



A novel clinical score (InterTAK Diagnostic Score) to differentiate Takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry

Jelena R. Ghadri¹, Victoria L. Cammann¹, Stjepan Jurisic¹, Burkhardt Seifert², L. Christian Napp³, Johanna Diekmann¹, Dana Roxana Bataiosu¹, Fabrizio D'Ascenzo¹, Katharina J. Ding¹, Annahita Sarcon⁴, Elycia Kazemian¹, Tanja Birri¹, Frank Ruschitzka¹, Thomas F. Lüscher¹, and Christian Templin^{1*}, InterTAK co-investigators: Milosz Jaguszewski^{1,5}, Jennifer Franke^{6,7}, Hugo A. Katus^{6,7}, Christof Burgdorf⁸, Heribert Schunkert^{8,9}, Holger Thiele¹⁰, Johann Bauersachs², Carsten Tschöpe^{11,12}, Lawrence Rajan¹³, Guido Michels¹⁴, Roman Pfister¹⁴, Christian Ukena¹⁵, Michael Böhm¹⁵, Raimund Erbel¹⁶, Alessandro Cuneo¹⁷, Claudius Jacobshagen¹⁸, Gerd Hasenfuß¹⁸, Mahir Karakas^{19,20,21}, Wolfgang Koenig^{8,9}, Wolfgang Rottbauer¹⁹, Samir M. Said²², Ruediger C. Braun-Dullaeus²², Florim Cuculi^{23,24}, Adrian Banning²³, Thomas A. Fischer²⁵, Tuija Vasankari²⁶, K.E. Juhani Airaksinen²⁶, Marcin Fijalkowski⁵, Andrzej Rynkiewicz²⁷, Grzegorz Opolski²⁸, Rafal Dworakowski²⁹, Philip MacCarthy²⁹, Christoph Kaiser³⁰, Stefan Osswald³⁰, Leonarda Galiuto³¹, Filippo Crea³¹, Wolfgang Dichtl³², Wolfgang M. Franz³², Klaus Empen^{33,34}, Stephan B. Felix^{33,34}, Clément Delmas³⁵, Olivier Lairez³⁵, Paul Erne^{1,2,4}, Stefan Frantz³⁶, Abhiram Prasad^{37,38}, and Jeroen J. Bax³

¹University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; ²Division of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; ³Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; ⁴University of Southern California, Keck School of Medicine, Division of Cardiovascular Medicine, Los Angeles, CA, USA; ⁵First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland; ⁶Department of Cardiology, Heidelberg University Hospital, Heidelberg, Germany; ⁷DZHK (German Centre for Cardiovascular Research), Partner Site Heidelberg, Heidelberg, Germany; ⁸Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; ⁹DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany; ¹⁰University Heart Center Luebeck, Medical Clinic II, Department of Cardiology, Angiology and Intensive Care Medicine, Luebeck, Germany; ¹¹Department of Cardiology, Charité, Campus Rudolf Virchow, Berlin, Germany; ¹²DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; ¹³Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, KY, USA; ¹⁴Department of Internal Medicine III, Heart Center University of Cologne, Cologne, Germany; ¹⁵Department of Internal Medicine III, Cardiology, Angiology, and Intensive Care Medicine, Saarland University, Homburg, Germany; ¹⁶Department of Cardiology, University Hospital Essen, Essen, Germany; ¹⁷Division of Cardiology, Asklepios Clinics St. Georg Hospital, Hamburg, Germany; ¹⁸Clinic for Cardiology and Pneumology, Georg August University of Goettingen, Goettingen, Germany; ¹⁹Department of Internal Medicine II—Cardiology, University of Ulm, Medical Center, Ulm, Germany; ²⁰Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany; ²¹DZHK (German Centre for Cardiovascular Research), Partner Site Hamburg/Kiel/Luebeck, Hamburg, Germany; ²²Internal Medicine/Cardiology, Angiology, and Pneumology, Magdeburg University, Magdeburg, Germany; ²³Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, UK; ²⁴Department of Cardiology, Kantonsspital Lucerne, Lucerne, Switzerland; ²⁵Department of Cardiology, Kantonsspital Winterthur, Winterthur, Switzerland; ²⁶Heart Center, Turku University Hospital and University of Turku, Turku, Finland; ²⁷Department of Cardiology and Cardiosurgery, University of Warmia and Mazury, Olsztyn, Poland; ²⁸Department of Cardiology, Medical University of Warsaw, Warsaw, Poland; ²⁹Department of Cardiology, Kings College Hospital, Kings Health Partners, London, UK; ³⁰Department of Cardiology, University Hospital Basel, Basel, Switzerland; ³¹Department of Cardiovascular Sciences, Catholic University of the Sacred Heart Rome, Rome, Italy; ³²University Hospital for Internal Medicine III (Cardiology and Angiology), Medical University Innsbruck, Innsbruck, Austria; ³³University Medicine Greifswald, Department of Internal Medicine B, Greifswald, Germany; ³⁴DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany; ³⁵Department of Cardiology and Cardiac Imaging Center, University Hospital of Rangueil, Toulouse, France; ³⁶Department of Internal Medicine III, University Hospital Halle, Halle (Saale), Germany; ³⁷Division of Cardiovascular Diseases Mayo Clinic, Rochester, MN, USA; ³⁸Cardiac Centre, St. George's, University of London, London, UK; and ³⁹Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands

