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Impact of Atrial Fibrillation on Clinical Outcome in Takotsubo Syndrome: Data from The International Takotsubo Registry

MASTERARBEIT

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Inhaltsverzeichnis

1. Zusammenfassung

Einleitung, Fragestellung: Vorhofflimmern (VHF) ist die häufigste anhaltende Herzrhythmusstörung und ist mit einem erhöhten Risiko für Schlaganfälle und Mortalität assoziiert. Die Prävalenz, die klinischen Korrelate und der prognostische Einfluss von VHF bei Patienten mit Takotsubo Syndrom (TTS) wurden bisher in keiner grossen Kohorte untersucht.

Methoden: TTS Patienten aus dem Internationalen Takotsubo Register wurden basierend auf dem Aufnahme-EKG und dem Vorliegen von VHF in zwei Gruppen unterteilt. Für die Einschlusskriterien wurden die modifizierten InterTAK Diagnostic Criteria benutzt. Patienten mit und ohne VHF wurden hinsichtlich kardiovaskulärer Risikofaktoren, demographischer Daten, Komorbiditäten, Stressfaktoren, Symptomen bei Eintritt, elektrokardiographischer Befunde, echokardiographischer und koronarangiographischer Parameter, Therapie und Krankheitsverlauf miteinander verglichen.
In einer Subanalyse wurden die Patienten mit VHF bei Eintritt aufgeteilt in Patientengruppen mit oder ohne vorbekanntem VHF um die Kurzzeit- und Langzeitprognose zu analysieren.

Resultate: Von den 1584 in die Studie eingeschlossenen TTS Patienten konnte bei 112 (7.1%) ein VHF als initialer EKG Rhythmus nachgewiesen werden. Von diesen war bei 53% das VHF bekannt, bei 47% der Patienten wurde das VHF erstmals diagnostiziert. Im Vergleich von TTS Patienten mit oder ohne VHF wiesen die TTS Patienten mit VHF eine signifikant niedrigere linksventrikuläre Ejektionsfraktion (37.2±11.1% vs. 41.3±11.8%; P=0.001) auf. Bei TTS Patienten mit VHF konnte zudem eine höhere Inzidenz von kardiogenem Schock (37.2±11.1% vs. 41.3±11.8%; P=0.001) nachgewiesen werden. Des Weiteren hatte die Patientengruppe mit VHF eine nachweislich höhere Kurz- (P<0.001) und Langzeitmortalität (P< 0.006) im Vergleich zu TTS Patienten ohne VHF. Es konnten keine Mortalitätsunterschiede bei TTS Patienten mit vorbekannten VHF und neu diagnostiziertem VHF nachgewiesen werden.

Schlussfolgerungen: Das Vorliegen von VHF bei TTS Patienten ist mit einer erhöhten Rate an Komplikationen, sowie einer höheren Kurz- und Langzeitmortalität assoziiert. Es konnten keine Unterschiede hinsichtlich der Prognose im Zusammenhang mit dem Diagnosezeitpunkt des VHF festgestellt werden.

2. Liste der verwendeten Abkürzungen

VHF:	Vorhofflimmern
TTS:	Takotsubo Syndrom
EKG:	Elektrokardiogramm
ACS:	Akutes Koronarsyndrom
InterTAK Register:	Internationales Takotsubo Register
MACCE:	schwere kardiale und zerebrovaskuläre Komplikationen
KISIM:	Klinikinformationssystem für Innere Medizin

3. Begleittext

3.1. Einleitung

Das Takotsubo Syndrom (TTS) ist eine Erkrankung, die typischerweise gehäuft bei postmenopausalen Frauen nach einer emotionalen oder physischen Stressreaktion auftritt (1). Das Krankheitsbild des TTS äussert sich als vorrübergehende linksventrikuläre Dysfunktion (2), die initial aufgrund des transienten Charakters als gutartig eingestuft wurde (3). Aktuelle Studienergebnisse haben aber gezeigt, dass das TTS kurz- und langfristig mit einer vergleichbaren Komplikationsrate wie derjenigen des akuten Koronarsyndroms (ACS) einhergeht (4, 5). Akute Komplikationen eines TTS können sich unter anderem als linksventrikuläre Ausflussbahnobstruktion (6), kardiogener Schock sowie auch als Arrhythmien manifestieren (7, 8, 9).

VHF ist die häufigste anhaltende Arrhythmie und wird assoziiert mit einem bis zu fünffach erhöhtem Risiko für Schlaganfälle und einer bis zu zweifach erhöhten Mortalität (10, 11). In kleineren Studien wurde eine Prävalenz von VHF bei TTS Patienten von 5%-25% festgestellt (12, 13, 14). Zudem wurde bisher noch kein Vergleich zwischen TTS Patienten mit vorbekanntem und neu diagnostiziertem VHF im Zusammenhang mit einem akuten TTS Ereignis untersucht. Deshalb wurde anhand von Daten des Internationalen Takotsubo Registers (InterTAK Registry), der weltweit grössten Kohorte von TTS Patienten die Prävalenz, die klinischen Korrelate und der prognostische Einfluss von VHF bei Patienten mit TTS analysiert.

