Heart & Lung xxx (2016) 1–5

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

Development and validation of a simple integer risk score for prediction of in-hospital mortality following Takotsubo syndrome

Ahmed N. Mahmoud, MD [a,*], Mohammad Al-Ani, MD [a], Marwan Saad, MD, PhD [b], Akram Y. Elgendy, MD, MRCP [c], Islam Y. Elgendy, MD [a]

[a] Division of Cardiovascular Medicine, Department of Medicine, University of Florida, Gainesville, FL, USA
[b] Department of Cardiology, University of Arkansas for Medical Science, Little Rock, AR, USA
[c] Department of Medicine, University of Florida, Gainesville, FL, USA

ARTICLE INFO

Article history:
Received 24 April 2016
Received in revised form
19 August 2016
Accepted 25 August 2016
Available online xxx

Keywords:
Mortality
Takotsubo syndrome
Risk model
Stress cardiomyopathy
Heart failure

ABSTRACT

Background: Data regarding the characteristics associated with worse outcomes in Takotsubo syndrome (TTS) patients is lacking.
Methods and objectives: The National Inpatient Sample (NIS) 2012 database was utilized to calculate a risk score for in-hospital mortality following TTS that was internally and externally validated in both 2012 and 2013 databases, respectively.
Results: The incidences of in-hospital mortality in the 2012 development sample were 0.2%, 3.2% and 15.6% in the low risk (≤2), intermediate risk (3–4) and high-risk (≥5) score groups, respectively. The risk score C-statistics were 0.86 and 0.88 in the development and external validation samples, respectively ($p < 0.001$). Age ≥ 80 year was associated with the highest odds ratio (OR) of mortality (OR 8.07, 95% confidence interval (CI) 5.79–11.25). Other important predictors were acute cerebrovascular accident and acute respiratory failure.
Conclusions: The risk of in-hospital mortality following TTS could be predicted using a simple risk score, which could aid in identifying and proper management of a higher risk group.
Published by Elsevier Inc.

Introduction

Takotsubo syndrome (TTS) is an acute and likely reversible form of cardiomyopathy that is not explained by occlusive coronary artery disease.[1] Since its first description in 1990 by Sato, the condition has received great interest due to the unique population characteristics, predisposing factors, and clinical course when compared to garden variety coronary artery disease.[2] TTS could be broadly classified into two main categories, either primary TTS, or secondary TTS, which occurs in the setting of another primary pathology, e.g. subarachnoid hemorrhage or sepsis or malignancy.[1,3–5] There has been an apparent increase in the incidence of TTS as the condition is becoming more recognizable, with most estimates ranging between 5000 and 10,000 cases yearly in the United States.[6–8]

TTS has initially been described as benign when compared with acute coronary syndrome (ACS).[9,10] Subsequent registries showed an increased risk of heart failure, ventricular arrhythmias, thrombo-embolic phenomena, and cardiac arrest with this condition.[4,11] This risk is high despite accounting for associated non-cardiac acute illness. The international Takotsubo registry data (from 26 centers in the United States and Europe) showed a 21.8% incidence of a combined end point of serious in-hospital complications, with rates equal to or higher than those of patients with an ACS.[4] An analysis of a Swedish registry had demonstrated similar short and long term risk of mortality with TTS and ACS.[12] Hence, the demand of a risk-stratifying tool to help to identify those with an increased risk of mortality in patients with TTS. The National Inpatient Sample (NIS) is a nationwide inpatient database representing about 20% of yearly hospitalizations in the United States (US) thus it provides an excellent opportunity to evaluate the risk factors and outcomes of these patients. Therefore, we aimed to utilize the NIS database to construct and validate a risk score to predict in-hospital mortality in patients with TTS.

Methods

A retrospective cross-sectional study was conducted utilizing the NIS databases for years 2012 and 2013. The 2012 database was

Funding sources: None.
Disclosures: Authors have no conflict of interest to disclose.
* Corresponding author. Department of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, FL, 32610, USA. Fax: +1 352 265 1107.
E-mail address: Ahmed.Mahmoud@medicine.ufl.edu (A.N. Mahmoud).

0147-9563/$ – see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.hrtlng.2016.08.009

used for the development and internal validation of the proposed risk score, while the 2013 database was used for external validation. The NIS represents the largest inpatient database in the US representing a stratified sample of approximately 20% of US hospitalizations that is provided in a population-weighted format.[13] The NIS is publically available with de-identified data, and thus, the current study did not require an approval of the institutional review board.

Study population

Any adult patient with an International Statistical Classification of Diseases (ICD)-9 discharge code of TTS (429.83) was included. This code was used in prior NIS-based studies of TTS.[6,14] The discharge weights included in the NIS databases were used for calculation of the weighted national estimates of the incidence of various diagnoses. Multiple variables were available for each patient, including baseline characteristics (age, race, sex, and comorbidities), as well as in-hospital complications. All of the included variables were identified by their corresponding ICD-9 codes from the NIS database and by using the Clinical Classifications Software (CCS) for ICD-9 codes generated by the Healthcare Cost and Utilization Project (Supplementary Table1).[15] For the purpose of the risk-score validation, the 2012 NIS database was divided into a development and internal validations portions in a ratio of 4:1. External validation was conducted using a cohort of patients with principal diagnosis of TTS from the 2013 NIS database, in an attempt to test the validity of the proposed score on a subset of patients with higher likelihood of having a primary TTS diagnosis.

