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Takotsubo Syndrome - A New Algorithm with Insights in Susceptibility, Evolution, and Aftermath

Research Article

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Abstract

Background: Takotsubo syndrome [TTS] at presentation, raises significant questions of differential diagnosis.

Objectives: To develop an algorithm todistinguish TTS from acute myocardial infarction [MI] , based on comorbidities and conditions at presentation, derived from MIDAS, a New Jersey statewide database.

Methods: International classification of diseases-9 [ICD-9] codes as primary admission diagnoses were: for TTS 429.83 [747 patients] and for acute anterolateral wall MI [ALWMI] 410.01 [4118 patients].

Six clinical characteristics were identified: mitral valve disorder, disorders of magnesium metabolism, other chest pain, acute systolic heart failure, anxiety disorder, and other primary cardiomyopathy.

A logistic classification of above allowed for a more direct way to incorporate a weighting scheme to score each of the six factors and demographic information, to classify patients as having either TTS or ALWMI.

Results: The rate of TTS stabilized at around 2% of all MI's,female and white race were higher and event rates for heart failure and cardiovascular deaths were lower. The results for the logistic classification using the 6 prespecified features, race, sex, and age were: for TTS; sensitivity 0.84, specificity 0.71, precision rate 0.36, and correct classification rate 0.73. For MI; negative predictive value was 0.96.

Conclusions: The algorithm of above noted comorbidities and conditions at presentation is useful in differential diagnosis, points to potential mechanisms and may explain recurrences of TTS. It is derived from a non-selective database with no apparent bias and utilizes a bottom up approach.

Key Words

Mitral valve prolapse syndrome/ Genes/ Pathways

Introduction

Takotsubo syndrome [TTS], also described as Takotsubo cardiomyopathy or apical ballooning in its typical presentation, is a stress-precipitated syndrome, usually with acute onset, variable course and spontaneous resolution following the acute event. It was first reported by Sato and Dote in 1990 and 1991 [1].

Its prevalence in the United States is approximately 2% [up to 10% if only women are considered] of all patients presenting with clinical manifestations of ACS [acute coronary syndrome] [2]. It is uncommon in Hispanic and African Americans. Right ventricular [RV] involvement is present in one third of patients [1]. There has been an increase in incidence and hospitalization. About 85-90% are women ages 65-70 years of age. Recurrence rate of 0 to 22% is reported with cumulative incidence of recurrence of 1.2% at 6 months and 5% at 6 years [1]. Several hypotheses have been proposed and extensively reviewed regarding its pathophysiology [1]. Two expert consensus documents have been published by the largest international registry [InterTAC] [3,4].

Predominant hypotheses for the pathophysiology of TTS include microvascular dysfunction, epinephrine as a trigger factor, switch in signal trafficking and myocardial stunning [1,5].

At presentation, differential diagnosis is an important issue, considering that frequently TTS is misdiagnosed as acute myocardial infarction or ACS.

The purpose of this study was to assess the frequency of factors present in patients with TTS and MI at presentation, to analyze and describe significant differences between the two entities and present an algorithm suggesting the presence of either TTS or ALWMI, with meaningful sensitivity and specificity in order to separate the two conditions.

Specific Objectives

Establish that the state database is representative of the literature in terms of frequency of TTS vs all MI's, race, gender and outcomes.

1. By comparing TTS cases with MI's of other locations than ALWMI, point to an etiology other than coronary event/insufficiency.
2. By comparing TTS to ALWMI seek consistency with the previous analysis, expecting/seeking statistical differences and or weakening of such, considering the higher probability that typical TTS may be listed as ALWMI in the record.
3. Point to a relationship of the algorithm factors to a condition associated with TTS by assessing prediction of TTS using any two factors of the algorithm.
4. Explain survival benefit of TTS compared to MI by seeking/exploring relevant protection pathway/s as modified by a genetic condition.
5. Improve /Enhance consideration of TTS vs any MI at presentation, prior to proceeding with further testing.

Methods

Data sources

We used MIDAS, a statewide database in New Jersey. The cases and controls were derived from all admissions to NJ hospitals [VA hospitals excluded] that occurred from the

Table 1: Total number* of Acute MI's, initial episode of care, by ICD 9 Code by Year with Rate of TTS per 100 Acute MI's, initial episode of care

ICD 9 Code/Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*	*Row Total*
410: 01	426	390	465	431	428	411	401	429	419	318	4188
410: 11	1712	1624	1672	1512	1514	1353	1387	1413	1333	1412	14932
410: 21	344	292	338	316	313	301	337	308	311	231	3091
410: 31	251	228	205	212	217	206	173	211	213	197	2113
410: 41	2119	1898	1900	1964	1930	1778	1736	1787	1747	1734	18593
410: 51	233	213	205	185	201	162	180	153	187	143	1862
410: 61	54	40	43	44	60	52	46	61	62	43	505
410: 81	379	359	246	252	234	211	216	198	178	172	2445
410: 91	896	759	947	916	950	969	887	982	960	1076	9342
Total MI's	6414	5803	6021	5832	5847	5443	5363	5542	5410	5326	
Rate[$] of TTS per 100 MI's, initial episode of Care											
Year	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***	***2013***	***2014***	***2015***	
	0.09	0.3	0.6	0.9	1.1	1.5	2.1	2.0.	2.9	2.3	

*-The total number includes all the MI's for a patient for a given year. **MI**=Myocardial Infarction; **TTS** = Takotsubo.

years 2006-2015. TTS was identified by ICD-9 code 429.83 as the primary admission diagnosis.

