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Clinical paper

# Spatio-temporal distribution, prediction and relationship of three major acute cardiovascular events: Out-of-hospital cardiac arrest, ST-elevation myocardial infarction and stroke

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ABSTRACT

*Background:* Predicting the incidence of time-sensitive cardiovascular diseases like out-of-hospital cardiac arrest (OHCA), ST-elevation myocardial infarction (STEMI), and stroke can reduce time to treatment and improve outcomes. This study analysed the spatio-temporal distribution of OHCAs, STEMIs, and strokes, their spatio-temporal correlation, and the performance of different prediction algorithms.
*Methods:* Adults who experienced an OHCA, STEMI, or stroke in Canton Ticino, Switzerland from 2005 to 2022 were included. Datasets were divided into training and validation samples. To estimate and predict the yearly per-capita population incidences of OHCA, STEMI, and stroke, the integrated nested Laplace approximation (INLA), machine learning meta model (MLMM), the Naïve prediction method, and the exponential moving average were employed and compared. The relationship between OHCA, STEMI, and stroke was assessed by predicting the incidence of one condition, considering the lagged incidence of the other two as explanatory variables.
*Results:* We included 3,906 OHCAs, 2,162 STEMIs, and 2,536 stroke patients. INLA and MLMM yearly predicted incidence OHCA, STEMI, and stroke at municipality level with very high accuracy, outperforming the Naïve forecasting and the exponential moving average. INLA exhibited errors of zero or one event in 82%, 87%, and 72% of municipalities for OHCA, STEMI, and stroke, respectively, whereas ML had errors in 81%, 89%, and 71% of municipalities for the same conditions. INLA had a prediction error of 0.87, 0.77, and 1.50 events per year per municipality for OHCA, STEMI and stroke, whereas MLMM of 0.70, 0.74, and 1.09 events, respectively. Including in the INLA model the lagged absolute values of the other conditions as covariates improved the prediction of OHCA and stroke but not STEMI. MLMM predictions were consistently the most accurate and did not benefit from the inclusion of the other conditions as covariates. All the three diseases showed a similar spatial pattern.
*Conclusions:* Prediction of incidence of OHCA, STEMI, and stroke is possible with very high accuracy using INLA and MLMM models. A robust spatio-temporal correlation between the 3 pathologies exists. Widespread implementation in clinical practice of prediction algorithms may allow to improve resource allocation, reduce treatment delays, and improve outcomes.

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## Introduction

Among cardiovascular diseases, out-of-hospital cardiac arrest (OHCA), acute coronary syndrome (ACS) and stroke represent the main causes of out-of-hospital deaths.[1] Such diseases share several predisposing factors and a common pathogenesis. About two-third of all OHCAs are either related to ACS or ST-segment elevation myocardial infarction (STEMI).[2] In acute stroke patients, myocardial ischemia and arrhythmias frequently occur, even in the absence of primary heart disease.[3] Risks of stroke, ACS and heart failure is also higher in survivors of OHCA when compared with population controls.[4] In addition, OHCA, ACS, and stroke are all considered time-sensitive cardiovascular diseases, meaning that immediate access to the patient and rapid treatments significantly reduce morbidity and mortality, limits neurological damage, and improves long-term prognosis.

Evidence is accumulating that the incidence of cardiovascular diseases is influenced not only by time but also by geographic location.[5–7] Factors like air pollution, climate, socioeconomic status, and population density can all vary by location and impact the occurrence of these conditions.[6,8,9] Additionally, temporal patterns might vary based on demographic changes or fluctuations in environmental stressors.[7] For this reason, spatio-temporal analysis has been proposed[10] to identify patterns that may be region-specific or time-dependent, which can helps tailor prevention strategies and resource allocation more effectively. An immediate application of this approach may be found in the development of public health strategies targeting communities at higher risk (e.g., awareness campaigns and first aid training) and in the optimization of automated external defibrillator (AED) coverage. Spatio-temporal analysis has already been applied to identify areas with high OHCA incidence and low bystander CPR,[11,12] as well as to predict future OHCA events with high accuracy at municipality level and at a short time horizon.[13,14]

In contrast to OHCA, there have been no attempts to apply spatio-temporal predictive modelling to ACS and stroke. To address the knowledge gap in the spatio-temporal distribution of OHCA, STEMI, and stroke incidence at municipality level, we implemented statistical and machine learning methods and evaluated their performance in predicting the spatio-temporal variation (between municipalities, and between years) in the incidence of each of the three pathologies separately. Subsequently, to test our hypothesis that STEMI and stroke events can enhance the prediction of future OHCA incidence, we conducted a joint statistical analysis of the three time-dependent acute cardiovascular diseases to understand spatio-temporal correlation. Similarly, we evaluated how STEMI and OHCA events can improve the prediction of future stroke incidence and how strokes and OHCA can improve the prediction of future STEMI incidence. The performance of these advanced statistical and machine learning methods was then compared with simpler approaches.

## Material and methods

### *Patient population*

All individuals over 18 years old residing in the Canton Ticino of Swiss who suffered an OHCA of medical origin, STEMI, or stroke event in this region were included in the study. Cases with missing geolocalization coordinates and patients not residing in Ticino (e.g., tourists or occasional workers) were excluded. The exclusion of non-residents was on the basis that they were unlikely to be exposed to the same contextual influences (e.g. socio-economic and environmental factors) that could affect disease incidence.[5,6] Given that the analysis focused on the possibility of predicting each cardiovascular condition using data from others, paediatric patients were excluded because OHCA was rare ($< 2$ %), and no occurrences of STEMI or strokes were recorded in this population in our database.