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*Corresponding author. Acute Cardiac Care, Andreas Grüntzig Heart Catheter Laboratories, University Hospital Zurich, University Heart Center, Department of Cardiology, Raemistrasse 100, CH-8091 Zurich, Switzerland. Tel: +41 44 255 9585, Fax: +41 44 255 4401, Email: Christian.Templin@usz.ch

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Aims	Clinical presentation of Takotsubo syndrome (TTS) mimics acute coronary syndrome (ACS) and does not allow differentiation. We aimed to develop a clinical score to estimate the probability of TTS and to distinguish TTS from ACS in the acute stage.
Methods and results	Patients with TTS were recruited from the International Takotsubo Registry (www.takotsubo-registry.com) and ACS patients from the leading hospital in Zurich. A multiple logistic regression for the presence of TTS was performed in a derivation cohort (TTS, $n = 218$; ACS, $n = 436$). The best model was selected and formed a score (InterTAK Diagnostic Score) with seven variables, and each was assigned a score value: female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurological disorders 9, and QTc prolongation 6 points. The area under the curve (AUC) for the resulting score was 0.971 [95% confidence interval (CI) 0.96–0.98] and, using a cut-off value of 40 score points, sensitivity was 89% and specificity 91%. When patients with a score of ≥ 50 were diagnosed as TTS, nearly 95% of TTS patients were correctly diagnosed. When patients with a score ≤ 31 were diagnosed as ACS, $\sim 95\%$ of ACS patients were diagnosed correctly. The score was subsequently validated in an independent validation cohort (TTS, $n = 173$; ACS, $n = 226$), resulting in a score AUC of 0.901 (95% CI 0.87–0.93).
Conclusion	The InterTAK Diagnostic Score estimates the probability of the presence of TTS and is able to distinguish TTS from ACS with a high sensitivity and specificity. Trial registration: NCT0194762
Keywords	Takotsubo (stress) syndrome • Broken heart syndrome • Acute coronary syndrome • Clinical score • Diagnosis of Takotsubo (stress) syndrome • Disease prevalence

Introduction

Takotsubo syndrome (TTS) is an acute heart failure condition characterized by acute LV dysfunction with distinct wall motion abnormalities.^{1–3} Patients with TTS often present with symptoms similar to those of acute coronary syndrome (ACS) such as chest pain and dyspnoea.^{1,4} In addition, ECG and cardiac biomarkers including troponin and creatine kinase are commonly changed in both entities.^{5–7} As such, clinical presentation on admission is commonly indistinguishable from classical ACS.^{8,9} Based on currently available data, TTS is estimated to occur in 2% of all patients with ACS.⁸ However, TTS is still underestimated,¹⁰ and may actually occur at a higher prevalence.

