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Clinical paper

# Out-of-hospital cardiac arrest in patients treated for ST-elevation acute myocardial infarction: Incidence, clinical features, and prognosis based on population-level data from Hungary

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ABSTRACT

*Aim:* Out-of-hospital cardiac arrest (OHCA) is a severe complication of myocardial infarction. Literature data on the incidence of OHCA are inconsistent, and population-level data are incomplete.

*Methods:* Based on the Hungarian Myocardial Infarction Registry, the incidence of OHCA and its 30-day and 1-year mortality, as well as the significance of factors influencing the course of the disease in 28,083 ST-elevation myocardial infarction patients, were investigated using multivariable regression models.

*Results:* Of the 28,083 STEMI patients, 1535 (5.5%) had OHCA, which was more likely to occur in men. The long-term incidence of OHCA did not change significantly; no significant seasonality was found either. However, the daily distribution of cases showed that most OHCA patients were admitted to the hospital around 8 p.m. The occurrence of OHCA significantly worsened patients' prognoses; both 30-day and 1-year mortalities were considerably higher in the OHCA group than in the control group (46% vs 11.6%, 53.2% vs 18.7%, $p < 0.001$). This difference accumulated in the first few months; conditional survival after six months was no worse in those who had OHCA. Compared to those without OHCA, cardiogenic shock was more common at the time of hospitalisation (18.4% vs 2.2%) in the OHCA group. The highest risk of death was caused by the co-occurrence of OHCA and cardiogenic shock, which led to an eight times greater hazard of death (HR: 8.41, 95% CI: 7.37–9.60, $p < 0.001$).

*Conclusion:* Multivariable analysis confirmed the independent prognostic significance of age, catheter intervention during the index hospitalisation, OHCA, and cardiogenic shock.



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## Introduction

Out-of-hospital-cardiac-arrest (OHCA) is a condition characterised by impaired cardiac pump function and collapse of the systemic circulation. There may be cardiac and non-cardiac causes behind the disease process. The cardiac reason in the vast majority of cases is myocardial ischemia and acute myocardial infarction (AMI). OHCA is the leading cause of cardiac-related mortality worldwide; however, the exact number of diseases is unknown because a significant number of OHCA occur unattended. The population-level incidence of OHCA related hospitalisations (among patients treated for myocardial infarction) is unknown because the vast majority of available data come from single-centre studies.[1–3] The present study aimed to examine the incidence, prognosis, and significance of factors influencing the prognosis of patients with ST-elevation myocardial infarction complicated with OHCA based on the data of a large number of unselected patients in the framework of a continuously functioning national mandatory myocardial infarction registry.

## Methods

The Hungarian Myocardial Infarction Registry (HUMIR) is a prospective, comprehensive disease registry of patients treated for acute myocardial infarction. Since 1 January 2010, the Intenet-based registry collects personal and clinical data on consecutive patients treated for an event of AMI in Hungary, a central European country with 9.8 million residents. Between 2010 and 2013, the registry operated voluntarily. Registering every patient with myocardial infarction in the HUMIR has been compulsory for all healthcare providers by law since 1 January 2014. The patient's data are managed according to the statute of CCXLVI/2013 of Hungary. Data capture covers 178 structured categories, including those regarding prehospital data, medical history, hospital treatment, the performed coronary interventions. The data is recorded in the online database by healthcare professionals from hospital documentation. The information is continuously checked and validated online by six part-time dedicated personnel. Outcome data, including vital status and repeated hospitalisations, are regularly received from the electronic database of the national Health Care Insurance Fund, the only insurer that finances the health care of the insured Hungarian citizens.

The protocol of the study is following the Declaration of Helsinki and have permission from the Hungarian Medical Research Council. HUMIR has continuously recorded the following data, among others, of patients treated for myocardial infarction: previous history, duration of prehospital period, major cardiac events during this period (OHCA, thrombolysis), date of hospital admission, treatment data, complications during treatment and their management, results of non-invasive tests preceding hospital discharge (such as cardiac ultrasound and stress testing), and the pharmaceutical treatment recommended upon hospital discharge.[4] The registry includes 90–92% of all treatments funded by the single national health insurance fund with an I21-I23 diagnosis code of the International Classification of Diseases. In line with the current guidelines[5], the diagnosis was established by the attending physician in each case. The occurrence of OHCA and resuscitation were recorded on hospital admission. However, no data concerning the hospitalisation details are available (e.g. ECG recorded during the complaint and cardioversion). In the HUMIR database, 28,083 patients treated for ST-elevation myocardial infarction (STEMI) between 1 January 2014 and 20 November 2018 were identified. The incidence of OHCA, survival and conditional survival curves and factors influencing the prognosis were examined. The control group included patients treated for STEMI but without OHCA. Vital data regarding 1-year follow-up were obtained from the National Health Insurance Fund's mortality registry, with no patient lost to follow-up Data received up to 15 May 2020 were taken into account and we had information on the 1-year condition of each patient.