All cases of initial care of MI [except if it was subendocardial] were identified by ICD-9 codes 410:x1 [Table 1]. Acute myocardial infarction of anterolateral wall, initial episode of care by ICD-9 code 410.01 and acute myocardial infarction of other specified sites, initial episode of care by ICD-9 code 410.81. The cases of initial care of MI were used to see if the rate of TTS is consistent with the literature. TTS cases were 747, total MI's [410:x1:N=57001], ALWMI [410.01:N=4118] and MI of other specified sites [410.81:N= 2396]. When comparing TTS to the two types of MI [410.81 and 410.01 noted above], in addition to race, age and sex, seven clinical characteristics were identified with minimal frequency of 20 cases at presentation in subjects with TTS. They were: mitral valve disorder [ICD-9 code:424.0], tricuspid valve disorder [ICD-9 code: 397.0], disorders of magnesium metabolism [ICD-9 code:275.2], other chest pain[ICD-9code: 786.59], acute systolic heart failure [ICD-9 code: 428.21], anxiety disorder [ICD-9 code: 300.00] and other primary cardiomyopathy [ICD -9 code: 425.4]. In the case of ALWMI [410.01] six clinical characteristics were recorded [excluding tricuspid valve diseases].

Case and control groups - Demographics

A. The cases of initial episode of care of all MI's [ICD-9 code 410:x1] were used to see if the rate of TTS vs acute MI is consistent with literature reports. The number by year as well as analysis of death rates and CHF of case and controls were tabulated.

B. Initial episode of care of ALWMI [ICD-9 code: 410.01] was chosen as a control group in the final analysis, due to its similarity at presentation with the most typical presentation of TTS [apical ballooning].

C. Considering that TTS is mostly regional, preliminary analysis of initial episode of care of MI of other specified sites [ICD-9 code: 410.81] was used as another control MI group to assess possible differences post statistical analysis and/or establish consistency of analysis results with different MI controls.

D. Basic demographic information was collected from all three groups [age, sex and race]. For classification purposes the data was divided into training and testing sets [70% and 30% of data].

Statistical analysis

A. TTS vs ICD-9 code 410.81[acute myocardial infarction of other specified sites , initial episode of care]

A logistic classification was initially done to see how well the demographics could classify a

case or control in the training set. A logistic regression model using only demographic information as variables [age,sex, and race] seemed to classify TTS cases in the training set well [Figure 1] with an AUC of 0.82. Diagnosis codes [DX2-9] present in the discharge documents of TTS patients and controls were examined to see if they could improve the classification rate. The ICD codes that appeared with a frequency of either 2% of TTS patients or 2% of controls were tabulated to be used as potential features in a logistic model. A BimaxBiclustering algorithm was used to find clusters of diagnoses which contained at least 5% of patients in the training set so that these clusters could be used as potential features in a logistic model. In addition, any two-way interaction of diagnosis codes or demographic information [age, sex, and race] which contained at least 5% of patients in the training set were used as potential features as well. To determine which features were used, an elastic net penalized regression was carried out, followed by a post hoc stepwise regression, using Akaike Information Criterion [AIC] as

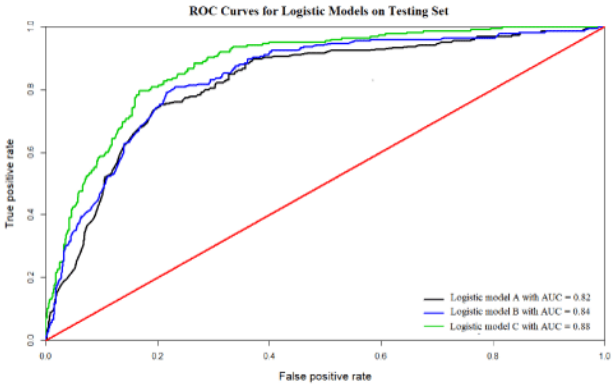


Figure 1: ROC Curves for Logistic Models on Testing Set. Evaluation of 3 different logistic models on the same test setafter being fitted on the training set classifying patients as TTS or acute MI of unspecified site. Of interest is how the AUC changes as more features are used in the logistic model.Logistic model **A** uses only sex, age, and race (Black, White, and other) as features. Logistic Model **B** uses sex, age, race (Black, White, and other), and 7 prespecified clinical characteristics. The features for Logistic model **C** were determined through an elastic net penalized regression followed by a stepwise regression on the features chosen by the elastic net regression.**AUC** = Area under curve; **MI**-myocardial infarction; **TTS**-Takotsubo; **ROC** = Receiver operating characteristic.