The definition of OHCA excludes cases with non-medical origin and obvious and irreversible signs of death (e.g., rigor mortis) for which resuscitation efforts are not initiated or when a do-not-resuscitate order is in place. OHCA is defined as cessation of cardiac mechanical activity, confirmed by the absence of signs of circulation, occurring outside of a hospital setting.[15] Because the definition of ACS has continuously changed over time,[16] we restrict our research only to those patients presenting with a STEMI. STEMI was defined as persistent chest discomfort or other symptoms suggestive of ischemia and ST-segment elevation in at least two contiguous leads.[17] Stroke was defined as a non-transient acute episode of neurological dysfunction caused by an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, non-traumatic intracerebral haemorrhage, and non-traumatic subarachnoid haemorrhage.[18] Diagnosis of STEMI and stroke were confirmed during hospital admission. The methodology of this study is consistent with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational studies.

### *Registries*

The Ticino Registry of Cardiac Arrest (TIRECA), the STEMI (Preh-STEMI) registry, and the Stroke (Preh-Stroke) registry are all web-based, prospectively designed, and have the respective goal to monitor OHCA, STEMI and stroke events in the Swiss Canton Ticino. These registries are designed to identify potential areas for improvement in cardiac and neurological emergency care. The TIRECA registry has been described previously.[19] In short, the registry was established on January 1, 2002; however, consecutive, and audited data have been entered starting on January 1, 2005. It contains a record of every individual with an emergency medical service (EMS)-confirmed OHCA of any aetiology, and includes patient's demographic data, comprehensive EMS-related data, detailed bystander and first responder activity including the use of AEDs or public access defibrillators as well as pre- and in-hospital treatments and outcomes. Prior to April 2009, OHCA events were manually geolocated based on the address provided by the ambulance; all subsequent OHCAs were automatically geolocated. The STEMI registry and stroke registry have been activated on January 1, 2009 and January 1, 2013 respectively. As for TIRECA, both Preh-STEMI and Preh-Stroke registries contain a record of every individual who presented a STEMI or stroke of any aetiology, and includes patient's demographic data, comprehensive EMS-related data, pre- and in-hospital treatment as well as outcome. Coverage is complete because the EMS is activated for all emergencies involving OHCA, suspected ACS, and stroke. Moreover, patients who self-present at the hospital with suspected ACS or stroke were also included in the registries, thanks to a data-sharing agreement between EMS and hospitals that ensures comprehensive data collection across the three registries. The location of each medical event was determined by the event location for patients where EMS was activated, or by the residence location for patients who self-presented at the hospital. Data are collected and stored following Good Clinical Practice Guidelines and the relevant legislation governing the use of patient data. The investigation complied with the Declaration of Helsinki's principles for physicians engaged in biomedical research involving human subjects and was approved by the ethics committee.

### *Geographical and municipalities data*

Canton Ticino, one of the 26 cantons forming the Swiss Confederation, covers an area of 2,812 square kilometres. As of December 31st, 2022, the population of Ticino was around 360,000 residents (128 inhabitants per square kilometre). The canton is divided into 117 municipalities that vary in both geographic size (ranging from 0.6 to 218 square kilometres) and population (ranging from 40 to 63,315 inhabitants). Some municipalities are small, densely populated urban areas, while others are larger, sparsely populated rural regions, with population densities ranging from 1.1 to 8,476 inhabitants per square kilometre.

Population totals by age and sex were retrieved from the Land Register of Canton Ticino (https://www3.ti.ch/DFE/DR/USTAT/index.php). To obtain prediction at another relevant, even if spatially coarser, level, municipalities were also aggregated according to the 5 EMS areas available in Canton Ticino. Each EMS area covers approximately 20 municipalities.

### *Statistical analysis*

The datasets for OHCAs, STEMIs, and strokes were divided into training and validation samples. The training datasets for OHCA, STEMI, and stroke spanned from 1st January 2005 to 31st December 2021; from 1st January 2013 to 31st December 2021; from 1st January 2015 to 31st December 2020, respectively. The models were tested on cases between 1st January and December 31, 2022 for OHCA and STEMI, and on cases between January 1 and December 31, 2021 for stroke.

To estimate and predict OHCA, STEMI and stroke yearly per-capita population incidences, two different models were applied: Integrated Nested Laplace Approximation (INLA) and Machine Learning Meta-Model (MLMM). In all the models, the outcome considered was the per-capita population incidence, and not the absolute number of cases, to avoid spurious correlations stemming from population sizes. This was achieved by including an offset term in the models, representing the population size in each municipality, in each year. The spatio-temporal analysis of OHCA using INLA was recently described [10,11,20,21], with the only difference that the currently proposed model is more parsimonious, since excludes, without loss of forecast precision, the joint spatial and temporal component. In brief, INLA is a numerically approximated spatio-temporal Bayesian statistical method, and MLMM is an ensemble of different machine learning models (e.g., random forest, gradient boosting, XGBoost, neural networks, and generalized linear model), in which a *meta*-model combines predictions from different base models to produce an improved final prediction. More details are available in the Supplemental Methods. All the algorithms and scripts used are available in an open-source repository on GitHub.com (https://github.com/Fede-stack/Spatio-temporal-distribution-prediction-and-relationship-of-three-major-acute-cardiovascular-events/).