Continuous variables are represented as mean ± standard deviation, while categorical variables as frequency (percentage). Survival and conditional survival curves are estimated with the non-parametric method of Kaplan and Meier. For the multivariable modelling of incidence, logistic regression was applied, while for survival time, the Cox proportional hazard model was used. For continuous variables, the potential non-linear effects were tested using spline expansion (i.e. generalised additive models were used). The admission date was entered into the model as a continuous variable with day precision, and the time was used with minute precision, i.e., no binning was applied. Calculations were carried out using the R statistical program package version 4.0.2, using the mgcv package version 1.8–31.

## Results

### *Temporal trends in the incidence of OHCA in STEMI*

Of the 28,083 STEMI patients, OHCA occurred in 1535 patients (5.5%). The annual incidence of OHCA patients is summarised in Table 1 (data from 2018 were processed until 30 November 2018) and is visualised in Fig. 1 using the continuous (i.e., day precision) date of the event. In a multivariable model controlling for age and sex, the occurrence of OHCA events did not significantly change over the years ($p = 0.1664$); similarly, the seasonal pattern was not significant either ($p = 0.4581$). However, the daily pattern was significant ($p < 0.001$): the admission of OHCA patients most likely took place around 8 p.m. (Fig. 2). OHCA was more likely to occur in men (OR = 1.23, 95% CI: 1.10–1.38, $p < 0.001$) but less likely with increasing age (OR = 0.93, 95% CI: 0.89–0.97 for +10 years, $p < 0.001$).

### *Comparison of clinical data of patients with and without OHCA*

Of the OHCA patients, 67.4% were male, with the corresponding percentage in the control group being 61.6%. The age of men in both groups was similar (61.4 ± 12.2 vs 61.8 ± 12.3 years). In the case of women, patients in the control group were older (66.7 ± 13.3 vs 69.4

**Table 1 – Incidence of OHCA within patients treated for for STEMI by year (95% confidence interval in parenthesis).**

| | OHCA+ | OHCA- | OHCA + incidence (%) |
|---|---|---|---|
| 2014 | 263 | 4284 | 5.78 [5.12–6.50] |
| 2015 | 306 | 5253 | 5.50 [4.92–6.14] |
| 2016 | 288 | 5733 | 4.78 [4.26–5.35] |
| 2017 | 342 | 5894 | 5.48 [4.93–6.08] |
| 2018 | 336 | 5384 | 5.87 [5.38–6.52] |
| Total | 1535 | 26548 | 5.47 [5.20–5.74] |

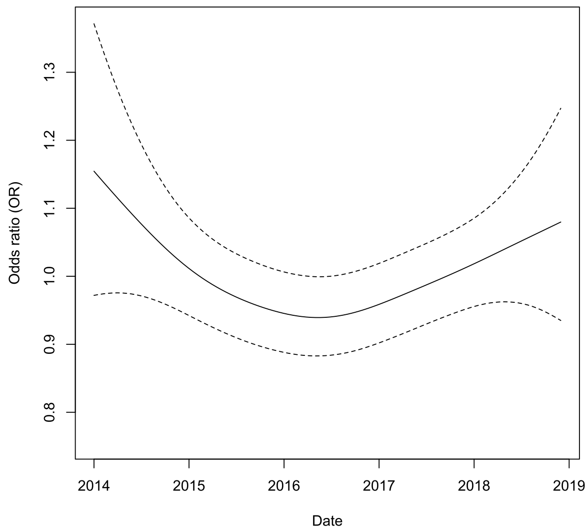


**Fig. 1 – The long-term trend (secular trend) of the occurrence of OHCA among STEMI cases. Dotted lines indicate 95% confidence interval.**