Table 2: Evaluation of Models in the Testing Set for Takotsubo vs Acute MI for Other Specified Sites, initial episode of care ICD 9 code 410:81

MODEL	A	B	C	D	E	F	G	H	I
Decision Rule:	**Point on the ROC curve closest to the point (0,1)**								
Sensitivity of being Takotsubo	0.24	<0.01	0.05	0.79	0.86	0.79	0.84	0.84	0.78
Specificity of being Takotsubo	0.76	>0.99	0.99	0.78	0.79	0.83	0.75	0.72	0.80
Precision for TTS	0.24	0.5	0.55	0.53	0.56	0.59	0.51	0.48	0.54
Neg predictive power for MI	0.76	0.76	0.77	0.92	0.95	0.93	0.91	0.94	0.92
Correct classification rate	0.64	0.76	0.77	0.79	0.82	0.81	0.77	0.75	0.79
Decision Rule:	**Youden Index**								
Sensitivity of being Takotsubo	0.24	<0.01	0.05	0.81	0.89	0.92	0.84	0.88	0.89
Specificity of being Takotsubo	0.76	>0.99	0.99	0.77	0.77	0.71	0.75	0.68	0.70
Precision for TTS	0.24	0.5	0.55	0.52	0.55	0.49	0.51	0.47	0.48
Neg predictive power for MI	0.76	0.76	0.77	0.93	0.96	0.96	0.91	0.95	0.95
Correct classification rate	0.64	0.76	0.77	0.78	0.80	0.76	0.77	0.73	0.75

A: Bernoulli random variable with probability of Takotsubo equal to 0.24;
B: At least two factor classified as havingTakotsubo;
C: At Least 3 factors is classified is classified as Takotsubo;
D: Logistic classification using 7 pre-selected features and demographics;
E: Penalized (L1) SVM ;
F:Logistic classificationwith features selected from an elastic net penalized regression and stepwise regression.;
G: SVM with linear kernel on same features as model F;
H: SVM with Polynomial kernel on same features as model F;
I: SVM with radial kernel on same features as model F.
MI = myocardial infarction; **SVM**= Support Vector Machine; **TTS** = Takotsubo.

a means of deciding which variables would be discarded . Age, white race and sex remained as features after the stepwise regression, indicating that the diagnostic codes could not explain the effects of these variables. However, several diagnosis codes and interaction effects remained as features resulting in an improved AUC of the ROC curve in the testing set to 0.88 [figure1].

As a means of comparison , the logistic model described above was compared to a baseline model [model A:Table 2], several SVM models [model E, G, H, and I in Table 2], and a logistic regression model using only 7 pre-specified features and demographic information [age,sex, and race]. This was done to verify the appropriateness of the logistic regression model.

After a model was trained using the training set so that the probability of having TTS can be evaluated as a function of the features involved in the model, ROC curves were determined on the training set, so that cut off points specifying what probability was needed for a patient to be classified as having TTS, using either the Youden Index or the point on the ROC curves closest to the point [0,1] was determined. After this cutoff point was determined for each model, specificity, sensitivity, precision, and negative predictive power was evaluated on the testing set. All statistical analysis was done using R version 3.2.3 statistical software. ROC curves were generated using the "ROCR" package, while the BimaxBiclustering algorithm used the "biclust" package available through R.

The logistic model with features selected by elastic net and stepwise regression seemed appropriate as it had a similar or better performance in terms of sensitivity, specificity, precision, and negative predictive power, when compared to all SVM models [Table 2 and Figure 2]. The logistic model with the 7 pre-specified factors showed improvement in terms of precision and negative predictive power when compared to a baseline model [Model A in Table 2], while maintaining a reasonably high sensitivity

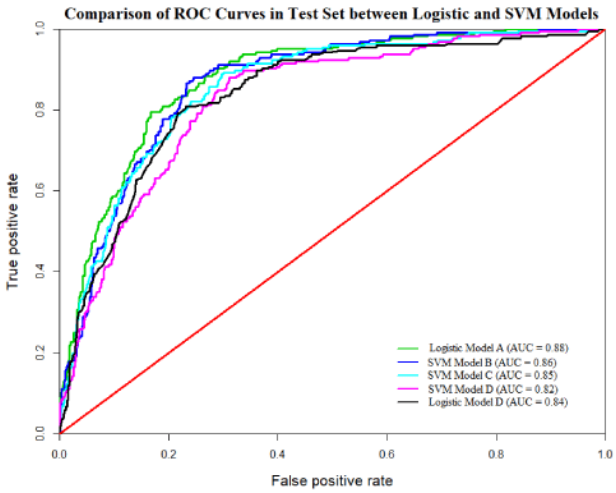


Figure 2: Comparison of ROC Curves in Test Set between Logisticand SVM models.

A comparison of the ROC curves in the testing set between 2 different logistic models and 3 different SVM models in order to determine the appropriateness of using logistic classification. The models classify patients as TTS or acute MI of unspecified site. The features of logistic model **A** were determined through an elastic net penalized regression followed by a stepwise regression on the features chosen by the elastic net regression. Model **B** is a tuned SVM model using a linear kernel on the same features as model A. Model **C** is a tuned SVM model using a radial kernel on the same features as model A. Model **D** is a tuned SVM using a polynomial kernel on the same features as Model A. Model **E** is a logistic model using only demographics (sex, age, and race) and 7 prespecified clinical characteristics. **AUC** = Area under curve;**MI**-myocardial infarction;**ROC** = Receiver operating characteristic; **SVM** = Support vector machine; **TTS**-Takotsubo.

and specificity. When comparing the logistic model with features selected by elastic net and stepwise regression with the logistic model with pre-selected features, when the decision rule was determined by the point close to [0,1], the logistic model with features selected by elastic net and stepwise regression was uniformly better in terms of sensitivity, specificity, precision, and negative predictive power. However, when the decision rule was determined by the Youden Index , the logistic model with the pre-selected features had a higher precision [52% vs 49%] while lower negative predictive power [93% compared to 96%] than the logistic model with features selected by elastic net and stepwise regression. In total 6 of 7 factors [excluding other chest pain] in the logistic model with pre-selected features, along with age, race, and sex variables, were also in the logistic model with features selected by elastic net and stepwise regression.