INLA and MLMM were each compared with two simpler statistical models: the Naïve Prediction and the Exponential Moving Average. The Naïve Prediction model predicts next year incidence to be equal to the one in the previous time instant, whereas the Exponential Moving Average uses an exponential smoothing factor to weight recent data more significantly than older data when computing the moving average that serves as the prediction.

The goodness of prediction was verified on the test sets by two different approaches: 1) the mean absolute error (i.e., the average, over all municipalities, of the differences in absolute value between the actual and predicted number of OHCAs, STEMIs, and strokes); 2) the Chi squared statistic (i.e., the sum, over all municipalities, of the squared prediction error, divided by the predicted number of events, and regularized to avoid computational problems with null predictions (the denominator of the statistic is increased by a fixed quantity 0.5).

Finally, the relationship between OHCA, STEMI and stroke was assessed by estimating and predicting OHCAs including the lagged values of STEMI and stroke among the explanatory variables, to appreciate if the knowledge of past STEMI and stroke improved forecast of OHCA. A similar exercise is then performed by looking at the prediction of STEMI using lagged values of OHCA and stroke, and at the prediction of stroke using lagged values of OHCA and STEMI.

In all models, the percentage of the population divided by age groups and the percentage of people for the two sexes are the only external covariates used, plus a dummy variable that takes value equal to one in correspondence of big cities (Lugano, Bellinzona, Mendrisio, Locarno, and Chiasso).

Descriptive statistics were used to summarize data on characteristics and outcomes. Categorical data were reported as absolute values and percentages, while continuous variables were presented as mean and standard deviation. R and Python were used for statistical analysis and models implementation.

## Results

### *Population*

Throughout the study period, 5,257 OHCAs, 2,556 STEMIs, and 4,219 S occurred. After excluding OHCA patients not residing in Ticino (N = 728), those with a non-medical aetiology (N = 573), age less than 18 years or missing (N = 31), and missing geolocation data (N = 19), 3,906 adults constituted the OHCA study population (Supplemental Fig. 1). For STEMI, following the exclusion of 376 cases in patients not residing in Ticino, six cases with age less than 18 years or missing, and 12 cases with missing geolocation data, the STEMI population comprised 2,162 adults (Supplemental Fig. 1). In the case of stroke, after excluding 669 cases occurring in the same patients, 365 cases in patients not residing in Ticino, 94 cases of traumatic aetiology, 546 cases of transient ischemic attacks, and nine cases with missing geolocation data, the stroke analysis included 2,536 adults (Supplemental Fig. 1). Repeated cases of STEMI and OHCA were not excluded from the analysis. The demographic and clinical characteristics of patients with OHCA, STEMI, and stroke are presented in Supplemental Table 1.

### *Accuracy of OHCA, STEMI, and stroke event prediction*

Fig. 1 depicts the model performance for each disease. Overall, both INLA and MLMM demonstrated high prediction accuracy at the municipality level. When utilizing the INLA prediction model, there was an error of zero or one event in 96 municipalities (82 %) for OHCA, 102 municipalities (87 %) for STEMI, and 84 municipalities (72 %) for stroke. Similarly, the MLMM exhibited an error of zero or one event in 98 municipalities (84 %) for OHCA, 100 municipalities (85 %) for STEMI, and 83 municipalities (71 %) for stroke (Fig. 1). Notably, from the same figure, the largest OHCA prediction errors of 8 and 11 obtained with INLA decreased to 4 and 5 with MLMM. The largest STEMI prediction errors only marginally decreased from 7 and 8 STEMIs with INLA to 5 and 6 with MLMM. Similar results were reported for the benchmark models Naïve and EMA, showing a significantly worse performance for OHCA and STEMI (Fig. 1).

In comparison to simpler statistical estimates, INLA and MLMM consistently achieved more accurate predictions of OHCAs, STEMIs, and strokes, as evidenced by lower mean absolute errors and chi-square measures (Table 1). Regarding OHCA, MLMM exhibited a prediction error of 0.70 events per year per municipality, making it the most accurate model compared to INLA and simpler statistical methods. INLA and the simpler EMA performed similarly, with a prediction error of 0.87 and 0.88 OHCAs per year per municipality, respectively, but INLA had a greater number of predictions with null error.

Concerning STEMI prediction, from the same table, the MLMM model demonstrated a prediction error of 0.74 events per year per municipality, establishing itself as the most accurate model. INLA outperformed simpler statistical methods (NP and EMA) to a more significant extent. Regardless of the model used, stroke event prediction had the highest error compared to OHCA and STEMI. However, MLMM exhibited the highest accuracy. Similarly to OHCA, MLMM and INLA are particularly better in STEMI and stroke predictions with zero or one error.

When predicting events at the level of the EMS area (Fig. 2), MLMM was superior or comparable to the other approaches; in contrast, INLA overestimated the number of strokes, and both the proposed approaches seem to predict better than the simpler NP and EMA methods, for all diseases.