Study outcomes

Our aim was to develop and validate a prediction tool for in-hospital mortality for patients with TTS (both general and primary TTS patient populations). The in-hospital correlation between TTS and length of hospital stay was considered a secondary outcome. Both outcomes were assessed in the NIS 2012 and 2013 samples, and then stratified in each sample by the risk group category.

Statistical analysis and risk score construction

A national weighted descriptive analysis was conducted for the 2012 TTS patient population, reporting the mean and standard deviation (SD) for continuous variables, and percentages for the categorical variables. Eighteen pre-specified independent variables were included in the initial construction of the predictive model based on previous studies, illustrating an increased risk of morbidity or mortality with these individual variables.[3,14,16–20] Those variables included age, race, sex, hypertension, diabetes mellitus, chronic kidney disease (CKD), atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, ventricular arrhythmias, sino-atrial node dysfunction, complete heart block, non-complete heart block, acute kidney injury, shock, acute cerebrovascular disease, acute respiratory failure and congestive heart failure. For the purpose of detection of data based multicollinearities, Pearson's correlation was performed for all variables and those with a correlation coefficient >0.60 were excluded from the model construction. A multivariable logistic regression was constructed using stepwise backward elimination method, with a cut level p-value of 0.10 for entry and 0.05 for elimination. A similar approach was adopted in development of prior risk score tools.[21,22] The final variables that achieved odds ratio (OR) > 1 and a p-value <0.05 were assigned risk score weights equal to the following equation:

$$\mathscr{W}_i = \sqrt[3]{\beta_i \times 2.5}$$

where $\mathscr{W}_i$ = The assigned weight value of each predictor approximated to the nearest integer, and β_i = The beta coefficient value of each predictor.

With respect to the age variable, score weights were assigned an ascending ordinal order. Although the weight assignment might be nonreflective to the actual OR of the variables, the qualitative nature of the risk score and the primary aim of constructing a simple score tool necessitated the use of such weighing method.

The score distribution over the development sample was used to equally divide the output range into three ordinal risk categories, low risk category (risk score $\leq$ 2), intermediate risk category (risk score 3–4) and high-risk category (risk score $\geq$ 5). The discrimination capacity was evaluated by calculating the receiver operator curve (C-statistic) for both the development and validation (internal and external) of the prediction model.[23] Furthermore, the model was calibrated using the Hosmer–Lemeshow goodness-of-fit test, wherein a p-value $\leq$ 0.05 was considered as poor calibration.[24] All data analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). The construction of in-hospital mortality predictive risk scores, using the NIS database had been previously performed in various clinical setting.[25,26]

Results

The 2012 sample database included 25,300 patients with a diagnosis of TTS during their hospital stay. The development sample included a total of 20,330 TTS patients (80% of 2012 database). The eighteen variables previously described were included in the initial logistic regression analysis. Age was categorized into four groups. The reference characteristic profile for the score was "Caucasian female" who is <50 years old; given the statistical association with a benign clinical course.[27] Thirteen variables were included in the final model (Table 1). The score ranged from 0 to 18 and divided into low-risk (≤2), intermediate risk (3–4) and high-risk (≥5) groups.

The risk-score demonstrated an incremental increase in the incidence of in-hospital mortality as the value of the score increased (Table 2). The incidence of in-hospital mortality was 0.2%, 3.2% and 15.9% for the low-risk, intermediate risk and high-risk groups, respectively (Fig. 1). Similar results were obtained when the risk score was applied to the internal validation sample with an in-hospital mortality of 0.2%, 3.9% and 11.2% in each group, respectively (Fig. 1). The mean length of stay varied significantly according to the risk group being 3.7 (±3.8) days in the low-risk group, 6.5 (±10.5) days in the intermediate risk group and 12.4 (±12.6) days in the high-risk group ($p < 0.001$ for trend).

The receiver–operator curve for the multivariable regression and the risk-score models on the development sample had a C-Statistic of 0.87 (95% CI 0.86–0.88, $p < 0.001$) and 0.86 (95% CI 0.84–0.85, $p < 0.001$), respectively (Supplementary Fig. 1). The internal validation of the risk score also illustrated similar results with good discrimination as evident by a C-Statistic of 0.79 (95% CI 0.76–0.82, $p < 0.001$) (Supplementary Fig. 2), and good calibration as indicated by a non significant p-value (0.26) for Hosmer–Lemeshow goodness-of-fit test. External validation of the risk score was conducted using the 2013 NIS weighted database, which included 7070 patients with a principal diagnosis of TTS. The risk score demonstrated a good discrimination capacity with a C-Statistic of 0.88 (95% CI 0.85–0.92, $p < 0.001$) (Supplementary Fig. 3) and good