B. TTS vs ICD-9 code 410.01 [acute myocardial infarction of anterolateral wall, initial episode of care]

Considering the regional nature of TTS [apical ballooning] and the need for differential diagnosis at presentation, and visual similarity at imaging, anterolateral wall MI [ICD-9 code 410.01] was used as a control in the second [and final] analysis. There were 747 cases of TTS and 3923 cases of ALWMI analyzed. The percentage of TTS cases to ALWMI cases was 16.1%. Starting from the discharge day, Kaplan Meier Survival curves were calculated comparing the 5 year survival from cardiovascular disease death and readmission free of heart failure between the two groups. Differences between the two groups were accessed using the log rank test. Prior to analyses, 6 pre-selected factors were chosen [same factors as in analysis A , excluding tricuspid valve disorder], and a logistic model was run on these factors along with age, sex, and race , and compared in a similar fashion as the previous analysis to other logistic and SVM models [Table 3].

Table 3: Evaluation of Models in the Testing Set for Takotsubo vs Acute AWMI, initial episode of care ICD 9 code 410:01

MODEL	A	B	C	D	E	F	G
Decision Rule:	**Youden Index**						
AUC (Area Under Curve)	NA	NA	NA	0.82	0.86	0.72	0.87
Sensitivity of being Takotsubo	0.16	0.38	0.08	0.84	0.79	0.86	0.80
Specificity of being Takotsubo	0.84	0.8	0.98	0.71	0.78	0.27	0.78
Precision for TTS	0.16	0.28	0.43	0.36	0.41	0.18	0.41
Negative predictive value for MI	0.84	0.87	0.85	0.96	0.95	0.91	0.95
Correct Classification Rate	0.73	0.74	0.84	0.73	0.79	0.36	0.78

A: Bernoulli random variable with probability of Takotsubo equal to 0.18;
B: At least one factor classified as havingTakotsubo;
C: At Least 2 factors is classified is classified as Takotsubo;
D: Logistic classification using 6 pre-selected features;
E: Tuned SVM with linear kernel;
F: Tuned SVM with radial Kernel;
G: Logistic classification with features selected from an elastic net penalized regression and Akaike information criterion. **ALWMI**-=anterolateral wall myocardial infarction; **MI**= myocardial infarction; **SVM**= support vector machine; **TTS** = Takotsubo.

C. Statistical Comparison of Frequency of clinical characteristics; TTS vs ICD-9 Code 410.01 and TTS vs ICD -9 Code 410.81

Both the logistic model using the 7 prespecified features and demographic information in Acute MI of an unspecified site and TTS patients, and the logistic model using the 6 prespecified features and demographic information in ALWMI and TTS patients have similar performance in terms of classifying TTS patients in their respective testing sets with an AUC=0.82 vs an AUC=0.84 respectively [central illustration]. The rate of disorders of magnesium metabolism, anxiety state disorder, mitral valve disorder, cardiomyopathy, systolic heart failure, and other chest pain are significantly higher in TTS patients in both training sets [central illustration]. When comparing the rate of the 6 common factors in ALWMI patients vs acute MI of unspecified site patients, only the factors of magnesium metabolism [P-Value=0.01] and a systolic heart failure [P-Value=0.0005] have a different occurrence at the 0.05 level with ALWMI having a higher rate than acute MI of unspecified site. Of note ,both classification models have an AUC of 0.70 on white female patients, indicating that the non-demographic features in the models classify TTS with a comparable false positive and true positive rate. This indicates in part that the clinical factors can classify TTS patients in both testing sets for the majority demographic of TTS.

Results

The rate of TTS appears to stabilize at around 2% starting from the year 2012 [Table 1]. The percentage of inhospital , 30 day, 90 day, and 1 year all-cause mortality was higher in patients with an acute MI at the 0.0001 level [Table 4]. Event rates for CVD and heart failure deaths are higher in patients with all MIs at the 0.0001 level [figures3-4] and in patients with ALWMI at the 0.0001 level [figures 5-6].

The rate of females is higher in TTS than ALWMI. White race is more prevalent in TTS. The best method in terms

Table 4: All-Cause in Hospital, 30-day, 90-day, and 1-year Mortality Rates Comparing TTS with Acute MI

Outcome	TTS (N (%))	MI (N (%))	P-value
In Hospital Mortality	6 (1)	2303 (9)	<0.0001
30 Day Mortality	15 (2)	5745 (13)	<0.0001
90 Day Mortality	23 (4)	6563 (14)	<0.0001
1 Year Mortality	46 (8)	8173 (18)	<0.0001

MI= myocardial infarction; **TTS** = Takotsubo.

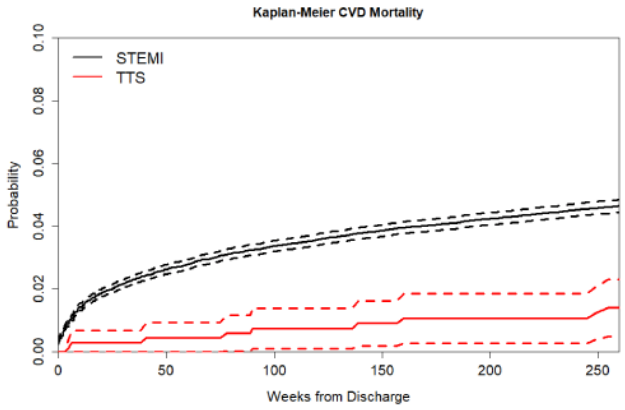


Figure 3: 5-Year Kaplan Meier CVD Mortality Curves for TTS and STEMI. 5-year Kaplan Meier mortality curves plotting the rate of death from cardiovascular disease as a function of time between TTS and STEMI patients. The time to death was determined using weeks after discharge from TTS or STEMI. The curves show that the unadjusted rate of death islower in TTS patients. The dashed lines represent 95% confidence intervals. **CVD**-cardiovascular disease; **STEMI**= ST-elevation myocardial infarction; **TTS**-Takotsubo.

