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RESEARCH ARTICLE

Machine learning-based prediction of in-hospital death for patients with takotsubo syndrome: The InterTAK-ML model

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Aims Takotsubo syndrome (TTS) is associated with a substantial rate of adverse events. We sought to design a machine learning (ML)-based model to predict the risk of in-hospital death and to perform a clustering of TTS patients to identify different risk profiles.

Methods and results A ridge logistic regression-based ML model for predicting in-hospital death was developed on 3482 TTS patients from the International Takotsubo (InterTAK) Registry, randomly split in a train and an internal validation cohort (75% and 25% of the sample size, respectively) and evaluated in an external validation cohort (1037 patients). Thirty-one clinically relevant variables were included in the prediction model. Model performance represented the primary endpoint and was assessed according to area under the curve (AUC), sensitivity and specificity. As secondary endpoint, a K-medoids clustering algorithm was designed to stratify patients into phenotypic groups based on the 10 most relevant features emerging from the main model. The overall incidence of in-hospital death was 5.2%. The InterTAK-ML model showed an AUC of 0.89 (0.85–0.92), a sensitivity of 0.85 (0.78–0.95) and a specificity of 0.76 (0.74–0.79) in the internal validation cohort and an AUC of 0.82 (0.73–0.91), a sensitivity of 0.74 (0.61–0.87) and a specificity of 0.79 (0.77–0.81) in the external cohort for in-hospital death prediction. By exploiting the 10 variables showing the highest feature importance, TTS patients were clustered into six groups associated with different risks of in-hospital death (28.8% vs. 15.5% vs. 5.4% vs. 1.0.8% vs. 0.5%) which were consistent also in the external cohort.

Conclusion A ML-based approach for the identification of TTS patients at risk of adverse short-term prognosis is feasible and effective. The InterTAK-ML model showed unprecedented discriminative capability for the prediction of in-hospital death.

Keywords Takotsubo syndrome • Outcome • Mortality prediction • Machine learning • Artificial intelligence

Introduction

Despite being initially perceived as a relatively benign condition when first described in 1990, takotsubo syndrome (TTS) subsequently turned out as a potentially life-threatening condition, associated with an impaired prognosis both at short- and long-term follow-up.[1,2] Existing evidence suggests similar rates of in-hospital complications and long-term major adverse cardiac and cerebrovascular events (MACCE) in patients with TTS compared with those suffering from acute coronary syndrome.[2,3] In this context, predicting patients' clinical course is of paramount relevance for clinical decision-making and prognostic assessment.

Several studies sought to identify predictors of unfavuorable outcomes among patients admitted for TTS.[4–6] The German and Italian Stress Cardiomyopathy (GEIST) score was derived through a classical stepwise multivariable logistic regression analysis, showing a moderate accuracy (area under the curve [AUC] around 0.70) for the prediction of in-hospital complications in TTS patients.[7]

Artificial intelligence (AI) is emerging as a promising tool in the setting of medical risk prediction performing better than traditional risk scores in several cardiovascular applications, ranging from the prediction of death among patients with suspected coronary artery disease to the estimation of the offsetting ischaemic and bleeding risk among patients suffering from acute coronary syndrome.[8,9] Thus, as primary aim we sought to develop a machine learning (ML)-based risk stratification model integrating common clinical variables to predict the risk of in-hospital death among patients included in the largest TTS registry.[10,11] As secondary endpoint we sought to derive a clinically meaningful clustering of patients with TTS according to their risk of in-hospital death by selecting the most relevant variables associated with impaired prognosis. Clustering may indeed facilitate personalized patient management by enabling physicians to tailor interventions based on specific cluster characteristics and shared clinical profiles.

Methods

Data collection

Two datasets were exploited for the aim of the present analysis (*Figure 1*). The train and the internal validation cohorts derived from the International Takotsubo (InterTAK) Registry. The InterTAK Registry is an observational, prospective, and retrospective registry established in 2011 at the University Hospital of Zurich in collaboration with 58 cardiovascular centres across 17 countries.[10,11] Patients were included in the registry between 2011 and 2021 as previously reported. The external validation cohort was derived from the Takotsubo Italian Network and enrolled patients from 2007 to 2018 (sites that also participated in the InterTAK Registry were excluded). Patients were included in this study based on the InterTAK diagnostic criteria[12] as reported in online supplementary *Appendix S1* (diagnosis of TTS). Data on demographics, triggering factors, cardiovascular risk factors, haemodynamic and angiographic findings, electrocardiography and echocardiography parameters, laboratory values, use of medications, in-hospital complications and management were collected through standardized forms or during revision of clinical charts. The study was conducted according to the Declaration of Helsinki. For both registries, the study protocol was reviewed by the respective local ethics committees or investigational review boards at each collaborating site.

Study outcomes

In-hospital all-cause death was the outcome of interest. The performance of the ML-derived model to predict such outcome, assessed by means of the area under the receiver operating characteristic curve (ROC-AUC), along with the specificity and sensitivity, were the primary endpoints. As a secondary endpoint we sought to categorize patients into phenotypic clusters and to estimate the observed risk of all-cause death for each identified cluster.

Feature selection and data preprocessing

The InterTAK Registry, encompassing 3703 patients, was cleaned by removing discharge-related features and proxy ones for death. Subsequently, variables and records with more than 30% missing values were discarded (see online supplementary *Appendix S1* for variables discarded). To avoid data leakage or bias, missing values were imputed using the median for continuous variables and the mode for categorical variables during the cross-validation process. Finally, 31 clinically relevant and easy obtain variables were carefully selected to be included in the prediction model.

These variables were selected based on their clinical relevance, but also considering potential collinearity effects. The correlation between the included variables is displayed in online supplementary *Figure Appendix S1*.

Data on left ventricular ejection fraction (LVEF) were collected from echocardiography and angiography. If both modalities were available, LVEF estimated from angiography was preferred. Definitions of all variables included in the registry have been previously published.[3,12-17] After the data cleaning process, 3482 patients' records were included in the present analysis.