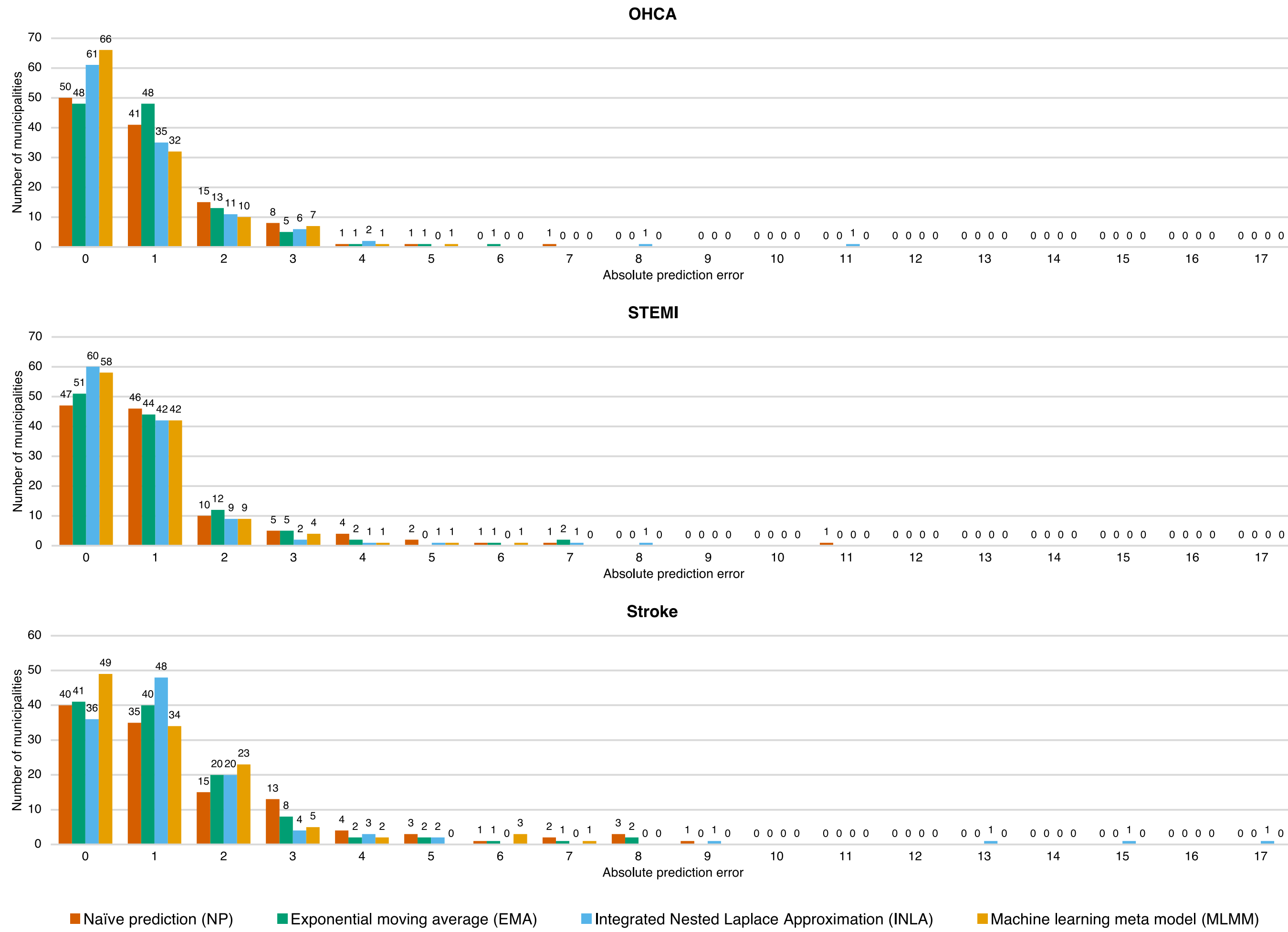


**Fig. 1.** Absolute prediction error (x axis) by number of municipalities (y axis) for out-of-hospital cardiac arrest (OHCA), ST-segment elevation myocardial infarction (STEMI) and stroke with Naïve prediction (NP), exponential moving average (EMA), integrated nested Laplace approximation (INLA) and the Machine Learning Meta Model (MLMM).

**Table 1**
Prediction performance of the four models in terms of mean absolute error and Chi squared statistic (lower values indicate better performance) in different scenarios: prediction of out-of-hospital cardiac arrest (OHCA), prediction of ST-segment elevation myocardial infarction (STEMI), prediction of stroke.

| | OHCA | | STEMI | | Stroke | |
|---|---|---|---|---|---|---|
| **Model** | **Mean absolute error** | **Chi squared statistic** | **Mean absolute error** | **Chi squared statistic** | **Mean absolute error** | **Chi squared statistic** |
| Naïve prediction (NP) | 0.95 | 98.31 | 1.12 | 207.42 | 1.61 | 301.09 |
| Exponential moving average (EMA) | 0.88 | 66.74 | 0.98 | 119.32 | 1.30 | 145.08 |
| Integrated Nested Laplace Approximation (INLA) | 0.87 | 65.57 | 0.77 | 83.77 | 1.50 | 95.49 |
| Machine learning meta model (MLMM) | 0.70 | 55.84 | 0.74 | 78.86 | 1.09 | 80.82 |

## Relationship between OHCA, STEMI, and stroke

Including past STEMIs and strokes as covariates improved the prediction accuracy of OHCA using the INLA model: the prediction error decreased from 0.87 (Table 1) to 0.79 (Table 2) OHCAs per year per municipality. The inclusion of STEMI and stroke also reduced the largest errors from 8 and 11 (Fig. 1) to 6 and 8 (Fig. 4, **left**). However, for municipalities in which past OHCA alone predicted OHCA in 2022 with an error of zero or one event, the inclusion of past STEMIs and strokes did not improve the model performance.