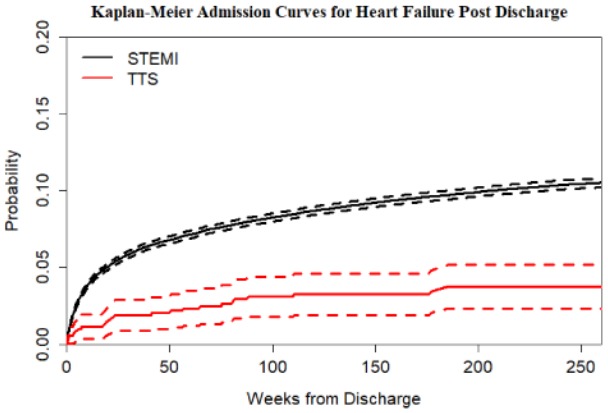


Figure 4: 5-Year Kaplan Meier HF Admission Curves for TTS and STEMI. 5-year Kaplan Meiercurves plotting the rate of admission forheart failure as a function of time between TTS and STEMI patients. As a condition only patients that survived hospitalization were included. The time to admission for heart failure was determined using weeks after dischargefrom TTS or STEMI. The curves show that the unadjusted rate of admission for heart failure is much lower in TTS patients. The dashed lines represent 95% confidence intervals. **HF**=Heart Failure; **STEMI**= ST-elevation myocardial infarction;**TTS**-Takotsubo.

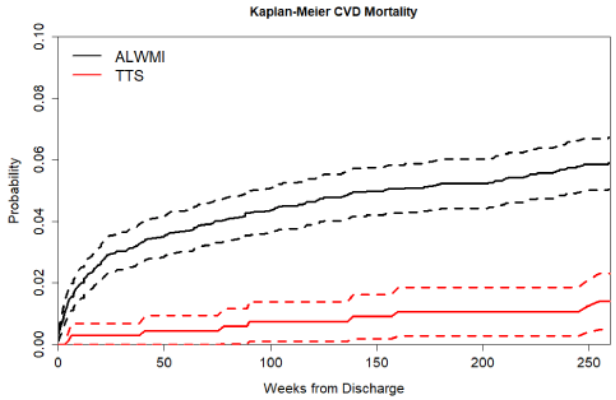


Figure 5: 5-Year Kaplan Meier CVD Mortality Curves for TTS and ALWMI. 5-year Kaplan Meier mortality curves plotting the rate of death from cardiovascular disease as a function of time between TTS and ALWMI patients (a subset of STEMI patients). The time to death was determined using weeks after discharge from TTS or ALWMI. The curves show that the unadjusted rate of death is much lower in TTS patients. The dashed lines represent 95% confidence intervals. **ALWMI**= anterolateral wall myocardial infarction; **CVD**-cardiovascular disease; ; **STEMI**= ST-elevation myocardial infarction**; TTS**-Takotsubo.

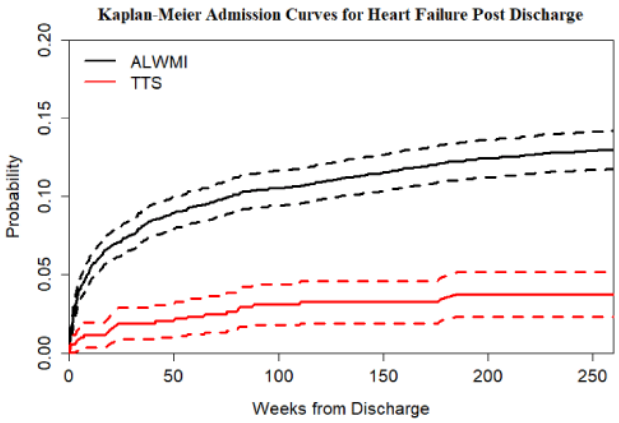


Figure 6: 5-Year Kaplan Meier HF Admission Curves for TTS and ALWMI. 5-year Kaplan Meier curves plotting the rate of admission for heart failure as a function of time between TTS and ALWMI patients (a subset of STEMI patients). As a condition only patients that survived hospitalization were included. The time to admission for heart failure was determined using weeks after discharge from TTS or ALWMI. The curves show thatthe unadjusted rate of admission for heart failure is much lower in TTS patients. The dashed lines represent 95% confidence intervals. **ALWMI**= anterolateral wall myocardial infarction; **HF**=Heart Failure;; **STEMI**= ST-elevation myocardial infarction;**TTS**=Takotsubo.

of classification is the SVM with a linear kernel with the following results: for TTS; sensitivity 0.79, specificity 0.78, precision rate 0.41, and correct classification rate 0.79. For MI; negative predictive value rate 0.95 [Table 3-E]. The Logistic classification using feature selection from the elastic net and stepwise regression [43 total variables] performed similarly to the SVM with a linear kernel [Table 3 -G]. The AUC for logistic classification with features selected by elastic net and stepwise regression was: 0.87 [figure 7].