Baseline statistical analysis

Continuous data are shown as mean ± standard deviation, skewed variables are presented as median (interquartile range [IQR]),

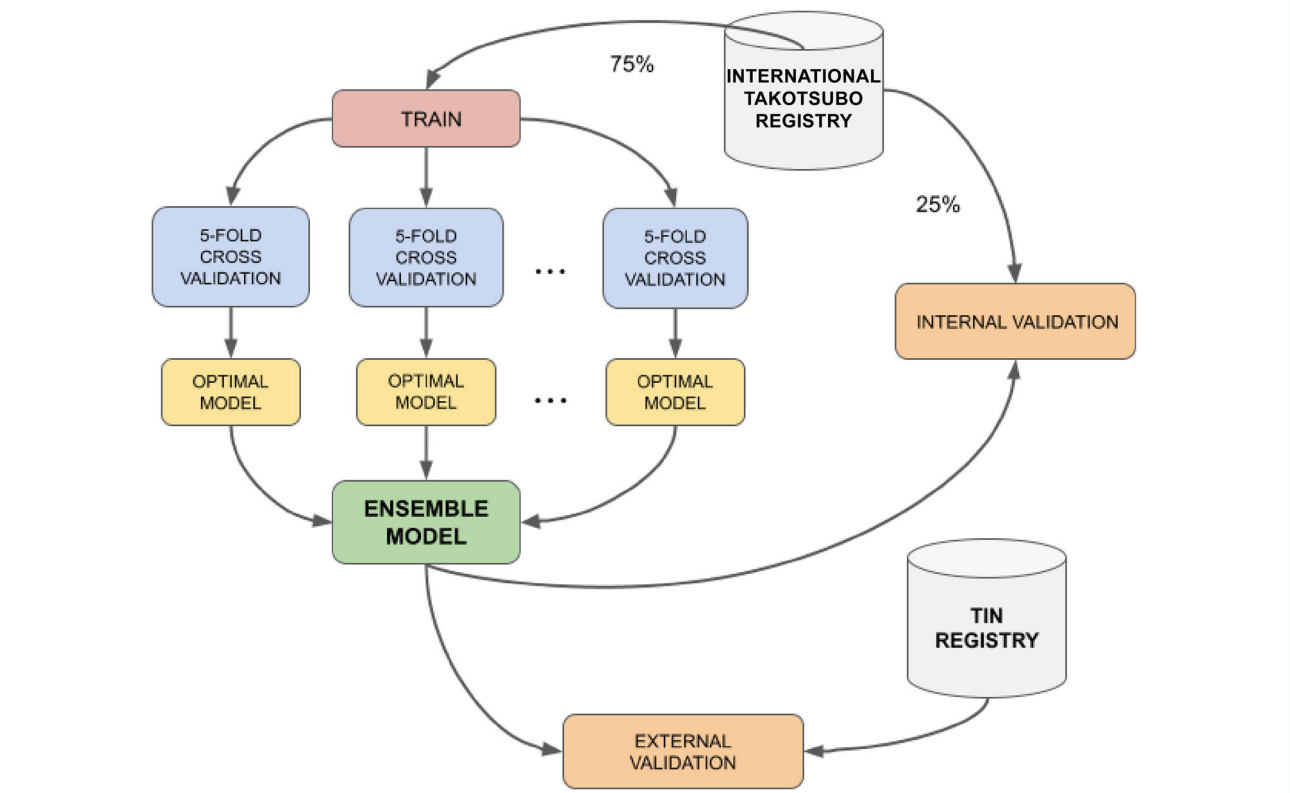

Figure 1 The InterTAK-ML workflow. A schematic representation of the workflow implemented for the InterTAK-ML model. The original dataset is randomly split in a train set (75%) and an internal validation set (25%) considering the imbalance toward the survivor class. On the train set a five-fold cross-validation is repeated 100 times with different random split obtaining 100 optimal model. The final model consists of a consensus (ensemble) model of 100 penalized logistic regression models. The final model performance was assessed on the internal validation set and on an external validation cohort. TIN, Takotsubo Italian Network.

and categorical variables are given as numbers and percentages. Comparisons of patients' baseline characteristics according to the in-hospital survival were performed with one-way analysis of variance test for continuous data and the Pearson chi-square test for categorical variables. A two-sided $p < 0.05$ was considered statistically significant. All analyses were conducted with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Model development and cluster identification

A ridge penalized logistic regression-based ML model (PLR) and a K-medoids clustering algorithm were designed to predict patients' risk of death and to stratify patients into phenotypic groups, respectively.[18]

First, the original cohort was randomly split into a train (75%) and an internal validation set (25%) considering the imbalance of the dataset toward the survivor class on the in-hospital death distribution.

An ensemble of PLR was built through a five-fold cross-validation procedure repeated 100 times with different randomizations on the train set.

The k-fold cross-validation procedure consists in partitioning the training set into k equal sized groups. Among these k subsamples, k-1 are used as training data and the remaining one as the internal validation data. The process is repeated k times so that all k groups are used as validation data. In this study, k was set to 5.

The final InterTAK-ML model thus consists of a consensus model of 100 optimal PLRs internally validated in a repeated cross-validation procedure. The decision to employ an ensemble of 100 optimal models was based on the objective of constructing a final consensus prediction that was robust to fluctuations. During our investigation, we experimented with ensembles of varying sizes, starting with 10, 30, 50, and ultimately 100 models. Our findings indicated that increasing the ensemble size beyond 100 did not significantly improve performance. To account for variability and to obtain confidence intervals (CI) for the evaluation metrics, a bootstrap with replacement strategy was performed 1000 times.

Model performance was assessed both on the internal and on an external validation set derived from the Takotsubo Italian Network cohort.[19]

Moreover, performance of the InterTAK-ML model was compared with that of the InterTAK 'traditional' model[20] on the original cohort and with the Geist score[7] on the Takotsubo Italian Network cohort.[19]

A graphical workflow for the InterTAK-ML model implementation is displayed in *Figure 1*.

In addition, to highlight the advantages of using a ML approach, we compared our PLR ensemble model with a classical logistic regression built with the same variables used to develop the ML-based model. The

performances of the two models in terms of ROC-AUC, sensitivity and specificity was tested in the internal validation cohort.

To draw patients' clusters, K-medoids was implemented by considering the 10 features showing the best predictive value at PLR model together with the triggering factor (that is physical, emotional, both emotional and physical stress, or no stress factor). K-medoids is a centroid-based method whose main objective is to minimize the sum of distances between the points and their respective cluster centroid, and it was performed to find phenotypic groups. The first crucial step is to identify the correct number of clusters. In the present analysis, to obtain reliable and robust clusters, we perform the K-medoids using the partition around medoids (PAM) algorithm by varying the number of clusters from 2 to 10 and calculating the within-cluster sum of squared distance (explained variance) and the silhouette coefficient score for each number.

The optimal number of clusters was chosen based on the elbow method, which consists in picking the elbow of the explained variance curve as the number of clusters to use, together with the Silhouette coefficient score. The Silhouette coefficient measures how each sample is well clustered into a specific group. It is calculated through the mean intra-cluster distance (a) and the mean nearest-cluster distance (b) for each sample. The Silhouette coefficient for a sample is given by (b-a)/max (a, b). As sensitivity analyses, we assessed the performance of the InterTAK-ML model according to sex (male vs. female patients), in patients with or without coexistent coronary artery disease and according to cardiogenic shock presence on admission within the InterTAK cohort. The distribution of the clusters was also assessed in the mentioned subgroups and in the external validation cohort.[19] All analyses were performed using Python software. An online, free calculator for the InterTAK-ML model depicting both risks and phenotypes can be found at https://compbiomed.hpc4ai.unito.it/intertako/.

