**Online Material**

**ECG interpretation & clinical assessment**

The ECG was reinterpreted by a cardiologist afterwards, who based the diagnostic criteria for ischemia on the **universal definition of MI.**[**1**](#_ENREF_1) **This included any ST-depression (≥0**.**05 mV) or T-wave inversion (≥0**.**1mV) in two contiguous leads, or ST-elevation (≥0**.**1 mV or ≥0**.**2 mV in V2/3). Additionally, the heart rhythm and any blocks (bundle branch or atrio-ventricular) were recorded. The ECG was determined to be ischemic, when ischemic signs, ventricular arrhythmias, high-grade (>1) atrio-ventricular block, right, left, or bifascicular bundle branch block were observed. Echocardiography was performed in most patients admitted to the ED and acutely interpreted by a cardiologist. It was deemed pathological when reduced left-ventricular function or wall-motion-abnormalities were observed. Atrial fibrillation was defined by the admission ECG or prior diagnosis in the medical records. The assessment of other clinical parameters and cardiovascular risk factors has been reported before.**[**2**](#_ENREF_2)

****Outcome****

All patients were followed by questionnaire via mail or phone, contact to the general practitioner, or review of medical records. In cases without any follow-up information, the local register of death was contacted and all cases of death were assessed. Mortality, any incident MI or any percutaneous coronary intervention (PCI) after discharge, and cardiac rehospitalization (any rehospitalization for a cardiac reason, including MI or revascularization) were registered. The exact cause of death was adjudicated by two cardiologists (JTN and DW) and based on the death certificate or the hospital letter. This information was available for all patients that had died during the follow-up period.

****Score development****

In order to build the diagnostic prediction model, we excluded non-MI patients from the analyses. We built receiver operating characteristic (ROC) curves to find the optimal cutoff of hs-TnI to distinguish T2MI from T1MI patients (one per hs-TnI sampling time point, i.e. at 0, 1, and 3 hours). The optimal cutoff for each of the three hs-TnI measurements was defined as the value that minimized the distance to the point (0, 1) in the respective ROC curve. This approach weights sensitivity and specificity equally, i.e. the “costs” of a false negative finding are assumed to be equal to the “costs” of a false positive finding. Other methods that weight sensitivity and specificity differentially exist. In our study, we did not have estimates for the “costs” of false negative or false positive findings. We chose, therefore, the approach that weights sensitivity and specificity equally. Using univariable logistic regression analysis, we assessed the associations between diagnosis of T2MI and the potential predictors age (<70 or ≥70 years), sex, hypertension (yes or no), systolic blood pressure (≤160 mmHg or >160 mmHg), hyperlipoproteinemia (yes or no), family history of CAD (yes or no), history of MI (yes or no), diabetes (yes or no), history of CAD (yes or no), smoking (yes or no), atrial fibrillation (yes or no), congestive heart failure (yes or no), hemoglobin (<10 g/dL or ≥10 g/dL), glomerular filtration rate (≤30 mL/min for 1.73 m² or >30 mL/min for 1.73 m²), radiating chest pain (yes or no), pathological changes in echocardiography or ECG (any or none), and the optimal cutoffs for hs-TnI (as defined above). We then built a multivariable logistic model starting with all potential predictors. The model was reduced using backward step-down selection with total residual AIC as the stopping rule.[3](#_ENREF_3) For each predictor in the final multivariable model as well as for the entire model, we built an ROC curve and computed the area under the curve (AUC). To account for over-optimism, we repeated the model selection procedure (including definition of optimal cutoffs of hs-TnI) in 1,000 bootstrap samples. Model calibration was investigated with a calibration plot. Based on the regression coefficients, we built a point-based score according to the method by Sullivan et al.[4](#_ENREF_4) All analyses were performed using R software (version 3.3.3; R Foundation for Statistical Computing).

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**Online Table 1: Baseline characteristics for non-MI and T2MI patients**