The prediction error for STEMI with the INLA model remained unchanged at 0.77 STEMIs per year per municipality (Table 1**,** Table 2), regardless of whether past OHCAs and strokes were included as covariates in the prediction. The inclusion of OHCA and stroke reduced the largest error from 8 (Fig. 1) to 7 (Fig. 4**, middle**), but it did not increase the number of municipalities where the prediction error was zero or one event.

The inclusion of past STEMIs and OHCAs for predicting stroke events reduced the prediction error with INLA from 1.50 S per year per municipality (Table 1) to 1.42 (Table 2). The incorporation of STEMIs and OHCAs improved the performance of the INLA model, reducing the four largest errors from 9, 13, 15, and 17 (Fig. 1) to 7, 13, 13, and 14 (Fig. 4**, right**). The number of municipalities with a prediction error of zero or one event increased from 84 to 89.

The predictions obtained by MLMM remained the most accurate model for OHCA, STEMI, and stroke prediction and were not improved

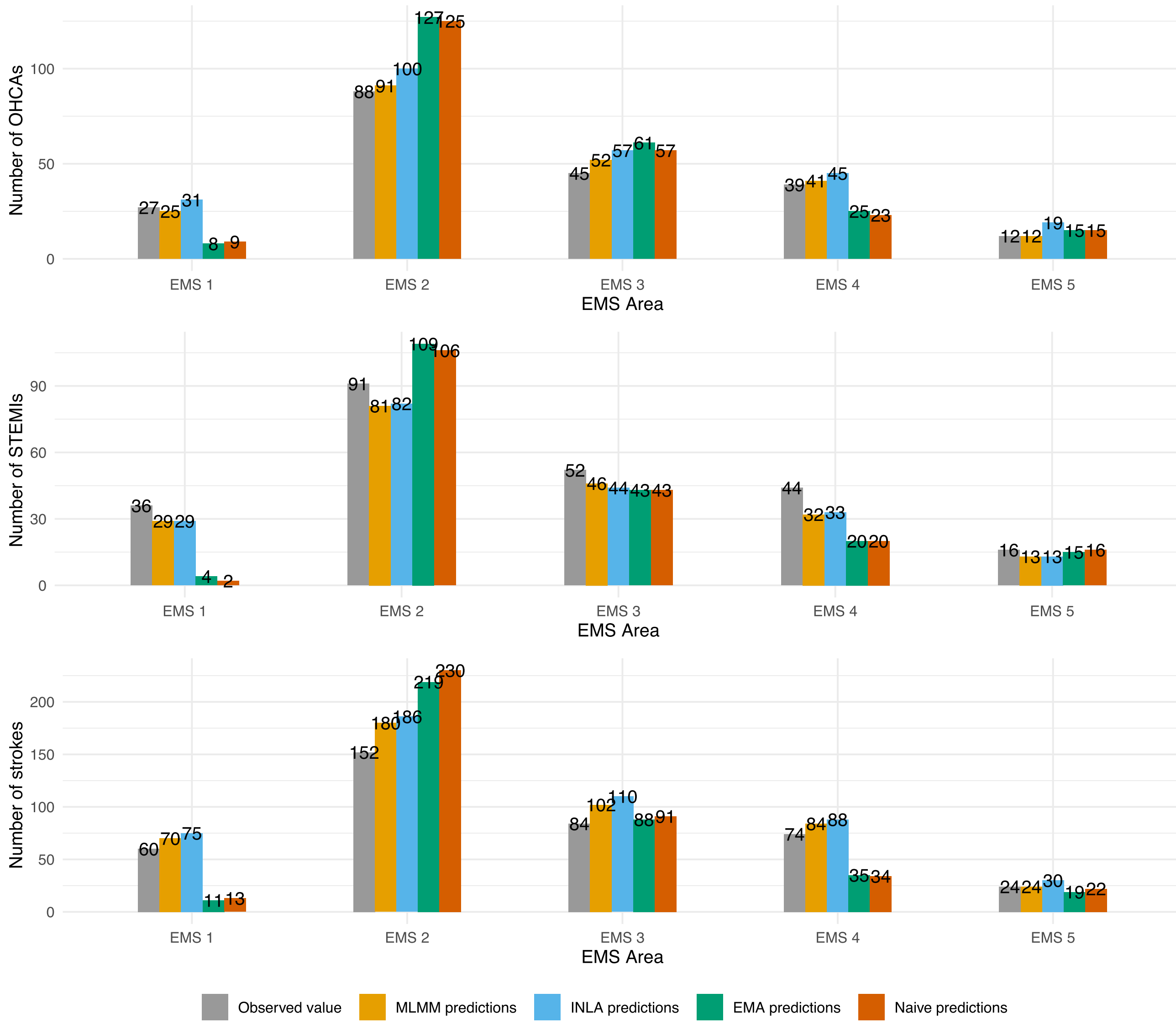


**Fig. 2.** Observed and predicted values of out-of-hospital cardiac arrest (OHCA), ST-segment elevation myocardial infarction (STEMI), and stroke with Naïve prediction (NP), exponential moving average (EMA), integrated nested Laplace approximation (INLA) and the Machine Learning Meta Model (MLMM) at emergency medical service (EMS) area level.