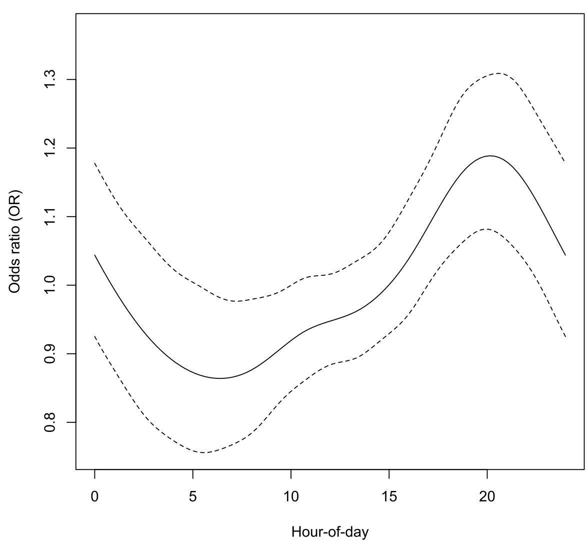


**Fig. 2 – Impact of the hour of the day (i.e., within-day pattern) on the occurrence of OHCA. Dotted lines indicate 95% confidence interval.**

± 12.9 years). Events and accompanying diseases in medical history are summarised in Table 2. A positive cardiac medical history (prior myocardial infarction, heart failure, PCI, or CABG) was not more common in the OHCA group. In the control group, the prevalence of hypertension, diabetes, known hyperlipidaemia, and active smoking was higher. At the time of hospital admission, cardiogenic shock (CS) occurred in 283 (18.4%) patients in the OHCA group and 573 (2.2%) patients in the control group.

### *Comparison of hospital care in the OHCA and control groups*

Coronary angiography (CA) was performed as soon as possible after admission to facilitate primary coronary intervention. Thrombolysis was not used in this patient population. CA was performed in 82.6% of the control group patients and 79.2% of OHCA group patients. Severe coronary status (main stem stenosis, three-vessel disease, and left main stem stenosis + three-vessel disease) was confirmed in 19.7% of OHCA group patients and 15.5% of control group patients. The proportion of negative coronary angiography results was similar in both patient groups (2.41% and 2.23%, respectively). In 79.2% of OHCA patients, stent implantation was performed during the primary percutaneous intervention (PCI), while 82.6% of control group patients underwent such an intervention.

### *Survival of patients with and without OHCA*

Total follow-up time was 71,204 person-years, the median duration of follow-up was 907 days (IQR: 438−1429 days).

The 30-day mortality in the control group was 12.0%, and in OHCA patients, it was 46.0%, while the 1-year mortalities were 19.2% and 55.6%, respectively. In the OHCA group, 43.7% in men and 49.2% in women died at 30-day, 51.2% and 57.4% at 1-year. In the control group, the corresponding figures were 8.9% and 15.8% at 30-day and 15% and 24.7% at 1-year in men and women. The mortality of OHCA patients was significantly higher on all examined dates and in both sexes. Within the groups, on all examined dates, the mortality of women was found to be higher. As Fig. 3 already suggests, most of the survival difference is accumulated in the first few months. This is more directly illustrated in Fig. 4, which shows conditional survival curves conditional on surviving six months. While the probability of surviving six months is much lower in the OHCA group, should a patient survive this time, his or her later survival is not negatively affected by the OHCA

### *Multivariable analysis of factors influencing mortality*

Using multivariable survival analysis, the following factors were identified as significant from a prognostic point of view: age, PCI performed during index hospital treatment, OHCA, and CS. In the model, the interaction was allowed between OHCA and CS, which turned out to be significant; the presence of both is, of course, associated with a higher risk than the presence of either but not as high as if their effect would have been additive. Interaction between age and sex was also allowed initially but turned out to be insignificant ($p = 0.5832$) and its impact on the main effects was also negligibile (hazard ratios being the same to one decimal points). The hazard ratios (HRs) of the covariates in the multivariable model are summarised in Table 3. The co-occurrence of OHCA and CS caused a more than eight-fold increase in death risk (HR: 8.41, 95% CI: 7.37−9.60, $p < 0.001$).