Finally the logistic classification using six out of the seven prespecified features, along with race, sex and age in comparing TTS to ALWMI [Table 3-D], resulted in the following classification rates : for TTS; sensitivity 0 .84, specificity 0.71, precision rate 0.36, and correct classification rate 0.73. For MI: negative predictive value was 0.96.

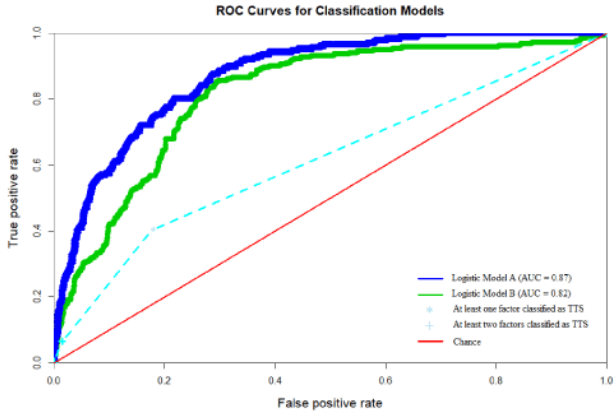


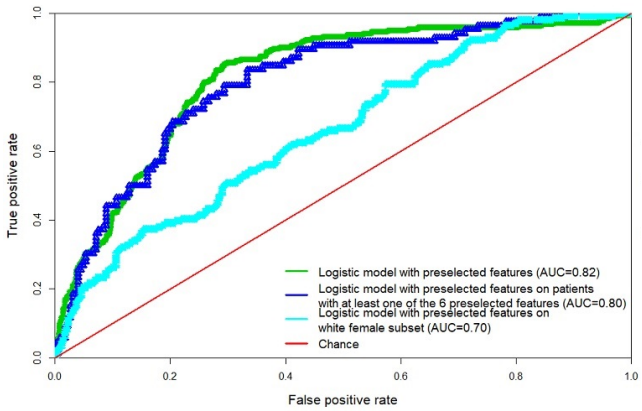
Figure 7: ROC Curves for Classification Models. Evaluation of two logistic models on the testing set classifying patients as TTS or ALWMI. The features of Logistic Model **A** were determined through an elastic net penalized regression followed by a stepwise regression on the features chosen by the elastic net regression. The features of logistic model **B** include race (Black, White, and other), sex, age, and 6 prespecified clinical characteristics. The true positive rate as a function of the false positive rate when any of the clinical characteristics, as well as when at least 2 of the clinical characteristic of logistic model B are also plotted. *= classification model where TTS was classified when at least one of the 6 clinical characteristics is present; **+** = classification model where TTS was classified when at least two of the 6 clinical characteristics is present.**ALWMI**= anterolateral wall myocardial infarction; **AUC** = Area under curve; **ROC** = Receiver operating characteristic;**TTS**=Takotsubo.

Central Illustration Panel A: Factors Identifying Takotsubo

Comparison Between Takotsubo and ALWMI Patients in the Training Set

Variable	Takotsubo (N=526)	AWMI (N=2,746)	P-Value
Mean Age (sd) in Years	66.7 (12.6)	65.0 (14.8)	0.008
	Takotsubo (# (%))	AWMI (# (%))	
Non-White	82 (15.6)	585 (21.3)	0.003
MALE	37 (7.0)	1799 (65.5)	<0.001
Disorders of Mag. Metabolism	12 (2.3)	26 (1)	0.017
Anxiety State Disorder	75 (14.3)	62 (2.4)	<0.001
Mitral Valve Disorder	45 (8.6)	112 (4.1)	<0.001
Cardiomyopathy	57 (10.8)	168 (6.1)	<0.001
Systolic Heart Failure	48 (9.13)	132 (4.8)	<0.001
Other Chest Pain	11 (2.1)	21 (0.8)	0.010
No Factors	314 (59.7)	2261 (82.3)	<0.001
At Least 1	212 (40.3)	485 (17.7)	
At least 2	34 (6.5)	40 (1.4)	<0.001

ROC Curves on Test Set for Logistic Model on Important Subsets



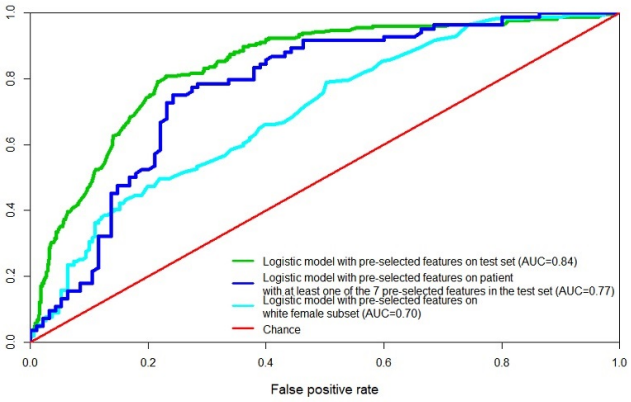
Central Illustration Panel A: Factors Identifying Takotsubo. The logistic models used for classification of TTS patients have their features presented as variables in the tables. The table on the left compare the rate of these features in the training set between TTS and ALWMI patients while the table on the right compares the features between TTS and acute MI patients of an unspecified site. All clinical characteristics used as features in these logistic models occur at a higher frequency in TTS patients. **ALWMI**= anterolateral wall myocardial infarction; **MI**-myocardial infarction; **TTS**=Takotsubo.

