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Prediction of short- and long-term mortality in takotsubo syndrome: the InterTAK Prognostic Score

Recent evidence suggests comparable in-hospital and long-term outcomes between takotsubo syndrome (TTS) and acute coronary syndrome.[1,2] Medical scoring systems are practical tools for decision making and prognostic assessment. However, TTS-specific scoring systems for risk stratification have not yet been established. Recently, classification based on triggering conditions proved useful in predicting adverse outcomes in TTS (InterTAK Classification).[1] Since clinical parameters other than triggering conditions can be associated with adverse outcomes in TTS, such as systolic blood pressure and heart rate,[3] the present study aimed to establish a scoring system combining triggering factors with other important but easily- obtainable clinical parameters of daily clinical practice.

Takotsubo syndrome patients were enrolled from the International Takotsubo (InterTAK) Registry, which is an all-comers TTS registry in collaboration with 26 centres worldwide.[2] Univariate Cox regression analyses for all-cause mortality were performed with variables of interest based on updated knowledge and recent literature[1–6]: age (cut-off = 70 years), triggering factors (InterTAK Classification), sex, hypertension, diabetes mellitus, typical or atypical TTS type,

A

InterTAK Prognostic Score	
Variable	**Points**
TTS secondary to neurologic disorders (Class IIb)	15
TTS secondary to physical activities, medical conditions, or procedures (Class IIa)	9
Age > 70 yr	8
SBP < 119 mmHg on admission	7
Diabetes mellitus	6
LVEF ≤ 45 % on admission	6
Male sex	6
Heart rate > 94 bpm on admission	4
TTS without an identifiable triggering factor (Class III)	3

Total Points			
≤ 15 points	16-22 points	23-28 points	≥ 29 points
Low	Intermediate	High	Very high

B

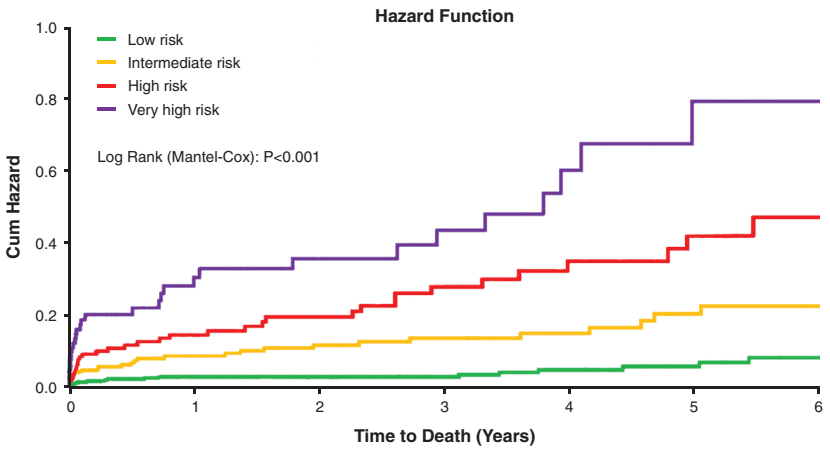

Figure 1 (*A*) Beta coefficients of the bootstrap model were multiplied by 10 and rounded to the nearest integer to derive points for each risk factor. For each patient, the InterTAK Prognostic Score was derived by summing the points associated with the given risk factors. Score cut-off values for four risk groups were obtained: low risk ≤ 15 points; intermediate risk 16–22 points; high risk 23–28 points; and very high risk ≥ 29 points. (*B*) The InterTAK Prognostic Score identifies four different risk groups. Five-year overall survival in low risk, intermediate risk, high risk, and very high risk groups rated as high as 93.5%, 79.9%, 65.6%, and 45.1%, respectively. Using the low-risk group as the reference group, the following hazard ratios (HR) with 95% confidence intervals (CI) were obtained: intermediate risk: HR 3.15, 95% CI 1.74–5.72, $P < 0.001$; high risk: HR 6.16, 95% CI 3.46–10.98, $P < 0.001$, and very high risk: HR 11.82, 95% CI 6.56–21.28, $P < 0.001$. LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TTS, takotsubo syndrome.