## Discussion

Myocardial infarction is a major, daily problem of emergency care, which is also indicated by the fact that questions concerning this clinical picture were also summarised in an editorial statement.[6] According to Kern's data,[7] out of 100 patients on whom resuscitation is performed due to OHCA, 40 reach hospital admission, and 10 leave the hospital alive. Several studies have confirmed the continuous improvement of STEMI patients' prognoses. At the same time, the prognosis of patients with STEMI who also had OHCA showed no change. In the United States, the incidence of OHCA in a quarter of a million patients treated for myocardial infarction was 3.8% based on data from 252 hospitals; this complication was 1.6% in NSTEMI, while 7.5% in the STEMI group.[10] Population data on the incidence of OHCA

**Table 2 – Patient characteristics according to the presence of out-of-hospital cardiac arrest.**

| | OHCA+ (n = 1535) | | OHCA- (n = 27,083) | | |
|---|---|---|---|---|---|
| Age ± SD | | | | | |
| Men | 61.38 ± 12.23 | | 61.8 ± 12.34 | | |
| Women | 66.67 ± 13.27 | | 69.37 ± 12.85 | | |
| Previous history | Valid N | Count (%) | Valid N | Count (%) | p |
| Myocardial infarction | 1326 | 300 (19.54) | 25,951 | 4063 (15.3) | 0.1133 |
| Congestive heart failure | 1288 | 188 (12.3) | 25,704 | 2305 (8.7) | <0.0001 |
| Stroke | 1308 | 103 (6.7) | 25,831 | 1978 (7.5) | 0.9853 |
| Hyperlipidaemia | 1143 | 300 (19.5) | 23,006 | 6899 (26) | <0.0001 |
| Smoking | 668 | 385 (25) | 17,909 | 8811 (31.4) | <0.0001 |
| PCI | 1363 | 250 (16.3) | 25,944 | 3456 (13.2) | 0.0882 |
| CABG | 1425 | 55 (3.6) | 26,122 | 660 (2.6) | 0.0318 |
| Co-morbidities | | | | | |
| Diabetes mellitus | 1320 | 350 (22.8) | 25,800 | 7457 (28.1) | 0.2478 |
| Hypertension | 1350 | 961 (62.6) | 26,904 | 19,525 (73.5) | 0.1189 |
| Peripheral artery disease | 1230 | 142 (9.3) | 24,650 | 2503 (9.4) | 0.5765 |

*p*-values not indicated in the table: age (p = 0.0016), sex (0.3767), age × sex interaction (0.2183).

*p*-values pertain to a logistic regression model which includes all the above covariate except for smoking (which was omitted from the model due to the higher number of missingness) with OHCA + being the response variable.

PCI = percutaneous coronary intervention; CABG = coronary bypass surgery.

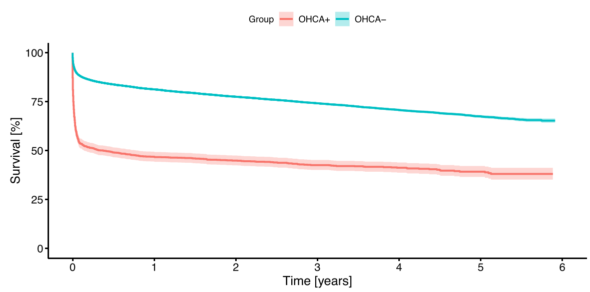


**Fig. 3 – Long-term survival after infarction stratified according to OHCA. Shaded areas indicate 95% confidence interval.**

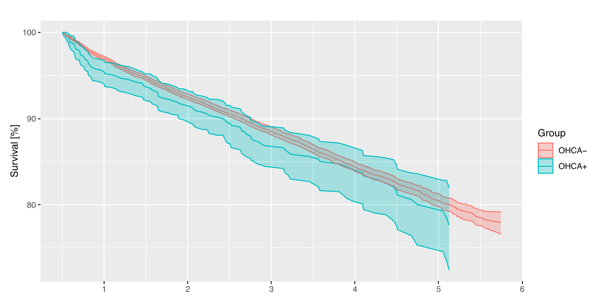


**Fig. 4 – Conditional survival after infarction given the survival of the first six months, stratified according to OHCA. Shaded areas indicate 95% confidence interval.**

were published by Dutch authors.[11] In half of this patient group OHCA occurred as a complication of acute myocardial infarction.[11] According to the AMIS Plus Registry, the incidence of OHCA was 6.8% in STEMI patients[8].