Central Illustration Panel B: Factors Identifying Takotsubo

Comparison Between Takotsubo and Acute MI of Unspecified Site in the Training Set

Variable	Takotsubo (N=526)	MI (N=1680)	P-Value
Mean Age (SD) in Years	66.19 (12.6)	65.7 (14.6)	0.422
	Takotsubo (# (%))	MI (# (%))	
Non-White	82 (15.6)	507 (30.2)	<0.001
Male	37 (7.0)	1082 (64.4)	<0.001
Disorders of Mag. Metabolism	12 (2.3)	4 (0.2)	<0.001
Anxiety State Disorder	75 (14.3)	39 (2.3)	<0.001
Mitral Valve Disorder	45 (8.6)	50 (3.0)	<0.001
Cardiomyopathy	57 (10.8)	104 (6.2)	<0.001
Systolic Heart Failure	48 (9.1)	50 (3.0)	<0.001
Other Chest Pain	11 (2.1)	6 (0.4)	<0.001
Tricuspid Valve Disorder	16 (3.0)	12 (0.7)	0.001
None of the Above	307 (58.4)	1435 (85.4)	<0.001
At least 1	219 (41.6)	245 (14.6)	
At least 2	40 (7.6)	19 (1.1)	<0.001

ROC curves on Test Set for Logistic Model on Important Subsets



Central Illustration Panel B: Factors Identifying Takotsubo. The figures represent how well these models classify patients in a testing set using ROC curves. The different curves for each figure represent the performance on a different subpopulation of patients which include the whole testing set, the set of patients with having at least one of the clinical characteristics represented in the table, and white females. Of note is that the two different logistic models seem to classify TTS patients at similar rates even though the set of MI patients are different. **MI**-myocardial infarction; **TTS**=Takotsubo.

Discussion

The results of this study demonstrate that an algorithm, that includes observations at the time of presentation of a patient with acute ALWMI and /or ACS, could assist in differential diagnosis raising a credible question of possible event of TTS.

Furthermore, the algorithm results are derived from a real life, non-selective database, and are independent of age, sex or race. The relative frequencies of all MI's and TTS are consistent with reported epidemiologic data and related outcomes of CHF and mortality. The components of the algorithm raise important questions of underlying factors affecting the occurrence, course and outcomes of TTS.

Exposure to severe acute and /or chronic stress results in responses that are either systemic or limited to certain systems. Inappropriate neurohumoral activation includes the hypothalamic pituitary-adrenal axis [HPA], adrenergic nervous system [ANS] and renin-angiotensin-aldosterone system [RAAS]. Their effector hormones are cytotoxic to cardiomyocytes. Hyperadrenergic state accompanies stressor states and usually results in acute or chronic tissue damage and, in regarding the heart, acute or chronic progressive myocardial necrosis [5,6].

The question then is: How do patients with TTS largely avoid significant myocardial necrosis, and the syndrome reverses itself ,once the patient escapes acute mortality? Residual myocardial dysfunction following recovery is

documented as mild and could even be present prior to the TTS occurrence, and unrelated to the event [7]. TTS occurs mostly in postmenopausal women and white race.

A systemic syndrome in response to acute and/or chronic stress states with associated excessive neurohormonal activation and associated with cardiomyocyte death is cation dyshomeostasis and has been reported in association with CHF [6].

Hyperadrenergic state and response to excessive epinephrine have been reported in TTS, with epinephrine-induced switch in signal trafficking involving beta2 adrenergic receptor [b2 AR] from Gas to Gai, following intense activation of beta one adrenergic receptor [b1AR], with antiapoptotic and antiarrhythmic effects, negative inotropism and protein kinase [PKA] mediated b2AR phosphorylation. In canine models, increased b2AR density has been reported from the basal toward the apical region, which might explain why in patientsakinesistypically occurs in the midventricular and apical regions [5,8].

Protein phosphatase activity has been reported to be increased after beta adrenergic stimulation. In TTS there is reduction in PKA dependent phosphorylation ofphospholamban[PLN]. In the unphosphorylated state PLN inhibits sarcoplasmic/endoplasmic reticulum Calcium ATPase [SERCA] by lowering its apparent Ca2+ affinity. There is an increase in the amount of phosphatase PP1in TTS. In TTS ventricular expression of sarcolipin [SLP] and dephosphorylation of PLN reduces SERCA2a activity and its Ca++ affinity [9].

In TTS apoptosis is limited, mitochondrial loss of integrity and increased oxidative state are not prominent issues during the acute phase. Activity of protein phosphatase tended to higher levels when compared with levels measured after functional recovery [9].

The expression of PLN was significantly increased in TTS. An increased PLN/SERCA 2a ratio represents a crucial factor of depressed sarcoplasmic reticulum [SR] function as well as an altered Ca2+ cycling in failing human myocardium.

The distribution of apical ballooning in TTS does not match a specific coronary artery region/distribution. Reduction of coronary perfusion of the affected myocardial region during the acute/subacute phase of TTS, likely reflects down regulation of coronary flow to prevent myocardial tissue injury [10]. The location of contractile abnormality is not subendocardial but subepicardialor transmural, unlike primary microvascular coronary insufficiency [11-13].

The ECG ST abnormalities identified in the InterTAK registry are consistent with an event involving the ascending limb of the apical myocardial band [subepicardial distribution] with prominent ST elevations in mid anterior leads [14].

