment elevation (< 20 minutes) is associated with better outcomes (9, 15, 17). The data on the prognostic value of T-wave inversion are inconsistent (10, 12, 13). Our results confirmed that the presence of ST-segment depression has a high predictive value for the incidence of MACE and clearly showed no influence on the outcome of isolated negative T-waves.

The current guidelines highlight the need for a complex patient assessment (2, 6, 8). Hs-cTn tests are the most sensitive and the most specific markers of myocardial injury available for common use. They became the cornerstone in the diagnostic and prognostic assessment of ACS (2–6, 8, 23–27). Researchers worldwide continue to analyze this field to further improve and shorten available diagnostic troponin-based protocols (2–6, 8, 23–26, 28, 29). However, we have to be aware of delays in cTn-based algorithms. Firstly, cardiac troponin release is a time-dependent phenomenon, thus we can come across the “troponin-blind interval” (time between the myocardial injury and cTn release) (23). This issue commonly causes the need for serial blood sampling. Secondly, the turn-around time between obtaining the blood sample and receiving the final cTn concentration is a time-consuming process and may take up to one hour, depending on the local logistics (30). Unlike the Hs-cTn test, ECG is one of the most available and fast diagnostic tools in patients with chest pain and the suspicion of ACS. Nevertheless, given the limited correlation of ischemia on the admission ECG and positive result of hs-TnT testing in admission blood sample, it is advisable to combine these two tests Such an approach enhances the individual prognostic capabilities of each o test and seems to be valuable and easy-to-use in clinical practice.

The rate of MACE in presented study was driven by the death rate and AMI. The incidence of reinfarction resembles those shown in several previous studies. Importantly, it demonstrated a considerable increase in patients presenting with ischemia on admission ECG. Although there is some discrepancy in the literature on the influence of the initial diagnosis of AMI on reinfarction occur-

rence (31); consistent up-to-date data substantiate that the final diagnosis of AMI stands as one of the most robust predictive factors for subsequent AMI in the follow-up period (32–34), which is in contrast to our results. Moreover, our study showed that the initial assessment based on ECG and hs-TnT measurement upon admission demonstrated superior prognostic capabilities compared to relying solely on the final diagnosis of AMI. Considering the potentially life-threatening nature of recurrent AMI during long-term follow-up can lead to mortality rates as high as 50 % (35), our results suggest that in a real-life population of patients with chest pain, initial risk stratification based on ischemic ECG and positive hs-TnT might be more effective than the assessment conducted at the end of hospitalization after setting the final diagnosis. In our case, the median duration for such delayed assessment was 6 days. This approach may significantly influence patient management in sense of earlier implementation of protective strategies, rehabilitation or more intense education on modifying the behavioral actions.

The delay in risk stratification with ECG and cTn measurement combination may be further minimalized by implementation of point-of-care tests (POCT) (28, 29). As it is a novel approach, more data are still needed in this field, but some recent publications revealed promising results and confirmed the utility of POCT (28, 29). On the other hand, it has been recently reported that the combination of non-ischemic ECG and a single hs-cTn measurement (below the limit of quantitation) is a safe approach for ruling out ACS indicating a very low risk of adverse events (2, 36, 37). This approach exhibits an even higher negative predictive value and sensitivity for MI or death compared to relying solely on very low concentrations of cTn (37). Fast triage (high or low-risk group) substantially reduces time necessary for implementing the potential treatment, and thus lowers the costs and period of ED/hospital stay (30).

It is worth noting that groups with types 1 (NSTEMI) and 2 of AMI differ in baseline characteristics, but have comparable long-term outcomes (38, 39). This seems particularly relevant when we consider the heterogeneity of AMI type 2 group as well as the fact that in clinical practice, such patients are frequently treated solely with medical therapy. Moreover, in such cases, the dual antiplatelet therapy is used less often than in the PCI-treated group, which contradict the available evidence (40). Our study confirmed similar mid-term outcomes in NSTEMI and AMI type 2 patients. Interestingly, all MACE cases in the group with AMI type 2 were observed in the subgroup with ischemic changes on baseline ECG. The result did not reach statistical significance presumably due to the low number of events but it suggests a potentially useful tool for identifying patients at the highest risk of adverse events wherefore, considering more strict supervision for such a group would be warranted.

Conclusions

The presence of ischemic pattern on admission ECG in patients presenting with chest pain and suspected for AMI but without ST-segment elevation is a significant risk factor of adverse events at one year. By incorporating an additional early stratification step that includes a a single hs-TnT measurement upon admission identifies the group at the highest risk of adverse events, thus enabling a faster and more accurate risk stratification process compared to relying solely on delayed assessment based on the final diagnosis at the end of the hospital stay. The predictive ischemic pattern on admission ECG should be as attributed to ST-segment depression rather than to negative T wave. The group of patients finally diagnosed with AMI type 2 have a similar mid-term prognosis compared to the group with the final diagnosis of NSTEMI. However, the presence of ischemic pattern on the admission ECG seems to worsen the prognosis in this population.

Study limitations

The main limitation of our study is its single-center nature, To furter validate and generalize our findings, multicenter analysis would be necessary. Additionally, the limited number of AMI type 2 cases restricts our ability to draw definitive conclusions regarding this specific group of patients. Another limitation is the use of standard ECG as the diagnostic tool. While evaluating patients with high frequency ECG would be scientifically valuable, it is not commonly available in clinical practice, and our study did not aim to specifically assess this aspect.

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