Results

Incidence of in-hospital death and baseline features of the train and internal validation cohort

Out of 3482 patients included in the present analysis, 183 (5.2%) died during the index hospitalization, and 3299 (94.8%) were discharged alive. Of the 183 patients with in-hospital death, the cause of death was recognizable in 169 (92.3%) patients. There were 84 (45.9%) cardiovascular deaths, 85 (46.4%) non-cardiovascular deaths, and 14 (7.6%) deaths from unknown causes. Among patients with in-hospital death, 20 (11%) had a documented recovery of LVEF and wall motion abnormalities before death.

Baseline, angiographic and electrocardiographic features along with vital parameters at admission according to the in-hospital survival status are summarized in *Table 1*. Features of InterTAK sub-cohorts used for the train and as internal validation (75% and 25% of the sample, respectively) are presented in online supplementary *Tables Appendix S1* and *S2*.

The two groups of patients surviving the index event or experiencing in-hospital death had a similar mean age. Patients experiencing in-hospital death were less frequently female (75.4% vs. 89.0%, $p < 0.001$), less likely to suffer from hypertension (53.0% vs. 63.4%, $p = 0.005$) and hyperlipidaemia (18.5% vs. 32.6%, $p < 0.001$) but more frequently had diabetes (20.9% vs. 15.4%, $p = 0.05$) as compared with patients discharged alive.

A physical trigger was more frequently reported by patients who died in the hospital (82.0% vs. 39.3%, $p < 0.001$). No significant differences between groups were observed in the patterns of left ventricular akinesia, while patients with impaired short-term prognosis were more frequently diagnosed with coexisting coronary artery disease (28.9% vs. 18.6%, $p = 0.002$).

Patients not surviving to the index hospitalizations were characterized by a worse haemodynamic status at admission, as suggested by a significantly higher prevalence of cardiogenic shock (CS) (45.8% vs. 6.3%, $p < 0.001$), lower systolic blood pressure (120.2 ± 33.3 vs. 131.1 ± 29.2 mmHg, $p < 0.001$) and higher heart rate (99 ± 26 vs. 87 ± 21 bpm, $p < 0.001$) as compared with patients discharged alive. Patient dying during the index hospitalization had a significantly lower LVEF ($33.1 \pm 11.1\%$ vs. $41.0 \pm 11.9\%$, $p < 0.001$) and more frequently required pharmacological inotropic support with catecholamines (69.1% vs. 10.1%, $p < 0.001$). These patients were also more likely to suffer from atrial fibrillation (18.2% vs. 5.8%, $p < 0.001$) and to be admitted with ST-segment elevation (52.4% vs. 42.3%, $p = 0.01$) as compared with those discharged alive. Finally, a lower white blood cell (WBC) count was observed among patients discharged alive (10.6 ± 4.9 vs. 14.1 ± 7.4, expressed as $10 \times 10^3/\mu l$, $p < 0.001$).

Incidence of in-hospital death and baseline features of the external validation cohorts

Baseline features of these patients are reported in online supplementary *Table S3*. The incidence of in-hospital death in this sample was 2.2% ($n = 23$). As for the derivation cohort, patients experiencing in-hospital death were characterized by a worse haemodynamic status on admission as compared with patients surviving the index event, as testified by lower blood pressure values, higher heart rate, lower LVEF and a significantly higher prevalence of CS. Patients with impaired prognosis were also more likely to have experienced a physical trigger (47.8% vs. 19.1%, $p = 0.001$) and an acute neurological disorder (13% vs. 2.5%, $p = 0.002$) compared to patients surviving to the index hospitalization.

Machine-learning prediction of in-hospital death

The importance of each considered feature derived from the PLR coefficients is displayed in *Figure 2* and explicated in online supplementary *Table S4* (expressed as coefficients and 95% CI, ordered from the most positive to the most negative). The absolute value of the coefficients are the results of the logistic regression coefficients and correspond to a change in the log odds ratio for the outcome, indicating the strength of each variable's impact on the risk prediction. The metrics presented are the average with their CI over the models. The sign of the coefficient determines whether the variable increases (positive sign) or decreases (negative sign) the log odds of the outcome. For instance LVEF was the most

Table 1 Baseline features according to the incidence of in-hospital death

Features	Overall (*n* = 3482)	No in-hospital death (*n* = 3299)	In-hospital death (*n* = 183)	*p*-value
Age, years	67.8 ± 12.6	67.83 ± 12.4	67.9 ± 15.1	0.94
Female sex	3075/3482 (88.3%)	2937/3299 (89.0%)	138/183 (75.4%)	<0.001
BMI, kg/m^2	24.8 ± 5.3	24.8 ± 5.3	24.4 ± 6.4	0.33
Hypertension	2174/3459 (62.9%)	2077/3276 (63.4%)	97/183 (53.0%)	0.005
Diabetes mellitus	543/3464 (15.7%)	505/3282 (15.4%)	38 / 182 (20.9%)	0.05
Hypercholesterolaemia	1090/3421 (31.9%)	1057/3243 (32.6%)	33/178 (18.5%)	<0.001
COPD	401/3423 (11.7%)	385/3244 (11.9%)	16/179 (8.9%)	0.23
Asthma	161/3349 (4.8%)	157/3169 (5%)	4/182 (2.2%)	0.09
Coronary artery disease	606/3033 (19.1%)	565/3175 (18.6%)	41 /142 (28.9%)	0.002
Triggering factor				
Physical	1445/3482 (41.5%)	1295/3299 (39.3%)	150/183 (82.0%)	<0.001
Emotional	978/3482 (28.1%)	967/3299 (29.3%)	11/183 (6%)	<0.001
Emotional and physical	200/3482 (5.7%)	197/3299 (6.0%)	3/183 (1.6%)	<0.001
No stress	859/3482 (24.7%)	840/3299 (25.5%)	19/183 (10.4%)	0.014
Takotsubo type				
Apical	2487/3482 (71.4%)	2351/3299 (71.3%)	136/183 (74.3%)	0.42
Basal	54/3482 (1.6%)	49/3299 (1.5%)	5/183 (2.7%)	0.30
Midventricular	791/3482 (22.7%)	754/3299 (22.9%)	37/183 (20.2%)	0.46
Focal	150/3482 (4.3%)	145/3299 (4.4%)	5/183 (2.7%)	0.37
Chest pain	2167/3228 (67.1%)	2131/3089 (69%)	36/139 (25.9%)	<0.001
Dyspnoea	1436/3236 (44.4%)	1369/3089 (44.3%)	67/147 (45.6%)	0.76
Acute psychiatric disorder	241/3305 (7.3%)	232/3125 (7.4%)	9/180 (5%)	0.22
Acute neurological disorder	283/3306 (8.6%)	235/3126 (7.5%)	48/180 (26.7%)	<0.001
Atrial fibrillation	208/3215 (6.5%)	177/3045 (5.8%)	31/170 (18.2%)	<0.001
ST-segment elevation	1374/3206 (42.9%)	1285/3036 (42.3%)	89/170 (52.4%)	0.01
Complete AV block	20/3482 (0.6%)	19/3299 (0.6%)	1/183 (0.6%)	1.0
Pharmacological inotropic support with catecholamine	455/3463 (13.1%)	330/3282 (10.1%)	125/181 (69.1%)	<0.001
Cardiogenic shock	287/3423 (8.3%)	206/3246 (6.3%)	81/177 (45.8%)	<0.001
LVEF, %	40.6 ± 12.1	41.0 ± 11.9	33.1 ± 11.1	<0.001
Heart rate, bpm	88 ± 22	87 ± 21	99 ± 26	<0.001
Systolic BP, mmHg	130.6 ± 29.6	131.1 ± 29.2	120.2 ± 33.3	<0.001
Diastolic BP, mmHg	76.6 ± 17.3	76.9 ± 17.1	70.5 ± 20.1	<0.001
WBC count, 10 × 10^3/μl	10.8 ± 5.1	10.6 ± 4.9	14.1 ± 7.4	<0.001
Troponin[a]	11.41 (3.27–26.64)	11.42 (3.20–28.42)	11.38 (3.28–26.65)	0.39