The location of the contraction abnormality matches the distribution of b1/b2 AR ratios. Despite extensive exposure to acute stresses in the general population TTS is seen in a minority of patients as compared to ACS and other syndromes, as mentioned previously. Instances of mother/daughter TTS suggest possible genetic predisposition. Above considerations led to a hypothesis that the unique characteristics and differences of TTS versus other stress-induced conditions are related to a genetic condition limited to a rather small number of individuals and evoking a specific and largely localized response to stress with the TTS characteristics, including spontaneous resolution/recovery.

The statistically significant differences in frequency of the components of the present algorithm between TTS and acute MI, noted in both analyses point to different etiological factors and events of these two conditions i.e. obstruction of coronary perfusion/flow in acute MI vs. sudden cessation of functioning of the contractile apparatus of a broad myocardial area not corresponding to a particular coronary distribution, with profound temporary local and systemic responses in TTS.

Some of the components of the algorithm, representing structural and /or functional issues are noted in their presence in a genetic condition, namely mitral valve prolapse. A recent publication described the predominant gene of this condition, DCHS-1, identifying mutations in the gene [single nucleotide variants] resulting in leaflet thickening and myxomatous degeneration with increased proteoglycan accumulation in the mitral leaflets [15].

DCHS-1 [protein dachsous homolog-1], also known as protocadherin-16, is a protein that in humans is encoded by the DCHS-1 gene [located in chromosomal locus 11p15.4.] [15]. Review of its ontology and relevant pathways points to downstream effects that,in the presence of loss of function mutations, could have significant cardiovascular implications. Catenin p120 [p120] regulates cadherin

stability and acts, at least in part, through regulation of Rho GTPases.Itinhibits the intrinsic GDP/GTP exchange activity of RhoA in a manner comparable to the Rho inhibitor, Guanine Nucleotide Dissociation Inhibitor [GDI] [16-20]. Loss of function of a cadherin gene is associated with diminished Rho/ROCK pathway downstream effects, involving the Ga subfamily of GPCRs [Gaq-11 and Ga12/13], nitric oxide synthase [eNOS], phosphorylation and/or dephosphorylation of important heart contraction -related proteins [phospholamban, sarcolipin, SERCA, phosphatases]. A potential influence of RhoA/ROCK pathway, losing and/or regaining its function[s] [via effects of GEFs] during stress, downstream from Gai,Gaq,Ga12/13, on the events of different stages of TTS, has not been explored thus far, either as a primary susceptibility or a protective issue altering the course and outcome of the syndrome [21]. Active RhoA/ROCK downregulates eNOSgene expression and inhibits eNOS phosphorylation at Ser-1177. Blocking RhoA/ROCK reverses above effects with release of NO that would be beneficial regarding tissue perfusion and reducing inflammation [21,22]. RhoGEFs [p115 and p63] have been shown to mediate Ang II AT1 receptor dependent RhoA activation in vascular smooth muscle cells [VSMCs] , with resulting benefit when blocked [21].

For the reasons above, loss of function with blockade of RhoA/ROCK pathway, could have a protective effect on cardiomyocytesandperipheralantioxidantandvasodilatory effects during and following TTS, with protection of vital organs during the acute event. They include diminished Ca++ sensitivity of the contractile apparatus and avoidance of excessive intracellular accumulations of Ca++ which could lead to mitochondrial degradation and necrosis noted in other stress-related syndromes. Inherited non-syndromic MVP is a developmentally based disease that progresses over the lifespan of affected individuals, consistent with previous reports on its natural history [15,22]. Of note, the incidence of TTS is similar but lower than MVP. The presence of this condition, if proven to be present in TTS, appears to convey a survival advantage to people subjected to acute and/or sustained chronic stress, resulting in TTS rather than a more harmful stress-related syndrome. The earliest characteristic of the condition, MV redundancy with or without prolapse, is easily ascertained by echocardiography at the point of care in most clinical settings, enhancing the value of the algorithm [23].

Conclusions

We present an algorithm to be used in assisting clinicians in differentiating TTS versus any acute myocardial infarction. The components of the algorithm are present at the inception of the acute event, essentially looking back and possibly pointing to a preexisting condition and pathways that, in aberration, precipitate TTS, in the presence of an excessive adrenergic stimulus. The algorithm could be enhanced by an echocardiogram and recruit specific significant observations from other relevant studies/algorithms shown to be important at prediction of TTS. By raising the probability of TTS at presentation, it alerts to important issues of treatment and need for further inquiry.

Strengths and limitations

The algorithm is based on a non-selective database with no apparent bias, validation of data, adjudication of mortality/morbidity, uses a bottom up approach of studying comorbidities/observations. It suffers the limitation of an administrative database and relies on discharge diagnosis documents of cases and controls

The concordance of statistical analyses using different locations of acute MI as controls when using the algorithm [with the exclusion of tricuspid valve disease factor] points away from a primarily vascular event and is consistent with the presence of TTS variants and substantial percentage of right ventricular involvement. The noted significance of the tricuspid valve disease factor in the analysis, likely reflects the presence of right ventricular involvement in MI other than anterolateral wall.

Of note, in the database 59.7% of TTS and 82.3% of MI cases had none of the factors appear in the first analysis. None of the cases had three factors. The difference in presence of any two factors [6.5% for TTS vs 1.4% for MI] was significant with a p value of <0.001. The p value of difference of four factors between TTS and MI was <0.001. Above analyses suggest that these factors should be actively sought for their presence or absence in patients who present with acute coronary syndrome/ acute MI. The consistency of differences for these four factors suggest possible etiologic connection to each other when two factors are present.

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