heart rate on admission (cut-off = 94 bpm), systolic blood pressure on admission (cut-off = 119 mmHg), left ventricular ejection fraction (cut-off = 45%) and white blood cell count on admission. Patients with missing values for these parameters were excluded. All variables with significance on univariate analysis were entered into a Cox regression model for all-cause mortality with respect to factor interactions. The Cox regression model was internally validated using 1000 bootstrap samples. The bootstrap was used to develop a regression coefficient-based scoring system in the presence of competing risks. The regression (beta) coefficients of the significant risk factors were multiplied by 10 and rounded to the nearest integer to derive item points. These points were then incorporated into the InterTAK Prognostic Score, calculated by the summation of points associated with each risk factor: InterTAK Prognostic Score = $\gamma_1 \times$ risk factor $A_1 + \gamma_2 \times$ risk factor $A_2 + \ldots + \gamma_n \times$ risk factor A_n, where $\gamma_1, \gamma_2, \ldots, \gamma_n$ denote the item points of the risk factor A_i. Optimal cut-off values were determined through decision tree analysis with exhaustive CHAID algorithm. Based on these cut-off values, patients were categorized into four groups: low, intermediate, high, and very high risk. Survival distributions and median survival times of each group were estimated using the Kaplan–Meier (KM) product–limit method and were compared using the log-rank test. Time-dependent receiver operating characteristic curves from censored survival data using KM or nearest neighbor estimation (NNE) method were used to assess score predictive performance in terms of area under the curve (AUC) for various time points. All tests were two-tailed and statistical significance was defined as $P < 0.05$. Statistical analyses were performed using R (version 3.5; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 25; IBM Corp., Armonk, NY, USA).

A total of 1160 patients (90.8% females; mean age 66.5 ± 13.0 years) were included in the present study. Overall, 80.6% of patients showed typical TTS type and mean left ventricular ejection fraction was 41.1% ± 11.6%. Mean systolic blood pressure and heart rate on admission were 130.2 ± 27.6 mmHg and 87.9 ± 21.9 bpm. The prevalence of diabetes mellitus was 13.4%. An emotional trigger (InterTAK Classification, Class I) was identified in 32.6% of TTS patients while 32.1% had preceding physical activities, medical conditions, or procedures (Class IIa) and 5.7% had preceding neurologic disorders (Class IIb). The remaining patients (29.7%) had no identifiable triggering factors (Class III).

According to bootstrap results, points were assigned to each risk factor that was independently associated with all-cause mortality (*Figure 1A*). Based on the total points, patients were categorized into four risk groups: low risk ≤ 15 points (37.8%), intermediate risk 16–22 points (23.4%), high risk 23–28 points (28.4%), and very high risk ≥ 29 points (10.4%). The four risk groups showed significant differences in all-cause mortality when using the low-risk group as reference [intermediate risk: hazard ratio (HR) 3.15, 95% confidence interval (CI) 1.74–5.72, $P < 0.001$; high risk: HR 6.16, 95% CI 3.46–10.98, $P < 0.001$, and very high risk: HR 11.82, 95% CI 6.56–21.28, $P < 0.001$] (*Figure 1B*). The AUCs for KM or NNE showed that the score predictive performance is almost stable from 30 days post-admission (KM/NNE-AUC 0.74/0.74) up to 5 years (KM/NNE-AUC 0.78/0.77).

Although well-known scores for other cardiac disorders, such as the CHA_2DS_2-VASc risk score,[7] have been applied as proxy scores for risk evaluation in TTS, there has been no TTS-specific risk score thus far. The present study establishes a novel risk stratification score for TTS (InterTAK Prognostic Score) that only requires variables that are easily obtainable in the acute phase and could identify low to very high risk of all-cause mortality both at short- and long-term. Thus, the InterTAK Prognostic Score could serve

as a useful clinical tool to stratify patients according to their risk.

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