The 5.5% incidence of OHCA found in the present study is therefore in accordance with the findings of both of the above-mentioned European studies, and it is somewhat lower than the data of the American research. According to our data, men had a higher probability of having OHCA, and this observation again corresponds to literature data.[9,11,12] One possible explanation for this is that in the case of cardiac death in women, the reaction skills of witnesses are weaker; that is, they are less likely to attempt resuscitation.[11] While conducting our study, we found nearly unchanged annual incidences of OHCA, and the incidence during the year did not show a significant pattern (seasonality). In our recent study on AMI's daily distribution, the highest STEMI incidence was in the morning (under publication). Present observation that OHCA patients are most often admitted to the hospital around 8 p.m. is unique requires further investigation. In other studies[11,12] cardiovascular disease was more often present in the medical history of patients in the OHCA group. Still, the prognostic significance of this fact with reference to mortality is questionable.[2]

**Table 3 – Predictor variables of the multivariate survival models.**

| Variables | HR | 95% CI | | p |
|---|---|---|---|---|
| Age (+10 year) | 1.83 | 1.79 | 1.87 | <0.001 |
| PCI (not performed)) | 2.21 | 2.10 | 2.32 | <0.001 |
| Sex (women) | 0.95 | 0.91 | 1.00 | 0.04245 |
| OHCA/CS: only OHCA | 3.54 | 3.27 | 3.84 | <0.001 |
| OHCA/CS: only CS | 5.24 | 4.76 | 5.78 | <0.001 |
| OHCA/CS: OHCA + CS | 8.41 | 7.37 | 9.60 | <0.001 |

OHCA = out-of-hospital cardiac arrest; CS = cardiogen shock; PCI = percutaneous coronary intervention.

In our study, coronary angiography was performed in almost all patients during hospital treatment, and the revascularisation ratio was also around 80%. The high rate of invasive procedures is considerable even in international comparison; in Khera's[13] meta-analysis of a large case count, early coronary angiography of OHCA patients is only 44%, while in other studies[3] primary PCI was performed only in two-thirds of the patients, even though most publications[3,11,14,15] underlined the significance of PCI (see

Khera[13]). In our study, the symptoms of CS were also identified at hospital admission in one out of five successfully resuscitated patients (18.4%). The frequent co-occurrence of OHCA and CS has been confirmed by several studies.[2,16,17] Our mortality data confirm the unfavourable prognostic value of OHCA, as the 30-day mortality of OHCA patients is four times higher than that of control group patients, and their 1-year mortality is three times higher. The presence of CS had a significantly adverse effect on prognosis. Several studies have confirmed similar results.[3,7,18] In our study, the long-term unfavourable prognosis of the OHCA patient group could also be established. Still, it should be noted that this stems from the higher mortality in the first few months, after which there is no longer difference. In other studies, the mortality rates of those leaving the hospital alive were similar in the long run,[12,16,19] in line with our findings, even though the follow-up patient count in these studies was <50; thus, their data are inconclusive. According to the Danish Cardiac Arrest Registry's observational data,[20] early ICD implantation (<day 40) reduces the late-mortality of OHCA patients, and a Dutch study showed similar results.[21] A randomised controlled trial would be necessary to clarify the significance of the early ICD implantation.

Strength and limitation of the study: The present study's main contribution is that it had a large sample size in which nearly all patients treated for STEMI in a country with almost 10 million inhabitants were included without selection. However, several data are still not available, such as how long after the OHCA did resuscitation took place, what kind of cardiac rhythm made the resuscitation necessary, how long it lasted, and what was the patient's state of consciousness on hospital admission. Knowledge of all these factors would have made a more detailed prognostic analysis possible. Besides, we had no data to investigate patients who died before hospital admission could have taken place and hence are not registered in the HUMIR. Thus, it is crucial to note that all results pertain to the patient group who reached hospital after OHCA.

## Conclusions

In the case of STEMI, one in twenty patients is admitted to the hospital after an OHCA, and men had a higher probability of having this severe complication. One out of five successfully resuscitated OHCA patients had CS at the time of hospital admission. In a multivariable model controlling for age and sex, the occurrence of OHCA events did not significantly change over the years; similarly, the seasonal pattern was not significant. This OHCA patient group's mortality risk is several times higher than that of the control group, especially if the patient presented with CS at the time of hospital admission. Catheterised revascularisation was performed in the vast majority of patients.

## Ethical approval

The study plan was submitted for proper review to Hungarian Medical Research Council, which permitted the investigation (Number: 34858-3/2019/EKU).

## CRediT authorship contribution statement

AJ, TJ and PA were responsible for the conception and designed of the study. TF performed the statistical analysis. All author participated in the revising of the manuscript.

## Conflict of interest

Nothing to declare.

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