Values of LVEF, systolic and diastolic BP, heart rate, and WBC are reported as measured on admission.
AV, atrio-ventricular; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; WBC, white blood cell.
[a]Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I. Data are given as factor increase in the upper limit of the normal.

relevant variable (mean importance −1.13, 95% CI −1.18; −1.08) with the negative sign indicating that the risk of in-hospital death reduces as LVEF increases. Ten variables were identified as leading ones: LVEF, WBC count, CS, diastolic blood pressure, physical stress as TTS triggering factor, acute neurological disorder, age, heart rate and atrial fibrillation at presentation, and asthma (online supplementary *Figure S2*).

The discriminative performance of the InterTAK-ML model for in-hospital all-cause death as expressed by the ROC curves in the internal validation cohort and in the external validation cohort is shown in *Figure 3*.

The InterTAK-ML model for in-hospital death prediction showed an AUC of 0.89 (0.85–0.92), a sensitivity of 0.85 (0.78–0.95) and a specificity of 0.76 (0.74–0.79) in the internal validation cohort and an AUC 0.82 (0.73–0.91), a sensitivity of 0.74 (0.61–0.87) and a specificity of 0.79 (0.77–0.81) in the external validation cohort (see also online supplementary *Table S5*). The accuracy of the InterTAK-ML model across several patterns of TTS included in the InterTAK cohort ranged from AUC values of 0.83 (95% CI 0.70–0.93) among patients with basal TTS to 0.93 (95% CI 0.87–0.98) among patients with focal TTS (online supplementary *Table S6*). Results of the sensitivity analysis assessing the performance of the InterTAK-ML model in predicting the risk of in-hospital death across several subgroups of the InterTAK cohort are presented in online supplementary *Table S7*. The model showed sufficient accuracy regardless of sex (AUC 0.85, 95% CI 0.80–0.89 and 0.87, 95% CI 0.84–0.89 in male and female subgroups, respectively), in patients with or without coexistent coronary artery disease (AUC 0.85, 95% CI 0.81–0.90 and AUC 0.88, 95% CI 0.85–0.90, respectively) and both in patients with and without CS

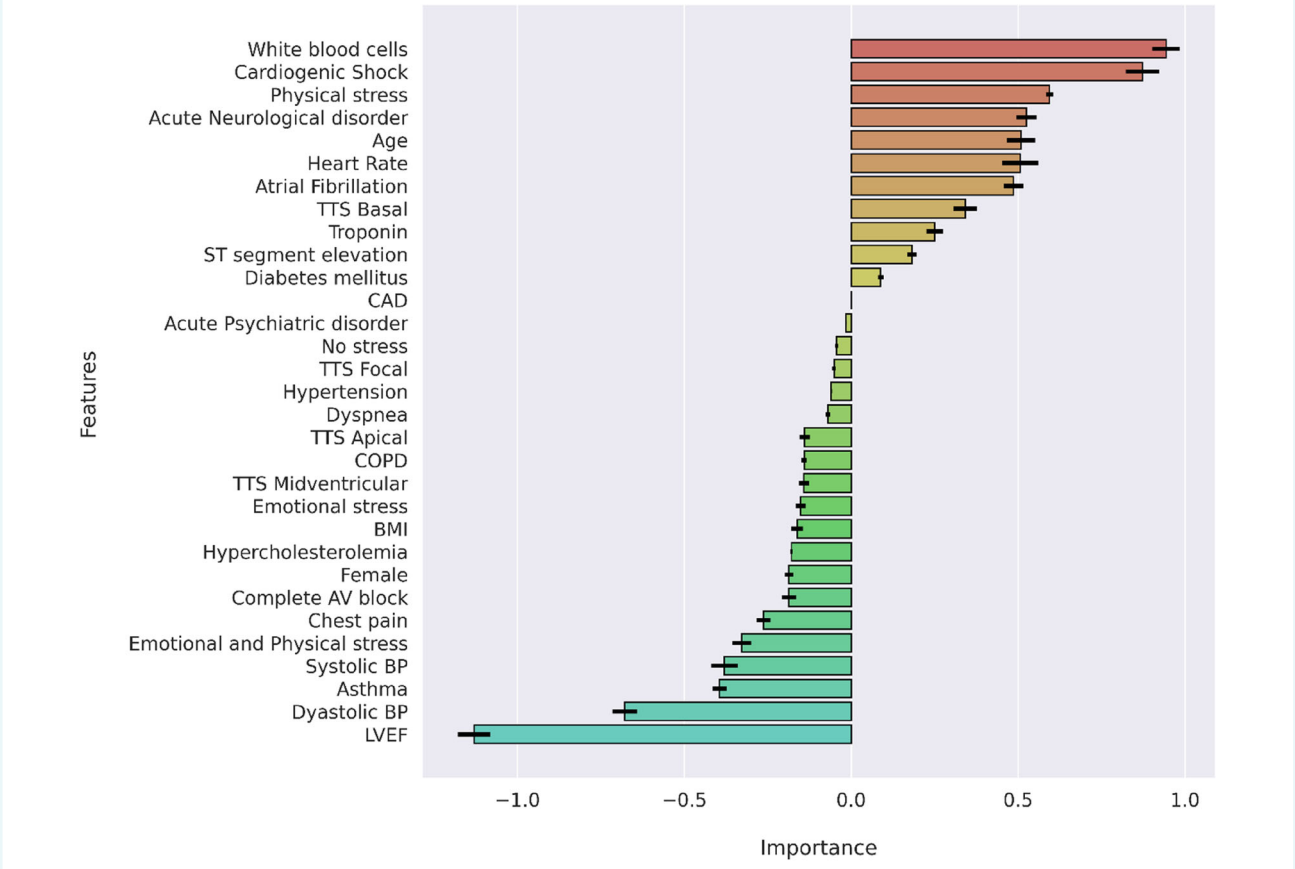

Figure 2 Penalized logistic regression feature importance. Coloured bars graphically represent the importance of the corresponding feature. The error bars correspond to the standard deviation over the multiple cross-validation runs. The greater the magnitude of the importance, the stronger the impact of the variable on the prediction. The sign of the importance shows how the variable impacts the prediction. For categorical variable, the coefficient of the importance represents the increasing (or decreasing in accordance with the sign) of risk in presence of that variable. For continuous variables, the coefficient of the importance represents the increasing (or decreasing in accordance with the sign) of risk as the variable increases. AV, atrio-ventricular; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; TTS, takotsubo syndrome.

on admission (AUC 0.79, 95% CI 0.77–0.83 and AUC 0.84, 95% CI 0.81–0.88, respectively). Regarding comparisons with other scores, the InterTAK 'traditional' model showed an AUC of 0.78 (0.76–0.82) (online supplementary *Figure S3A*) on the InterTAK original cohort, while the GEIST score achieved an AUC of 0.63 (0.50–0.76) (online supplementary *Figure S3B*) on the external validation cohort.