Recently, we have demonstrated that in-hospital outcome of TTS is comparable with that of ACS, which indicates that TTS is not as benign as previously assumed but is in fact a serious and life-threatening condition. Early cardiac catheterization is necessary to make a correct diagnosis and remains the reference standard diagnostic test for TTS as for most patients with ACS.¹¹ Non-invasive clinical parameters are urgently needed to identify those patients, who present with the clinical picture of ACS but instead suffer from TTS.

The aim of the present study was to develop a sensitive and specific score to estimate the probability of TTS and to distinguish TTS from ACS in its initial clinical presentation in the emergency room.

Methods

Study patients and score generation

This substudy included patients from the recently published International Takotsubo Registry (InterTAK Registry).¹ Patients with TTS

were included in the present study if they met modified Mayo Clinic Diagnostic Criteria:^{1,8} (i) systolic and diastolic LV wall motion impairment; (ii) absence of angiographic evidence of plaque rupture; absence of obstructive CAD which is responsible for the respective wall motion abnormality; (iii) ECG abnormalities or increased troponin values; and (iv) absence of myocarditis/pheochromocytoma. Exceptions to the criteria include: (i) concomitant CAD was not an exclusion criterion; (ii) patients with focal TTS matching all other criteria, in whom the wall motion abnormality was congruent with a single coronary artery territory, were not excluded; and (iii) patients who died in the acute setting before confirmation of wall motion recovery were not excluded. When eligibility for inclusion was unclear, cases were studied by all members of the TTS team investigators in order to reach consensus.

To generate the InterTAK Diagnostic Score, a univariate analysis was performed in a derivation cohort [218 TTS patients vs. 436 ACS patients from the Zurich Acute Coronary Syndrome Registry (Zurich ACS Registry), 1:2 random assignment]. From those parameters, which were significantly different between TTS and ACS and can be easily obtained in the emergency room without any imaging modality or laboratory values, seven were selected to build the score, as described in the statistical analysis section. Thereafter, the score was validated in an independent validation cohort (TTS, $n = 173$; ACS, $n = 226$) consisting of prospectively enrolled TTS patients from the InterTAK Registry and ACS patients from the Zurich ACS Registry.

Statistical analysis

For comparison of patients' characteristics between TTS and ACS in the derivation cohort Pearson χ^2 test for nominal data, paired Student's *t*-test, or Mann–Whitney U-test for continuous data were used. In order to develop a score for predicting the diagnosis of TTS, a logistic regression with the following potential predictors was performed in the derivation cohort: female sex, age, physical trigger, emotional trigger, ST-segment elevation, ST-segment depression,