**Table 2**
Prediction performance of the four models in terms of mean absolute error and Chi squared statistic (lower values indicate better performance) in different scenarios: prediction of out-of-hospital cardiac arrest (OHCA), prediction of ST-segment elevation myocardial infarction (STEMI), prediction of stroke, using the other two diseases as explanatory variables.

| | OHCA with STEMI and stroke as explanatory variables | | STEMI with OHCA and stroke as explanatory variables | | Stroke with OHCA and STEMI as explanatory variables | |
|---|---|---|---|---|---|---|
| **Model** | **Mean absolute error** | **Chi squared statistic** | **Mean absolute error** | **Chi squared statistic** | **Mean absolute error** | **Chi squared statistic** |
| Naïve prediction (NP) | 0.95 | 98.31 | 1.12 | 207.42 | 1.61 | 301.09 |
| Exponential moving average (EMA) | 0.88 | 66.74 | 0.98 | 119.32 | 1.30 | 145.08 |
| Integrated Nested Laplace Approximation (INLA) | 0.79 | 58.72 | 0.77 | 82.73 | 1.42 | 88.50 |
| Machine learning meta model (MLMM) | 0.70 | 56.88 | 0.74 | 78.86 | 1.09 | 79.92 |

by the inclusion of the other two past diseases as covariates (Table 1, Table 2).

The OHCA risk map with the INLA prediction of OHCA with the auxiliary of past STEMIs and strokes is showed in Fig. 3 (bottom right). The observed and predicted numbers of OHCAs, STEMIs, and strokes displayed statistically significant spatial variability between municipalities. However, all three diseases exhibited a similar spatial pattern in their variability (Supplemental Table 2, Fig. 3). The between-municipality variability in the predicted number of OHCAs, as well as a similar spatial pattern among the three different events, were confirmed even when including past STEMIs and strokes as covariates (Supplemental Table 2, Fig. 4). Finally, the temporal component was significant

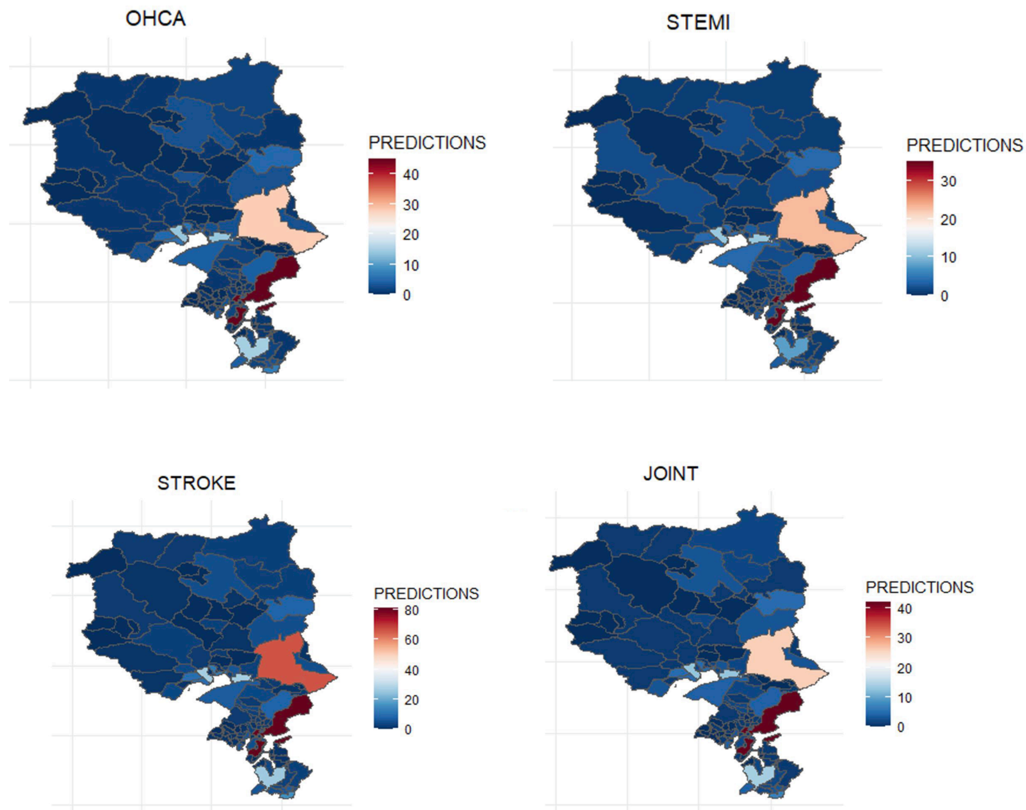


**Fig. 3.** Predicted INLA risk map of Ticino for out-of-hospital cardiac arrest (OHCA), ST-elevation myocardial infarction (STEMI), stroke, and OHCA supported by past STEMIs and strokes.