Displayed are the baseline characteristics for non-MI and T2MI patients.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **non-MI (N=1261)** | **T2MI (N=99)** | **p-value** |
|
| Age (years) | 63.0 (49.7, 74.0) | 72.0 (63.2, 78.0) | <0.001 |
| Female (%) | 460 (36.5) | 48 (48.5) | 0.023 |
| BMI (kg/m²) | 26.0 (23.6, 29.2) | 26.1 (22.7, 28.7) | 0.29 |
| Hypertension (%) | 819 (65.3) | 77 (77.8) | 0.015 |
| Systolic blood pressure (mmHg) | 145.0 (130.0, 160.0) | 143.0 (119.7, 160.0) | 0.22 |
| Hyperlipoproteinemia (%) | 461 (36.6) | 40 (40.4) | 0.51 |
| Family history of CAD (%) | 225 (18.5) | 14 (14.6) | 0.41 |
| History of MI (%) | 186 (14.8) | 14 (14.1) | 0.99 |
| Diabetes (%) | 153 (12.3) | 12 (12.1) | 1 |
| No history of CAD (%) | 856 (67.9) | 70 (70.7) | 0.64 |
| Former smoker (%) | 373 (29.7) | 28 (28.3) | 0.86 |
| Current smoker (%) | 288 (22.9) | 17 (17.2) | 0.23 |
| Atrial fibrillation (%) | 217 (17.2) | 34 (34.3) | <0.001 |
| Congestive heart failure (%) | 170 (13.5) | 25 (25.3) | 0.0021 |
| Hemoglobin (g/dl) | 13.8 (12.7, 14.8) | 13.7 (12.6, 14.7) | 0.39 |
| eGFR (mL/min for 1.73m²) | 79.6 (60.6, 93.9) | 62.8 (49.4, 79.2) | <0.001 |
| No radiating chest pain (%) | 923 (74.0) | 81 (82.7) | 0.075 |
| No pathological echo or ischemic ECG (%) | 883 (70.8) | 42 (43.8) | <0.001 |
| hs-TnI 0h (ng/L) | 5.2 (2.4, 10.3) | 24.6 (10.9, 159.2) | <0.001 |
| hs-TnI 1h (ng/L) | 5.0 (2.4, 10.5) | 49.0 (19.4, 253.8) | <0.001 |
| hs-TnI 3h (ng/L) | 5.8 (2.7, 12.1) | 108.4 (30.3, 602.2) | <0.001 |
| Angiography (%) | 176 (14.0) | 38 (38.4) | <0.001 |
| PCI (%) | 49 (3.9) | 0 (0) | 0.086 |
| **Only for T2MI patients** |  |  |  |
| No CAD confirmed by angiography (%) |  | 23 (60.5) |  |
| 1-vessel CAD confirmed by angiography (%) |  | 4 (10.5) |  |
| 2-vessel CAD confirmed by angiography (%) |  | 3 (7.9) |  |
| 3-vessel CAD confirmed by angiography (%) |  | 8 (21.1) |  |

**Online Table 2: Underlying diagnoses of patients with T2MI**

|  |  |  |
| --- | --- | --- |
| Cause of T2MI | N | % |
| Severe hypertension | 22 | 22.2% |
| Atrial fibrillation | 18 | 18.2% |
| Atrial tachycardia | 14 | 14.1% |
| Acute decompensated heart failure | 12 | 12.1% |
| Takotsubo cardiomyopathy | 7 | 7.1% |
| Ventricular tachycardia | 6 | 6.1% |
| Pulmonary embolism | 6 | 6.1% |
| Non-obstructive CAD | 5 | 5.1% |
| Vasospasm | 3 | 3.0% |
| Aortic value stenosis | 3 | 3.0% |
| Pneumonia | 1 | 1.0% |
| Hypertrophic obstructive cardiomyopathy | 1 | 1.0% |
| Bradycardia | 1 | 1.0% |
| **Total** | **99** | **100%** |

**Online Table 3: Adjusted outcome results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Mortality** | **Incident non-fatal MI** | **Revascularization** | **Rehospitalization** |
|   |   | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **T1MI vs non-MI** | Non-adjusted | 2.63 (1.63, 4.23) | <0.001 | 4.35 (1.58, 11.98) | 0.0044 | 3.07 (1.86, 5.05 | <0.001 | 1.80 (1.36, 2.39 | <0.001 |
| Adjusted for Sex and Age | 2.11 (1.31, 3.40 | 0.0023 | 4.26 (1.51, 11.97) | 0.0060 | 2.50 (1.51, 4.14) | <0.001 | 1.60 (1.20, 2.13) | 0.0012 |
| Adjusted for Sex, Age and CAD | 1.99 (1.23, 3.21) | 0.0052 | 3.51 (1.24, 9.91) | 0.018 | 2.26 (1.37, 3.74) | 0.0015 | 1.51 (1.14, 2.01) | 0.0043 |
| **T2MI vs non-MI** | Non-adjusted | 3.24 (1.85, 5.70) | <0.001 | - | - | 0.25 (0.03, 1.83) | 0.17 | 0.98 (0.61, 1.58) | 0.94 |
| Adjusted for Sex and Age | 2.34 (1.33, 4.11) | 0.0032 | - | - | 0.23 (0.03, 1.69) | 0.15 | 0.88 (0.54, 1.43 | 0.61 |
| Adjusted for Sex, Age and CAD | 2.41 (1.37, 4.23) | 0.0023 | - | - | 0.27 (0.04, 1.97) | 0.20 | 0.93 (0.58, 1.51 | 0.78 |
| **T1MI vs T2MI** | Non-adjusted | 1.22 (0.64, 2.35) | 0.54 | - | - | 0.08 (0.01, 0.61) | 0.015 | 0.55 (0.32, 0.93) | 0.025 |
| Adjusted for Sex and Age | 1.10 (0.57, 2.13) | 0.77 | - | - | 0.09 (0.01, 0.68 | 0.019 | 0.58 (0.34, 0.99 | 0.047 |
| Adjusted for Sex, Age and CAD | 1.16 (0.59, 2.26) | 0.67 | - | - | 0.10 (0.01, 0.77) | 0.027 | 0.65 (0.38, 1.13) | 0.13 |