Table 1 Characteristics of patients from the derivation cohort^a

Baseline characteristics	Takotsubo syndrome (n = 218)	Acute coronary syndrome (n = 436)	P-value
Demographics			
Female sex, n/total n (%)	206/218 (94.5)	103/436 (23.6)	<0.001
Age, years, mean ± SD	67.3 ± 13.2 (n = 218)	63.4 ± 12.1 (n = 436)	<0.001
Triggering factors, n (%)			
Physical	109/218 (50.0)	89/436 (20.4)	<0.001
Emotional	93/218 (42.7)	11/436 (2.5)	<0.001
Both emotional and physical trigger	19/218 (8.7)	0/436 (0.0)	<0.001
No evident trigger	37/218 (17.0)	336/436 (77.1)	<0.001
Takotsubo syndrome type, n/total n (%)			
Apical type	168/218 (77.1)		
Midventricular type	43/218 (19.7)		
Basal type	5/218 (2.3)		
Focal type	2/218 (0.9)		
Acute coronary syndrome type, n/total n (%)			
STEMI		235/436 (53.9)	
NSTEMI		163/436 (37.4)	
Unstable angina pectoris		38/436 (8.7)	
Symptoms on admission, n/total n (%)			
Chest pain	148/218 (67.9)	385/436 (88.3)	<0.001
Dyspnoea	113/218 (51.8)	110/436 (25.2)	<0.001
Cardiac biomarkers on admission, median (IQR)			
Troponin, factor increase in ULN ^b	6.67 (2.50–19.00) n = 199	3.75 (0.68–15.84) n = 378	0.003
Creatine kinase, factor increase in ULN	0.81 (0.48–1.42) n = 139	1.17 (0.61–3.16) n = 397	<0.001
BNP, factor increase in ULN ^c	5.14 (1.67–13.17) n = 107	1.69 (0.54–6.44) n = 253	<0.001
Inflammatory markers on admission, median (IQR)			
CRP, mg/L	5.40 (1.85–15.50) n = 125	3.65 (1.20–9.73) n = 362	0.06
WBC, 10 ³ /μL	10.05 (7.51–13.21) n = 201	10.16 (8.17–12.93) n = 397	0.39
ECG on admission, n/total n (%)			
Sinus rhythm	206/218 (94.5)	417/436 (95.6)	0.52
Atrial fibrillation	12/218 (5.5)	19/436 (4.4)	0.52
ST-segment elevation	94/218 (43.1)	202/436 (46.3)	0.44
ST-segment depression	23/218 (10.6)	126/436 (28.9)	<0.001
T-wave inversion	77/218 (35.3)	102/436 (23.4)	0.001
Left bundle branch block	11/218 (5.0)	16/436 (3.7)	0.40
QTc prolongation	83/218 (38.1)	111/436 (25.5)	0.001
Vital signs, mean ± SD			
Heart rate, b.p.m.	87.6 ± 23.0 (n = 205)	73.3 ± 14.8 (n = 336)	<0.001
Systolic blood pressure, mmHg	128.6 ± 31.8 (n = 209)	128.8 ± 25.6 (n = 401)	0.92
Diastolic blood pressure, mmHg	74.1 ± 18.4 (n = 209)	71.7 ± 13.7 (n = 401)	0.10
Cardiovascular risk factors, n/total n (%)			
Hypertension	142/218 (65.1)	243/436 (55.7)	0.021
Diabetes mellitus	27/218 (12.4)	69/436 (15.8)	0.24
Current smoking	77/218 (35.3)	239/436 (54.8)	<0.001
Hypercholesterolaemia	76/218 (34.9)	161/436 (36.9)	0.61
Positive family history	68/218 (31.2)	99/436 (22.7)	0.019
Co-morbidities, n/total n (%)			
Cancer (total)	39/218 (17.9)	48/436 (11.0)	0.015
COPD or asthma	32/218 (14.7)	23/436 (5.3)	<0.001
Neurologic disorders (total) ^c	76/218 (34.9)	31/436 (7.1)	<0.001
Psychiatric disorders (total) ^d	115/218 (52.8)	42/436 (9.6)	<0.001
Affective disorders (total) ^d	63 / 218 (28.9)	24 / 436 (5.5)	<0.001

CRP, C-reactive protein; IQR, interquartile range; NSTEMI, non-ST segment elevation myocardial infarction; QTc, QT interval corrected for heart rate; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; ULN upper limit of normal; WBC, white blood cell count.

^aDepicted are the cohorts of patients with Takotsubo syndrome and acute coronary syndrome: 1:2 random assignment.

^bIncluding upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.

^cIncluding upper limits of the normal range for BNP and the NT-proBNP.

^dIncluding patients with either acute/former/chronic disorders.