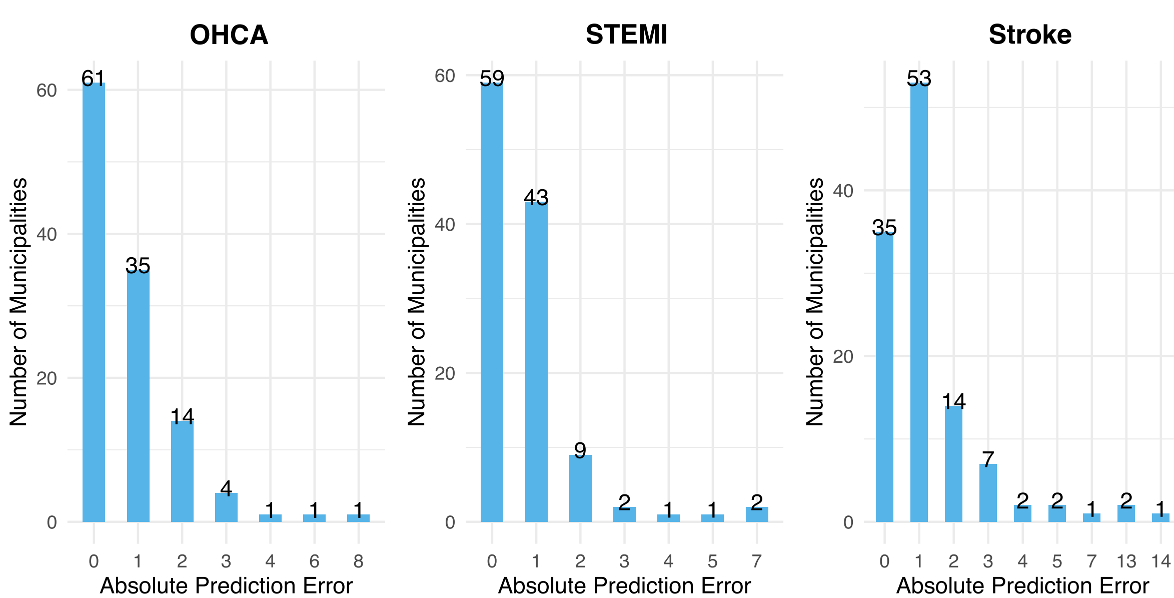


**Fig. 4.** Absolute prediction error of out-of-hospital cardiac arrest (OHCA) at municipality level (maximum number of municipalities: 117) with the auxiliary of past ST-segment elevation myocardial infarction (STEMI) and of past stroke using the integrated nested Laplace approximation (INLA).

for OHCA and STEMI, but not for stroke (Supplemental Table 3). When we included in the models the other past conditions for better prediction, we observed less temporal effect, even if still significant for STEMI prediction, since in some way captured by the temporal dynamics of the other past diseases.

## Discussion

To the best of our knowledge, this is the first study assessing the spatio-temporal distribution of three time-sensitive cardiovascular diseases: OHCA, STEMI, and stroke. We tested two different methods to predict their incidence and respective spatio-temporal distribution at the municipality level over a large European region, Canton Ticino, Switzerland, which includes both urban and extensive rural areas, characterized by rivers, lakes, valleys, and mountains. The use of INLA and MLMM successfully predicted OHCA, STEMI, and stroke with very high accuracy, outperforming simpler prediction procedures such as Naïve forecasting and the exponential moving average. Notably, the prediction of OHCA using INLA significantly improved when STEMI and stroke events were added as explanatory variables in the statistical model. This suggests the potential existence of a spatio-temporal correlation between the occurrence of OHCAs, STEMIs, and stroke events. A final noteworthy finding is the generalizability of the developed methodology, providing the ability to assess and predict the spatio-temporal distribution of one of the three considered acute pathologies when only basic demographic information, together with the temporal series of other acute cardiovascular diseases, are available.

### *Spatio-temporal distribution and prediction of OHCA, STEMI, and stroke*

Numerous studies have conducted spatial or spatio-temporal analyses to identify clusters (e.g., counties, neighbourhoods) at a higher risk of OHCA, OHCA-related mortality, or with an ineffective chain of survival.[11,12,22–25] Some studies have also aimed to improve resource allocation, such as the placement of public access defibrillators for better OHCA coverage.[21,26–28] More recently, a few studies employed machine learning to perform spatio-temporal analyses aimed at forecasting OHCA incidence.[11,13,14,29] Nakashima et al.[5] and subsequently Shimada-Sammori et al.[13,14] successfully predicted the daily incidence of OHCA of cardiac origin using machine learning, analysing data from a very large OHCA dataset (the All-Japan Utstein Registry) along with meteorological and chronological variables. Nakashima et al.[29] further confirmed the precision of their model in predicting the daily incidence of OHCA in the U.S. population. Taken together, these studies confirm the ability of modern machine learning algorithms to predict with high accuracy the incidence of OHCA at national and regional level.

Our study tested two different models: a spatio-temporal Bayesian model, known as INLA, particularly effective in analysing data that varies both in time and space, and the MLMM model that automatically optimizes the joint prediction performance of different machine learning algorithms. The results of our models showed a very high accuracy and prediction ability at municipality level. Compared to the current literature, our study significantly expands knowledge by applying modern prediction algorithms to two other time-sensitive cardiovascular diseases: STEMI and stroke. Both INLA and MLMM exhibited remarkable accuracy in predicting STEMI and stroke events individually. Furthermore, INLA and MLMM outperformed simpler prediction techniques such as Naïve forecasting and the exponential moving average. Importantly, by incorporating lagged values of STEMI and stroke events as explanatory variables within the INLA statistical model, we achieved a substantial improvement in the accuracy of OHCA prediction. These results support the inclusion of past cases of STEMI and stroke when predicting the future behaviour of OHCA, even when working with relatively short time series, as in our setting. This study provides initial evidence suggesting a possible spatio-temporal correlation between the occurrence of OHCAs, STEMIs, and strokes.