A simplified and easier to use InterTAK-ML model that exploits only the 10 top variables preserved sufficient accuracy, showing an AUC of 0.88 (0.85–0.91), a sensitivity of 0.83 (0.74–0.91) and a specificity of 0.75 (0.73–0.78) in the internal validation cohort and an AUC 0.83 (0.74–0.91), a sensitivity of 0.70 (0.52–0.87) and a specificity of 0.80 (0.78–0.83) in the external validation cohort (online supplementary *Table S5*).

The performance of a model based on a standard logistic regression along with its comparison with the InterTAK-ML model are provided in online supplementary Results and supplementary *Table S8*. Briefly, the model based on a standard logistic regression was characterized by an overall good accuracy (AUC-ROC 0.84, 0.79–0.90) and specificity (0.99, 0.98–1.00). However, such a model showed a very low sensitivity (0.09, 0.02–0.15). These findings suggest that a ML approach allows for optimal parameter tuning and cross-validation, enhancing prediction accuracy and clinical suitability as compared to conventional statistical methods.

Patients' clustering

Patients' clustering was performed using the 10 most relevant variables and adding the other potential TTS triggers (emotional, both emotional and physical or no identifiable stress factors). The identification of the optimal number of clusters is described in detail in online supplementary *Results*. Briefly, based on the elbow of the explained variance curve together with the Silhouette coefficient score (online supplementary *Figure S4*), we identified six as the best number of computable phenotypes. Such choice was also supported by the dimensionality reduction using t-distributed

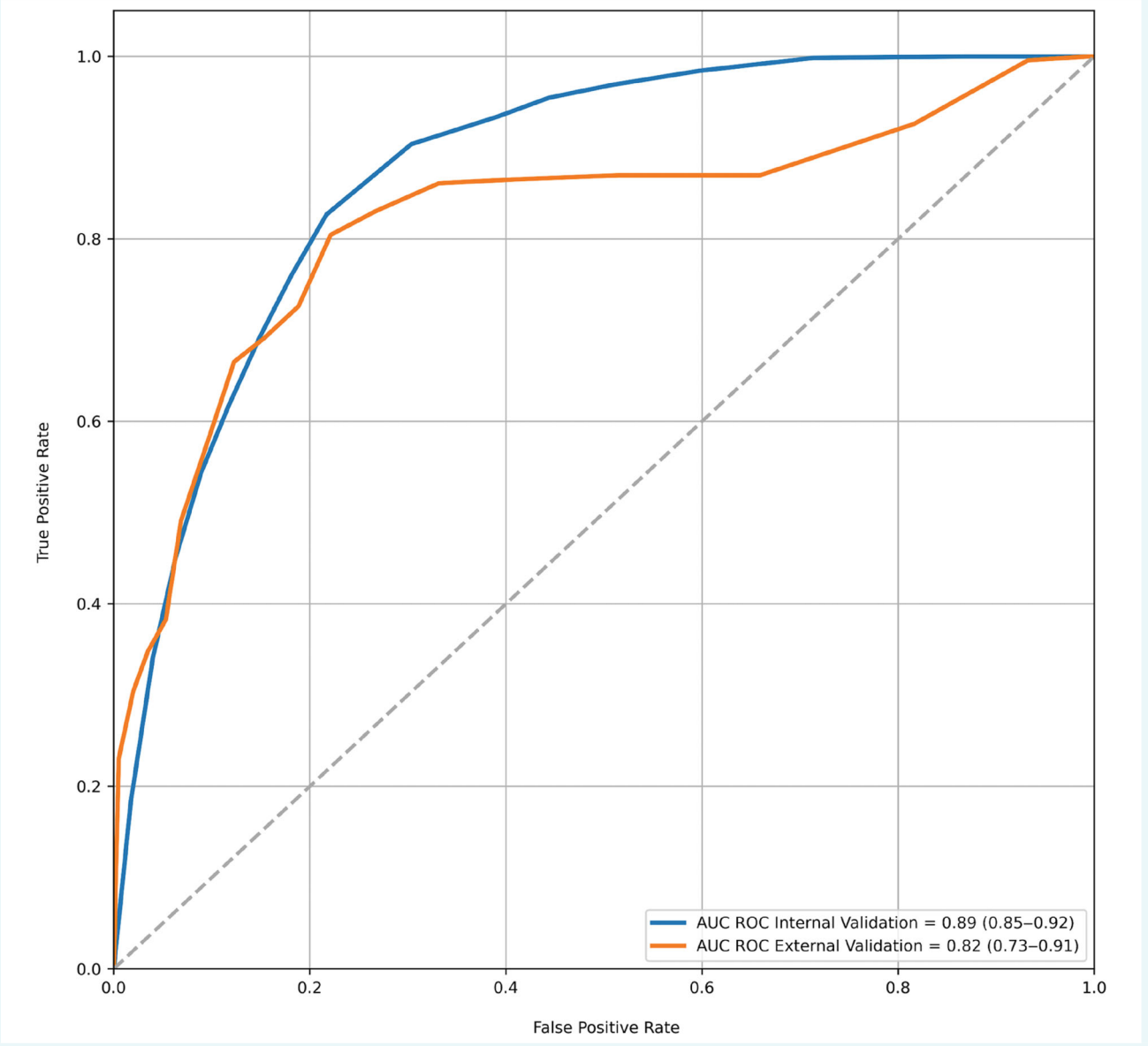

Figure 3 The receiver operating characteristic (ROC) curve. Mean ROC curves for the internal validation and external validation for 1000 bootstraps. The area under the ROC curve (AUC) is shown on the right corner. The dashed line (reference) represents a model with no skills.

stochastic neighbour embedding (t-SNE). The 2D t-SNE representation of the data post-hoc coloured by the K-medoids-derived cluster label is illustrated in *Figure 4A*. The t-SNE representation post-hoc coloured based on the in-hospital death status is illustrated in *Figure 4B*.