Criteria	Points	Prediction of TTS	OR (95% CI)	P Value
Female sex	25		68 (29.0 - 163.7)	P<0.001
Emotional trigger	24		65 (20.3 - 205.8)	P<0.001
Physical trigger	13		8.7 (4.6 - 17.3)	P<0.001
Absence of ST-segment depression*	12		7.2 (3.1 - 16.8)	P<0.001
Psychiatric disorders	11		7.0 (3.1 - 15.5)	P<0.001
Neurologic disorders	9		4.9 (2.2 - 11.3)	P<0.001
QTc prolongation	6		2.8 (1.3 - 5.7)	P=0.006

Figure 1 Clinical predictors for the diagnosis of Takotsubo syndrome (TTS). Multiple logistic regression analysis. Odds ratios (ORs) of the parameters female sex, emotional trigger, physical trigger, absence of ST-segment depression, QTc prolongation, psychiatric disorders, and neurological disorders, which were chosen to build the InterTAK Diagnostic Score. Error bars demonstrate the 95% confidence interval (CI). *Except in lead aVR.

T-wave inversion, LBBB, QTc prolongation, cancer, COPD/asthma, neurological disorders, psychiatric disorders, and affective disorders. The bestglm package¹² in R (version 2.15.1) was used for model selection with the Bayesian information criterion. We then developed a score by scaling and rounding the regression coefficients of the resulting multiple regression model.

A receiver operating characteristic (ROC) curve analysis, that reported the area under the curve (AUC) with a 95% confidence interval (CI), was performed to illustrate the predictive performance of the score.

A univariate logistic regression with the score as predictor was performed to develop a formula for the probability of TTS conditional on the score. The conditional odds in the derivation cohort is $\text{odds} = \exp(\text{intercept} + \text{coefficient} \times \text{score})$ and the corresponding probability is $\text{odds}/(1 + \text{odds})$.

The predictive performance of the score in the validation cohort was assessed using the AUC, and the calibration was assessed by comparing the observed proportion with the predicted probability. As the predicted probability depends on the prevalence, the conditional odds were adjusted accordingly: $\text{conditional odds in new cohort} = \text{conditional odds in derivation cohort} \times \text{overall odds in new cohort} / \text{overall odds in derivation cohort}$.

A two-sided P -value ≤ 0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Graphs were compiled with Prism 6 (GraphPad, La Jolla, CA, USA).

Results

Study groups

Patients with TTS were mainly females (94.5%) and significantly older than patients with ACS (67.3 ± 13.2 years vs. 63.4 ± 12.1 years, $P < 0.001$). Physical and emotional triggers were more prevalent among the TTS population ($P < 0.001$, for both comparisons). The leading symptom on admission was chest pain, however less frequently observed in the TTS group (67.9% vs. 88.3%, $P < 0.001$), while dyspnoea was more prevalent among TTS patients (51.8% vs. 25.2%, $P < 0.001$). The upper limits of normal for troponin and brain BNP showed higher admission

values in TTS, while creatine kinase was higher in patients with ACS. Inflammatory markers were increased in both entities but not significantly different by comparison. ST-segment depression occurred less frequently in the TTS group (10.6% vs. 28.9%, $P < 0.001$) while T-wave inversion was more often noted (35.3% vs. 23.4%, $P = 0.001$). Systolic blood pressure on admission was not substantially different between both groups, but higher heart rates were found in TTS (87.6 ± 23.0 b.p.m. vs. 73.3 ± 14.8 b.p.m., $P < 0.001$). Notably, the prevalence of the co-morbidities: cancer, COPD/asthma, and psychiatric and neurological disorders were substantially higher in the TTS group.

Baseline characteristics of patients with TTS and ACS are shown in Table 1.

Takotsubo syndrome score derivation and validation

The score derivation process resulted in seven parameters ranked by relevance using their respective odds ratios (ORs: InterTAK Diagnostic Score). Points were assigned to each criterion, depending on their diagnostic importance: female sex 25 points, emotional trigger 24 points, physical trigger 13 points, absence of ST-segment depression (except in lead aVR) 12 points, psychiatric disorders 11 points, neurological disorders 9 points, and QTc prolongation 6 points. Points were then added in a given patient to result in a score value ranging from 0 (no criterion fulfilled) up to 100 (all criteria fulfilled; Figure 1).