**Online Table 4: Cause of death of T2MI patients**

The individual causes of death of T2MI are provided in this table. Furthermore, the maximum (after 3 hours) hs-TnI, hs-TnT and CK of the initial hospital admission are presented.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient | Cause of death | Days until death | hs-TnI (ng/L) | CK (U/L) |
| 1 | Pulmonary embolism | 22 | 2022 | 96 |
| 2 | Sepsis | 23 | 6235 | 67 |
| 3 | Ileus | 32 | 7 | 25 |
| 4 | Gastric cancer | 46 | 27 | 41 |
| 5 | Pancreatic carcinoma | 71 | 103 | 39 |
| 6 | Cholangio carcinoma | 107 | 151 | 229 |
| 7 | Pulmonary embolism | 156 | 326 | 208 |
| 8 | Heart failure | 175 | 12 | 13 |
| 9 | Pneumonia | 190 | 386 | 1783 |
| 10 | Pneumonia | 287 | 8 | 153 |
| 11 | Pneumonia | 309 | 50 | 35 |
| 12 | Pneumonia | 358 | 20 | 74 |
| 13 | COLD | 373 | 281 | 302 |
| 14 | Mamma carcinoma | 428 | 435 | 117 |
| 15 | Heart failure | 530 | 220 | 129 |

Abbreviations: T2MI = Type 2 myocardial infarction, hs-TnI = high-sensitivity troponin I, hs-TnT = high-sensitivity troponin T, CK = creatininkinase, COLD = chronic obstructive lung disease.

**Online Table 5: AUC for differentiation of T1MI and T2MI**

We present the original area under the ROC curve (AUC) and the corrected AUC after 1.000 bootstrap samples to correct for over optimism.

|  |  |  |
| --- | --- | --- |
|  | AUC (original) | AUC (corrected) |
| Female sex | 0.586 (0.526, 0.647) | 0.585 (0.525, 0.646) |
| No radiating chest pain | 0.634 (0.581, 0.686) | 0.634 (0.582, 0.687) |
| Baseline hs-TnI ≤ 40.8 ng/L | 0.635 (0.575, 0.696) | 0.635 (0.575, 0.696) |
| All selected variables | 0.751 (0.695, 0.807) | 0.709 (0.674, 0.786) |

**Online Table 6: Diagnostic performance of the developed point score**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Score** | **Probability of T2MI (%)** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Total number ofT2MI cases** | **TP** | **FP** |
| 0 | 5 | 100.0 (96.2, 100.0) | 0 (0, 2.0) | 34.7 (29.0, 40.6) | NaN (0, 100.0) | 95 | 95 | 179 |
| 1 | 17 | 100.0 (96.2, 100.0) | 20.1 (14.5, 26.7) | 39.9 (33.6, 46.4) | 100.0 (90.3, 100.0) | 95 | 95 | 143 |
| 2 | 42 | 80.0 (70.5, 87.5) | 66.5 (59.1, 73.3) | 55.9 (47.1, 64.4) | 86.2 (79.3, 91.5) | 95 | 76 | 60 |
| 3 | 72 | 9.5 (4.4, 17.2) | 95.0 (90.7, 97.7) | 50.0 (26.0, 74.0) | 66.4 (60.3, 72.2) | 95 | 9 | 9 |

**Online Figure 1: Dynamic hs-TnI changes in patients with T1MI and T2MI**

Presented are the median concentrations of high-sensitivity troponin I for T1MI and T2MI patients over the course of 3 hours after admission.

**Online Figure 2: ROC-Curve for determination of the optimal hs-TnI cutoff concentrations**

**Online Figure 3: Calibration plot of the multivariable logistic regression model**

These results are based on the fitted multivariable regression model.



**Online Figure 4: ROC-Curve for the developed point score**

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**References**

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3. Harrell FE. Binary logistic regression: Regression modeling strategies. New York: Springer; 2006.

4. Sullivan LM, Massaro JM, D'Agostino RB, Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004; **23**(10): 1631-60.