The distribution of the variables according to the clusters is summarized in *Table 2*. The number of patients allocated in each cluster ranged from 186 (cluster 1, 5.3% of the sample size) to 1035 (cluster 4, 29.7% of the sample size). A different incidence of in-hospital death was observed according to cluster allocation, ranging from low (0.5% vs. 0.8% vs. 1.7% for clusters 1, 2, and 3 respectively), to intermediate (5.4% in cluster 4) and high (15.5% and 28.8% in cluster 5 and 6, respectively). Patients belonging to the cluster burdened by the highest mortality (cluster 6) were on average younger, but all characterized by CS, by a severely impaired haemodynamic status, a lower LVEF and higher WBC counts. More than two-thirds of this group had a physical triggering factor. Patients belonging to cluster 5 also showed a high risk of poor short-term outcome. Although these patients were characterized by a better haemodynamic profile as compared with cluster 6, all of them suffered an acute neurological disorder and were triggered by a physical stressor that may explain the high rate of in-hospital death.

The largest part was clustered into a group characterized by an intermediate risk of in-hospital death (cluster 4). All these patients experienced a physical stressor. However, none of them

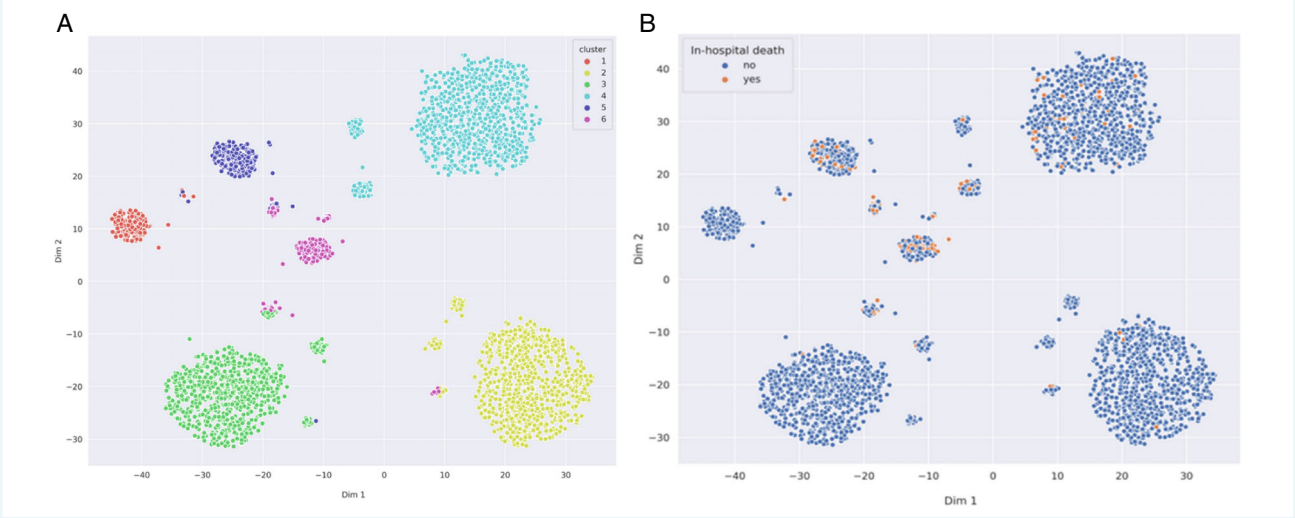

Figure 4 2D t-distributed stochastic neighbour embedding (2D t-SNE) manifolds representation of the original data. (*A*) 2D t-SNE representation of the data post-hoc coloured by the K-medoids-derived cluster label. (*B*) 2D t-SNE representation of clusters post-hoc coloured based on the in-hospital death status.

Table 2 Features of clusters

Features	Cluster 1 ($n = 186$)	Cluster 2 ($n = 960$)	Cluster 3 ($n = 829$)	Cluster 4 ($n = 1035$)	Cluster 5 ($n = 239$)	Cluster 6 ($n = 233$)
Age, years	68.67 ± 13.3	66.73 ± 11.5	69.76 ± 11.41	68.78 ± 12.81	65.6 ± 14.74	62.9 ± 14.64
LVEF, %	41.68 ± 10.35	42.32 ± 10.45	42.22 ± 10.32	40.10 ± 10.97	40.12 ± 10.14	27.76 ± 10.84
WBC count, 10×10^3/μl	10.06 ± 4.18	9.64 ± 3.23	9.86 ± 3.99	11.27 ± 5.12	12.51 ± 6.13	13.94 ± 7.52
Heart rate, bpm	87.44 ± 20.84	84.28 ± 16.19	85.09 ± 18.86	88.81 ± 20.38	89.6 ± 20.78	99.26 ± 25.57
Diastolic BP, mmHg	76.47 ± 16.43	77.44 ± 13.81	77.65 ± 14.99	75.90 ± 16.20	77.13 ± 18.95	70.52 ± 17.25
Cardiogenic shock	0 (0.0%)	12 (1.2%)	25 (3.0%)	0 (0.0%)	17 (7.1%)	233 (100.0%)
Acute neurological disorder	15 (8.1%)	0 (0.0%)	4 (0.5%)	0 (0.0%)	239 (100.0%)	25 (10.7%)
Atrial fibrillation	5 (2.7%)	40 (4.2%)	50 (6.0%)	70 (6.8%)	12 (5.0%)	31 (13.3%)
Asthma	7 (3.8%)	46 (4.8%)	26 (3.1%)	61 (5.9%)	11 (4.6%)	10 (4.3%)
Triggering factor						
Physical	–	–	–	1035 (100%)	229 (95.8%)	181 (77.7%)
Emotional	–	960 (100%)	–	–	–	18 (7.7%)
Physical and emotional	186 (100%)	–	–	–	8 (3.3%)	6 (3%)
No stress	–	–	829 (100%)	–	2 (0.8%)	28 (12%)
In-hospital death (a posteriori)	1 (0.5%)	8 (0.8%)	14 (1.7%)	56 (5.4%)	37 (15.5%)	67 (28.8%)

BP, blood pressure; LVEF, left ventricular ejection fraction; WBC, white blood cell.

was characterized by a severe haemodynamic impairment neither suffered an acute neurological event, thereby accounting for a lower risk of impaired prognosis as compared with clusters 5 and 6. Patients belonging to clusters associated with a lower risk of mortality experienced TTS following an emotional stress (cluster 2), a mixed physical and emotional stress (cluster 1) or no identifiable stressor (cluster 3). These clusters had a low prevalence of CS (0% to 3%) and encompassed patients with slightly variable mean ages and prevalence of comorbidities such as asthma and atrial fibrillation accounting for a minimally different (although overall low) risk of in-hospital death. The distribution of the features not exploited for the purpose of cluster derivation is presented in online supplementary *Table S9*.

For subgroups, the performance of the clusters was consistent for male patients, for those without coronary artery disease and for those without diagnosis of CS at admission (online supplementary *Tables S10–S12*). Consistently, the clustering maintained their

prognostic discriminative features also in the external cohort: the first three clusters were at low risk (online supplementary *Table S13*), while the other three showed an incremental risk. Performance in cross validation for clustering label prediction is shown in supplementary *Table S14*.