Using a cut-off value of 40 score points, sensitivity was 89% and specificity was 91% for the presence of TTS. When patients with a score value of ≥ 50 were diagnosed as TTS, nearly 95% of TTS patients were diagnosed correctly (sensitivity 94.7%). When patients with a score value ≤ 31 were diagnosed as ACS, ~95% of ACS patients were diagnosed correctly. The logistic regression with the InterTAK Diagnostic Score as predictor yielded an intercept of -7.63 and a regression coefficient of 0.171 (SE 0.015). The corresponding OR was 1.19 (95% CI 1.15 – 1.22) per point. Figure 2A shows the predicted probabilities of TTS for the patients in the derivation cohort. The AUC of the InterTAK Diagnostic Score in

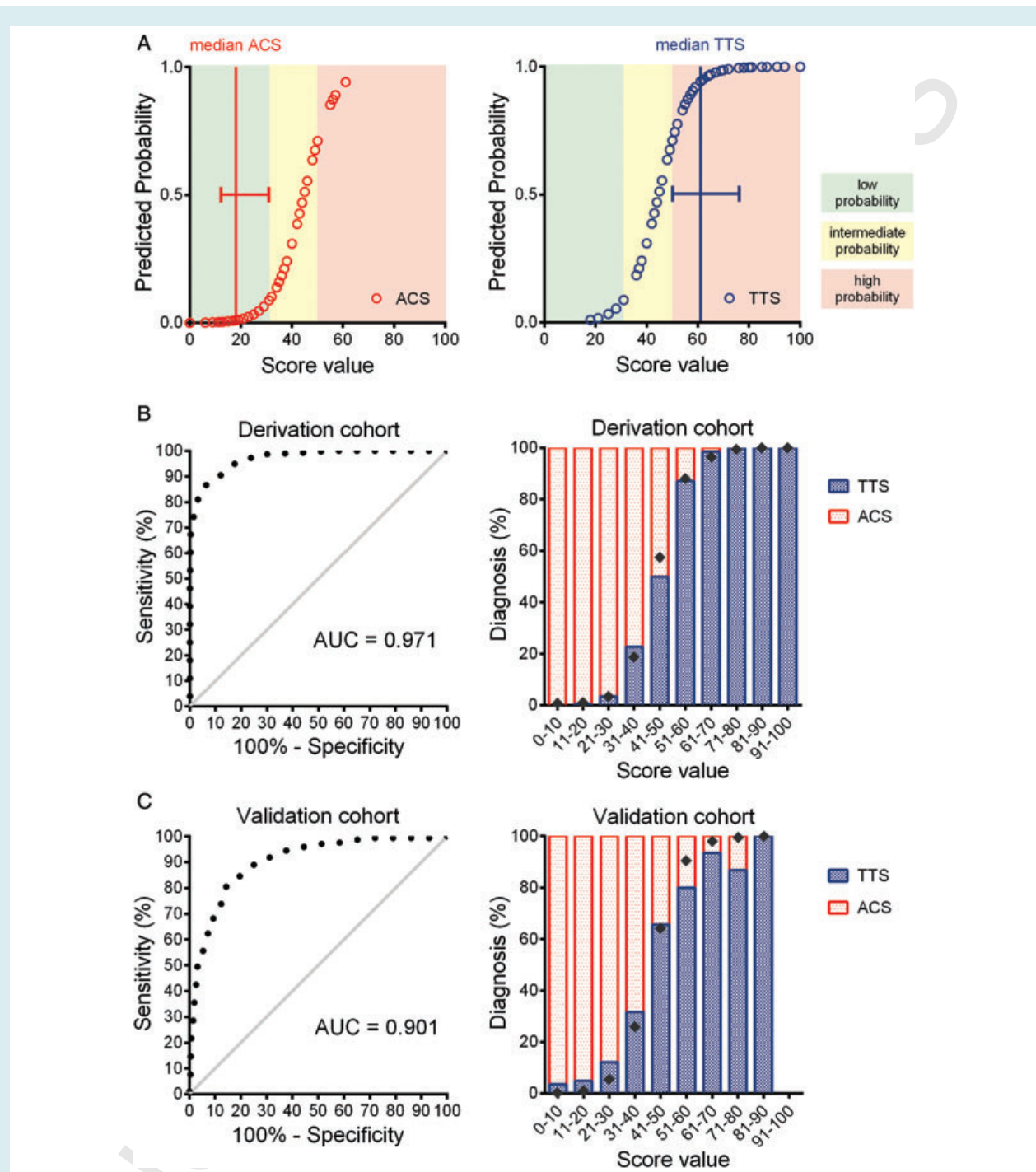


Figure 2 InterTAK Diagnostic Score for predicting the presence of Takotsubo syndrome (TTS). (A) Relationship of risk score values (x-axis) and predicted probability of TTS (y-axis), as computed by logistic regression. Every given score value matches a predicted probability of TTS resulting in a sigmoid curve. Left: values from the acute coronary syndrome (ACS) derivation cohort (red circles). Right: values from the TTS derivation cohort (blue circles). Median and interquartile ranges in each group were drawn into the corresponding graph. When patients with a score value of ≥ 50 are diagnosed as TTS, nearly 95% of TTS patients are found (sensitivity 94.7%). When patients with a score value between 0 and 31 are diagnosed as ACS, almost 95% of ACS patients are diagnosed correctly (specificity 93.6%). (B and C) Receiver operating