### *Implications of study findings for clinical practice*

OHCA, STEMI, and stroke are all time-sensitive cardiovascular diseases, making the evaluation and prediction of their spatio-temporal distribution paramount. Our study establishes the foundation for considering OHCA, STEMI, and stroke as proxies for each other concerning spatio-temporal distribution. The demonstration that these conditions share common geographical and temporal distributions creates a unique opportunity for targeted primary prevention strategies and treatment interventions. However, predicting stroke incidence was consistently more complex across different models. Stroke's heterogeneity, with its varied subtypes and risk factors, may make it harder to predict compared to the more homogenous OHCA and STEMI. Stroke may also be influenced by a broader range of chronic and acute factors that are harder to capture in models. In contrast, OHCA and STEMI share several pathophysiological mechanisms; for instance, the most common cause of OHCA is acute myocardial infarction. The ability to predict OHCA, STEMI, and stroke incidences with high accuracy provides decision-makers and healthcare institutions with a powerful tool. Such analyses are crucial for improving resource allocation, including the strategic placement of EMS, AEDs, and first responders. This can lead to increased patrolling in certain areas by small mobile intervention units to reduce response times and potentially improve outcomes. Furthermore, this predictive capability can be valuable for public health strategies targeting communities at higher risk. Initiating local public awareness campaigns or conducting focused training campaigns on first aid for these time-sensitive cardiovascular diseases can be informed by these predictions. Finally, user-friendly algorithms will be made accessible through interactive software, ensuring rapid access to updated estimations. The goal is to make information readily available for informed decision-making and proactive healthcare interventions.

### *Comparison of statistical methods used*

Another interesting aspect of our study is that we implemented and compared INLA, ML, and simpler prediction methods. In contrast, most other published studies have primarily used ML methods. It is worth noting that statistical and MLMM differ in key aspects beyond their different prediction abilities.[30] Machine learning algorithms typically show an automated ability to search and extract arbitrary complex features from data, removing the need to pre-specify features for prediction. Indeed, in our setting, the representations that synthesize the behaviour of each municipality, and that can be considered as the explanatory variables in the MLMM, are not easy interpretable. Also, one notable disadvantage of MLMM compared to INLA lies in the complexity of its hyperparameter optimization pipeline, which had an execution time of 20 minutes and 18 seconds. In contrast, the INLA model completed within 7 seconds under the same computational resources.

In future work, we will consider incorporating techniques such as permutation feature importance, as well as other explainability methods like LIME (Local Interpretable Model-agnostic Explanations)[31] and SHAP (SHapley Additive exPlanations)[32] to quantify the contribution of features to model performance. These techniques will help us better understand the model's decision-making process and enhance the transparency and interpretability of our models while maintaining the predictive power of the MLMM framework.

On the other hand, the explicit factors of age and sex in the INLA model are more intuitive and driven by domain knowledge. Explicit risk factors in more traditional models can help in gaining an understanding of the causes of acute cardiovascular events and in generalizing the evidence to new patients and geographies. Furthermore, our results confirm that machine learning methods can achieve higher prediction accuracy due to higher flexibility but require caution to avoid overfitting to data and the subsequent lack of reproducibility. In this regard, our joint usage of traditional statistical prediction methods, like INLA, alongside machine learning methods, specifically the MLMM method, can contribute to providing statistically meaningful predictions and can mitigate data-driven false associations in the data that do not correspond to clinical evidence.

### *Strengths and limitations*

Our study has several strengths. First, the Ticino Registry of Cardiac Arrest (TIRECA), the STEMI registry (Preh-STEMI) and the stroke registry (Preh-Stroke) are all prospectively designed registries to capture every individual who suffer an OHCA, a STEMI or a stroke of any aetiology. They collect detailed and comprehensive demographic, EMS, prehospital, in-hospital, and outcome data, allowing a complete coverage of Canton Ticino, Switzerland and representativeness of the predictive models. Second, compared with previous studies, we were able to improve the prediction of OHCA by adding STEMI and stroke events as covariates.

This study also has some limitations. First, variations over time in population density, weather changes, pollution, and the occurrence of public events were not considered in our model. These omissions expose our findings to the risk of missing confounders that, if appropriately included in a statistical model, could either improve or invalidate the demonstrated dependence between OHCAs, STEMIs, and strokes. On the other hand, limiting the external data used as inputs to the statistical models facilitates the implementation of our forecasting methods in clinical practice. Second, predictions were computed on a yearly basis because shorter-term predictions, although technically possible, were not feasible due to the high number of zero cases in small municipalities. Third, patients with missing geolocation coordinates were excluded: this could potentially bias OHCA incidence estimation and prediction; however, this group was extremely small (5 % of the total population), thus unlikely to affect our prediction model. Fourth, to avoid an excessive reduction in the sample size, since machine learning models require a substantial number of observations for training, the whole studies on the three diseases have been conducted on the whole population of patients, without discriminating along patients' features: analyses conducted on sub-populations of patients in predetermined age or sex groups could confirm our current findings or reveal different insights.

## Conclusions

Prediction of OHCA, STEMI, and stroke incidence was possible with very high accuracy in a mixed urban and rural area presenting with rivers, lakes, valley, and mountains using INLA and MLMM. Prediction performance of OHCA significantly improved when the incidence of STEMI and stroke events were added as explanatory variables in the INLA statistical model. This suggests the potential existence of a spatio-temporal correlation between the occurrence of these time-sensitive cardiovascular conditions. Widespread implementation in clinical practice of prediction algorithms may allow to improve resource allocation, reduce treatment delays, and improve outcomes.

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## CRediT authorship contribution statement

**Angelo Auricchio:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tommaso Scquizzato:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Federico Ravenda:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Ruggero Cresta:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation, Conceptualization. **Stefano Peluso:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Maria Luce Caputo:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Stefano Tonazzi:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Claudio Benvenuti:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Antonietta Mira:** Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100810.

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