Discussion

In this study, we used data of 3482 TTS patients to develop a ML-based predictive model to assess the risk of in-hospital death. To our knowledge, this is the first attempt to assess the effectiveness of AI to predict the risk of death in this syndrome. Our results can be summarized as follows: (i) the incidence of in-hospital death among patients suffering from TTS is not negligible, supporting the usefulness of a bedside prognostic assessment for clinical decision-making; (ii) the ML-based approach presented satisfactory and unprecedented discriminative abilities for the prediction of in-hospital death among patients admitted for TTS; (iii) ML-based logistic regression analysis identified LVEF, WBC count, CS, diastolic blood pressure, physical stress as TTS triggering factor, acute neurological disorder, age, heart rate and atrial fibrillation at presentation, and asthma as the 10 most relevant features associated with in-hospital death; and (iv) by exploiting the most relevant features accounting for the InterTAK-ML model, TTS patients could be clustered into six different groups entailing a different risk of adverse short-term prognosis.

Despite significant advancements in the understanding of the pathophysiological mechanisms underlying TTS, along with the identification of patient characteristics and external factors associated with unfavourable outcomes, the observed rate of in-hospital adverse prognosis suggests that TTS is still far from being a benign condition. We report indeed a 5.2% incidence of in-hospital death that is consistent with initial findings about such medical issues, reporting mortality rates ranging from 0% to 8%.[21,22] These findings highlight the need for a prompt prognostic stratification, aiming to identify patients at risk of not surviving to the index hospitalization to personalize the intensity of acute medical care.

In this context, AI algorithms are being increasingly explored as a novel approach to face the compelling requirement of a tailored risk assessment. The model we propose was obtained from a ML processing of 31 clinical and demographic variables, routinely collected during the management of patients admitted for TTS. This study aimed to focus on baseline features and their association with the risk of in-hospital death. However, we acknowledge that patients on mechanical or ventilatory support were excluded. This choice was due to potential confounding factors related to clinical management during hospitalization, the risk of introducing biases and multicollinearity with CS on admission and the relative low number of cases.[15]

The InterTAK-ML model appears to outperform the predictive abilities of two previously published risk scores obtained with classical statistical methodologies in a smaller sub-cohort of the InterTAK Registry and across 1007 patients enrolled in the GEIST registry.[7,20] It is worth mentioning that a risk stratification system for in-hospital complications of TTS was also proposed by Lyon *et al.*[24] However, despite being commendable for stressing for the first time the importance of some clinical and biochemical variables for a rapid assessment of TTS patients, such tool was based on experts' opinion and lacked appropriate derivation and validation.

To further support the incremental value of an AI-based approach as compared with classical statistical methods, we present and compare for the first time in the same population the performance of both the ML-based model and the conventional logistic regression-based model. Of note, despite both models displayed a satisfying overall accuracy for the prediction of in-hospital death, the InterTAK-ML model showed a strikingly superior sensitivity, thereby resulting in an ameliorative tool. This must be put in the context of the relatively low incidence of death across the spectrum of TTS patients, requiring the skill of accurately identifying patients with an actual risk of impaired short-term outcome. Our results suggest that the main difference between a classical and a ML-based approach lies in the parameters' optimization process, rather than in the model itself.

Features associated with in-hospital death

The application of ML models in medicine may generate concerns with respect to their applicability, due to the 'black-box' nature of this approach.[25] However, despite the 'assumptions-free' analytical method inherent to supervised learning algorithms, the variables showing the highest prognostic values according to the InterTAK-ML model appear to have thoughtful clinical relevance. The significance of impaired LVEF as a prognostic factor is consistent with previous findings and can be intuitively explained by a larger area of stunned myocardium following the catecholamine surge characterizing TTS.[5,7,26] Likewise, the impact of heart rate, atrial fibrillation and blood pressure confirms the relevance of the haemodynamic status at presentation.[27,28] To further support such findings, a significantly higher prevalence of CS was observed among patients with impaired in-hospital outcome. CS emerged indeed as the second most relevant feature predicting in-hospital death in the InterTAK-ML model. This is in line with previous reports showing an independent association between CS and impaired short- and long-term outcome.[14,29] This poses several clinical issues since the use of catecholamines as inotropic drugs for treating CS is controversial as these drugs are thought to be directly associated with TTS pathogenesis.[30] Notably, beyond being associated with a greater haemodynamic deterioration, a higher heart rate and atrial fibrillation at presentation may also reflect a stronger acute sympathetic activation in response to the trigger and/or a higher resting sympathetic tone. Both conditions have a well-defined role in the pathophysiology of TTS as well as a proven detrimental prognostic role in most cardiovascular diseases[31]; yet this is the first strong suggestion of a similar association also for TTS patients.

As for asthma, a growing body of evidence supports the concept that obstructive lung disease can be intrinsically connected with TTS.[32] Beyond representing potential physical triggers of TTS through acute attacks and exacerbations, we report for the first time that such conditions may also be associated with an adverse short-term prognosis. This finding may be intuitively explained by

the synergistic effect of respiratory impairment and acute cardiac stunning. However, a potential role of medications used for asthma (commonly anticholinergic agents, β_2-agonists and aminophylline) cannot be excluded and warrants investigation.

The relevance of acute neurological disorders and the relative prognostic implication of physical stressor (compared with emotional stressors) in influencing the clinical course of TTS patients was previously explored in the InterTAK and RETAKO registries and is confirmed by the present AI-driven model.[5,15]

The importance of WBC count in our prediction model may suggest a synergistic effect of an enhanced inflammatory response with cardiac dysfunction in conditioning unfavourable short-term outcomes. In a previous study by Scally *et al.*,[33] patients with TTS were found to show an increase in systemic pro-inflammatory cytokines further than myocardial inflammatory infiltrates as compared with a sex- and comorbidity-matched control cohort, thus supporting this hypothesis. The strong association between sympathetic tone and reflexes and inflammatory responses, as well as the anti-inflammatory effects of vagal activation, are very well characterized.[34]

Finally, we showed that age may act as an important modulating factor in TTS prognosis. We previously reported, using a conventional, statistical model, that younger and older age were not independently associated with in-hospital mortality using the middle-aged group as a reference.[13] A ML-based model may be better suited to unravel the complex relationship between age and short-term mortality in TTS, that probably encompasses the intrinsic interdependence with the type of stressor, the autonomic balance and the microvascular function.