characteristic curves demonstrating an area under the curve (AUC) of 0.971 [95% confidence interval (CI) 0.96–0.98 in the derivation cohort (B, left)] and an AUC of 0.901 (95% CI 0.87–0.93) in the validation cohort (C, left)]. The graphs on the right-hand side in (B) and (C) show the percentages of TTS (blue) and ACS (red) per 10 score value points. Squares indicate the predicted probability of each corresponding bar.

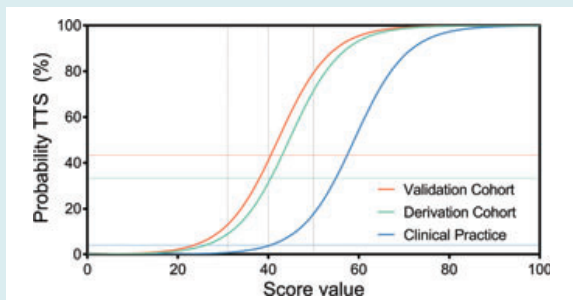


Figure 3 Predicted probability of Takotsubo syndrome (TTS) corresponding to the prevalence in clinical practice. Horizontal lines indicate the prevalence of TTS in the derivation cohort (green), validation cohort (orange), and in clinical practice at the University Hospital Zurich from 2011 to 2015 (blue). Sigmoid curves show the predicted probabilities for a given score value in the derivation cohort (green), validation cohort (orange), and in clinical practice (blue).

the derivation cohort was 0.971 (95% CI 0.96–0.98) (Figure 2B). The right-hand panel in Figure 2B shows the observed and the predicted proportions of TTS patients depending on the score value. Prospective validation of the InterTAK Diagnostic Score in an independent cohort (173 TTS patients and 226 ACS patients) revealed an AUC of 0.901 (95% CI 0.87–0.93) (Figure 2C). The overall calibration was excellent; the mean predicted probability of TTS was 42% compared with the prevalence of 43%. The right-hand panel in Figure 2C shows the observed and the predicted proportions of TTS patients in the validation cohort depending on the score value.