Clusters of patients with takotsubo syndrome

There is increasing awareness that TTS is a multifaceted syndrome. For long time the same label has been used to describe both a classic TTS patient (collective imagination envisions an old woman with apical ballooning following an emotional event) and patients with transient myocardial dysfunction after surgical procedures or critical illnesses. Several efforts have been made to indicate a clinically meaningful classification of TTS. Recently, Li *et al.*[35] for the first time suggested a classification of TTS patients into four phenotypic clusters (namely 'metabolic disease', 'chronic obstructive pulmonary disease', 'psychiatric disorders', and 'minimal risk factors') by applying latent class analysis to a cohort of 3139 patients from the National Inpatient Sample (NIS) database. A different risk of unfavourable short-term outcomes was detected among the identified clusters, although an overall low rate of in-hospital death was observed (ranging from 1% to 3.4%).[36] The study was mainly limited by the inability to account for potentially relevant variables that were not available in the NIS database. Among the others, the absence of specific TTS triggers is probably the most significant. Previous studies actually showed that the precipitating stress factor plays a major role in influencing patients' prognosis.[36,37] TTS triggered by physical factors indeed carries the worst prognostic implications as compared with emotional or no identifiable stress. Based on these findings, Ghadri *et al.*[3] suggested a three-class classification according to the type of triggering event. Of interest, as for the previous InterTAK prognostic score, the physical stress emerged as one of the most important features influencing prognosis also in our ML-derived model.

For the first time we used an AI approach to make data-driven clustering of TTS patients. We identified six different phenotypes based on the most-relevant ML identified variables. A different, non-linear, risk of death was observed for each cluster, with one of the smallest (233 patients, 6.7% of the sample) being burdened by a 1.5-to-57-fold higher risk of adverse prognosis as compared with the remaining five. Of note, all patients reporting a physical trigger fell into the three clusters associated with an intermediate or high observed mortality (from 5.4% to 28.8%). Such clusters were also characterized by lower values of LVEF and diastolic blood pressure, and higher heart rate and WBC count. Our results therefore confirm and extend the results of the existing body of evidence, suggesting that physical stress may indeed be associated with a worse prognosis. However, differently from what reported so far, we highlight that beyond the triggering factor, the haemodynamic status, the systemic inflammation associated with the syndrome, the underlying illnesses severity (i.e. acute neurological disorders) and the amount of sympathetic activation may confer an incremental risk of impaired prognosis, thereby better defining the granularity of TTS. Indeed, the group of patients with physical stress but with a null prevalence of CS (cluster 4) was characterized by an observed risk of in-hospital death of 5.4%. On the other hand, clusters encompassing the remaining portion of patients experiencing a physical trigger but with a high prevalence of CS or acute neurological disorder were characterized by an observed risk of mortality of 15.5% or 28.8%. Finally, while the mean heart rate in cluster 6 (99.26 ± 25.57 bpm) reflects the underlying presence of a CS in all patients, the mean heart rate in cluster 5 (89.6 ± 20.78 bpm) and in cluster 4 (88.81 ± 20.38 bpm), both with a low prevalence of CS (0% in cluster 4), strongly suggest a higher sympathetic tone compared to the other clusters.

Taken together these findings suggest that although the overall risk of short-term death associated with TTS is not trivial, it is mostly prerogative of a small subgroup of patients characterized by a worse haemodynamic status, an enhanced inflammatory response and sympathetic activation, a coexisting severe illness and a peculiar triggering factor. Thus, the inclusion of clustering may offer several clinical advantages. It indeed offers a more comprehensive and nuanced understanding of the relationship between variables and mortality risk by capturing distinct patterns and interactions within the data. By identifying distinct clusters, physicians can place individual patients' risks within an appropriate context, effectively communicating their intermediate-to-high or low-risk status. Additionally, the clustering analysis has research implication. It allows for the exploration of how variables modulate and interact in defining mortality risk within different clusters, offering insights into potential underlying mechanisms, and informing future research directions in the field of TTS.

It should be noted that there is no hierarchy among the variables adopted to set up the clusters. Therefore, the chance for a patient

to be allocated in one of each cluster depends upon the complex interplay among the features.

How to implement the InterTAK-ML model in clinical practice?

The InterTAK-ML model can be seamlessly implemented in clinical practice, aided by the availability of a free online calculator accessible at: https://compbiomed.hpc4ai.unito.it/intertako/.

This user-friendly tool enhances the practicality of utilizing the InterTAK-ML model for risk assessment and provides accurate estimations of in-hospital mortality. Additionally, the clustering approach incorporated into the model enables a contextualized risk assessment that can be effectively communicated to patients based on their intermediate-to-high or low-risk status and facilitates informed clinical decision-making. While missing variables may pose a challenge, the evidence supports the robustness of the InterTAK-ML model in handling missing data and providing accurate risk estimations. Indeed, our study demonstrates that even a simplified version of the model considering the top 10 relevant variables performs well. However, it is important to note that the expected accuracy may decrease with a lower number of variables provided.

Limitations

The InterTAK Registry has an observational and partly retrospective design, thus carrying the limitations of this kind of studies. The collection of comprehensive ethnic data within the InterTAK Registry was lacking. Nonetheless, the registry encompassed predominantly European patients, comprising approximately three-fourths of the sample, while the remaining one-fourth originated from Asian sites. This distribution suggests that the generalizability of the model to ethnicities beyond Europeans and Asians might be constrained. The choice of utilizing only the top 10 relevant variables to derive the AI-based patients' clustering was somewhat arbitrary and forced to leave out some features that were associated with the main outcome, although with a lower relative importance (i.e. ST-segment elevation, troponin value, etc.). However, such choice was made for the sake of simplification and to potentially promote the clinical implementation of the model also in its simplified version that indeed relies only upon the 10 most relevant variables. We choose to not include mechanical ventilation and mechanical circulatory support, mainly in order to avoid the model accounting for variables that may be related to physicians' judgment and evolving clinical course, further than potentially being collinear with CS, as discussed. Further, we sought to avoid the inclusion of discretional therapeutic strategies that may be required during the hospital stay in order to generate a bedside score that can be easily implemented and directly rely upon clinical and instrumental variables. The timing of TTS onset was available only for TTS patients admitted with acute neurological disorder, in which TTS was diagnosed with a median of 0 (IQR 0–1) days after the neurologic event. Whether timing of TTS diagnosis may represent an additional factor for adverse outcomes is an interesting issue, which will require a prospective study with serial cardiac imaging. Finally, from a methodological point of view, we used the K-medoids because it has been demonstrated to be more robust to noise and outliers and it is easily adaptable to different distance metrics, such as the Gower distance that we used to better take into consideration both categorical and continuous variables.

The choice of a short-term outcome rather than long-term survival was intentionally chosen in order to generate a model able to predict the hazard intrinsically connected with TTS.

Conclusions

We developed and tested the InterTAK-ML model, a ML-based tool to predict the risk of in-hospital death for patients admitted for TTS. The model outperforms current existing scores conceived for the same purpose. A ML data-driven approach identified six distinct clusters of TTS patients associated with different observed risks of death. As such, the InterTAK-ML model can both predict the actual risk of in-hospital death and allocate TTS patients to a specific cluster. This study showed that an AI-based approach in this setting is feasible and effective and with potential clinical implications for the optimization of quality of care. All the identified predictive variables have a strong pathophysiological rationale including the amount of sympathetic activation as reflected by an increased heart rate at presentation independently of CS, that for the first time is identified as a prognostic marker. A further validation of the model in an external cohort would be valuable.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: none declared.

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