Correction for disease prevalence

The predicted probability of TTS depends on the prevalence of the disease in clinical practice. Based on data from the leading hospital in Zurich from 2011 to 2015, we assume a prevalence of 4.1% in Figure 3. For each increase by 10 points, the odds increased by a factor of >5 ($OR^{*10} = 5.5$). Thus, a patient with 30 score points has a predicted probability of $<1\%$, a patient with 50 points has a probability of 18%, and one with 60 points has a probability of $>50\%$ of suffering from TTS (Figure 3).

The InterTAK Diagnostic Score calculator is accessible under www.takotsubo-registry.com.

Discussion

Takotsubo syndrome represents an acute heart failure syndrome but, due to similar clinical symptoms, ECG, and cardiac biomarker changes, is the most important differential diagnoses of ACS. To date, no non-invasive tools are available to distinguish between both entities in the acute phase. Therefore, early cardiac catheterization is necessary to differentiate TTS from ACS.

Scoring systems are widely used in clinical medicine to help guide clinical decision-making, such as the Wells score, TIMI risk score, or the CHA₂DS₂-VASc score, among many others.^{13–15} However,

to date, such scoring systems are not available to distinguish TTS from ACS based on clinical parameters in the emergency setting.

Therefore, in order to facilitate the initial evaluation in the emergency room prior to cardiac imaging, we developed a clinical score which estimates the probability of the presence of TTS and differentiates it from ACS. The InterTAK Diagnostic Score comprises seven clinical parameters, which can be easily obtained in the emergency department. Of note, all those parameters have previously been associated with TTS: the disease shows a strong preponderance toward female sex, with $\sim 90\%$ of all patients being women.¹ Emotional and physical trigger factors are a typical feature of TTS,¹⁶ although their occurrence is not mandatory.^{1,4} ST-segment depression is a common finding in ACS, but uncommon in TTS.^{1,17–19} In contrast, QTc prolongation is an ECG hallmark of TTS patients.^{1,17,19} The prevalence of neurological or psychiatric disorders is twice as high in TTS compared with ACS.¹ Therefore, neurological and psychiatric disorders may play a significant role in the development of TTS or serve as risk factors. As all these parameters can be easily obtained and were each strongly different between TTS and ACS, we reasoned that the combination of all seven parameters would result in a powerful predictive score for the diagnosis of TTS. While the InterTAK Diagnostic Score can be easily calculated on admission and would thus be helpful for initial evaluation, it provides a probability and is not diagnostic *per se*. As such, a low score does not absolutely rule out TTS, nor does a high score definitely confirm the diagnosis. Nonetheless, the InterTAK Diagnostic Score provides a probability of TTS on admission. This is of importance since TTS mimics ACS in terms of symptoms, biomarkers, and ECG findings. This score may also be valuable in clinical practice to weigh the risk and benefit of coronary angiography, especially in old fragile patients. In addition, it may help to avoid unnecessary coronary intervention and associated platelet inhibition, for example in patients with a moderate proximal LAD stenosis and apical ballooning.

Of note, the composition of the study cohorts used for score derivation does not reflect the true prevalence of TTS. In our study, the ratio of TTS vs. ACS was 1:2 for derivation (218 patients vs. 436 patients) and 1:1.3 for validation (173 patients vs. 226 patients). However, the real life ratio for TTS vs. ACS is between 1:50 and 1:25, which means that 2–4% of patients with ACS symptoms in fact suffer from TTS and not 30% or 50% such as in our cohorts. Mathematically, correction for this bias revealed that a given score value relates to a somewhat lower probability of TTS under real-life conditions, but with a still very strong association of high values with the diagnosis of TTS.

Conclusion

The InterTAK Diagnostic Score estimates the presence of TTS with high sensitivity and distinguishes TTS from ACS with high specificity. The score can be quickly calculated in the emergency room just with clinical parameters. Prospective studies under clinical routine conditions are now needed to assess the diagnostic validity of this novel non-invasive test.

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