3.2. Material und Methoden

3.2.1. Datensammlung und Gruppenzusammensetzung

Die Datenerhebung erfolgte anhand von vorliegenden Patientenakten des InterTAK Registers, welche Informationen zu kardiovaskulären Risikofaktoren, demographischen Daten, Komorbiditäten, Triggerfaktoren, Symptomen und bei Eintritt, elektrokardiographischen Befunden, Laborparametern, Bildgebung, Komplikationen und den akuten kardiologischen Massnahmen der Patienten beinhalteten. Follow-up Daten wurden mittels klinischer Visiten, eines persönlichen Telefoninterviews oder Patientenakten nach stattgefundenem TTS erhoben. Als Einschlusskriterien wurden modifizierte InterTAK Diagnostic Criteria (2), benutzt. Basierend auf dem Aufnahme-Elektrokardiogramms (EKG) und dem Vorliegen von VHF wurden die TTS Patienten in zwei Gruppen unterteilt. Es wurden das klinische Profil sowie die Kurz- und Langzeitprognose von TTS Patienten mit und ohne VHF untersucht.
Für einen Subgruppenvergleich wurden TTS Patienten mit VHF anhand eines vorbekannten oder neu diagnostizierten VHF stratifiziert, um die klinischen Charakteristika und die Prognose von diesen zwei Patientengruppen zu untersuchen. Patienten mit fehlenden Informationen bezüglich des Aufnahme-EKGs wurden von dieser Studie ausgeschlossen.

3.2.2. Statistische Analyse

Die Patientengruppen wurden verglichen mittels Chi-Quadrat-Test bzw. Fisher-Exakt-Test bei kategorischen Variablen und mittels T-Test sowie Mann-Whitney-U-Test bei kontinuierlichen Werten. Für die Analyse der Langzeitmortalität sowie der Rate an MACCE (schwere kardiale und zerebrovaskuläre Komplikationen) wurde die Kaplan-Meier-Schätzung angewendet und der Log-Rank Test für Gruppenvergleiche herangezogen. Um die Hazard Ratio (HR) und die 95%-Konfidenzintervalle des Langzeitoutcomes der TTS Patienten mit VHF zu berechnen, wurde eine multivariable Cox-Regression durchgeführt. Alle Tests wurden zweiseitig durchgeführt und ein P-Wert von < 0.05 wurde als statistisch signifikant definiert. Die statistische Analyse wurde mittels SPSS, Version 25.0, durchgeführt und Abbildungen mit GraphPad, Version 7.0, erstellt.

3.2.3. Ethik

Das Studienprotokoll wurde durch die lokale Ethikkommission unter der Nummer ID PB_2017-00279 bewilligt.

3.3. Resultate

Von den insgesamt 1584 eingeschlossenen TTS Patienten konnte bei 112 (7.1%) ein VHF mittels EKG bei Eintritt festgestellt werden. TTS Patienten mit vorliegendem VHF waren älter (73.8 ± 12.2 Jahre vs. 66.1 ± 13.0 Jahre; P < 0.001) und weniger oft weiblich (84.8% vs. 90.6%; P = 0.046) im Vergleich zu TTS Patienten ohne VHF. Patienten mit VHF wiesen häufiger einen apikalen TTS Typen (89.3% vs. 81.4%; P = 0.036) sowie physische Trigger (44.6% vs. 33.8%; P = 0.020) auf. Es konnte gezeigt werden, dass TTS Patienten mit VHF im Vergleich zu TTS Patienten ohne VHF eine signifikant niedrigere linksventrikuläre Ejektionsfraktion (37.2±11.1% vs. 41.3±11.8%; P=0.001) hatten, häufiger akut kardiologisch behandelt wurden (Insertion einer intraaortalen Ballonpumpe 6.3% vs. 2.3%; P = 0.011, Kardiopulmonale Reanimation 19.8% vs. 7.3%; P < 0.001, invasive oder nichtinvasive Beatmung 27.0% vs. 14.9%; P = 0.001, Verabreichung von Katecholaminen 19.8% vs. 7.3%; P < 0.001) und eine höhere intra-hospitale Mortalität aufwiesen (14.3% vs. 3.1%; P < 0.001). Im Vergleich zu Patienten ohne VHF war die Mortalität bei Patienten mit VHF in den ersten 60 Tagen nach dem TTS Ereignis (P<0.001), wie auch nach 60 Tagen bis 5 Jahren, (P=0.006) signifikant erhöht.

In der Subanalyse der TTS Patienten mit VHF wurde VHF bei 42% der Patienten als erstmalig diagnostiziert während bei 58% VHF in der Krankengeschichte vorbekannt war. Bis auf Unterschiede der Herzfrequenzen (87.0 ± 23.6 /min vs. 103.4 ± 15.9 /min, P=0.002) konnten keine weiteren signifikanten Unterschiede zwischen den beiden Untergruppen festgestellt werden.

3.4. Diskussion

In dieser bisher grössten Kohorte von TTS Patienten wurde der Einfluss von VHF auf die klinische Prognose untersucht und es wurden folgende Resultate festgestellt:

1) TTS Patienten mit VHF im EKG haben signifikant höhere Mortalitätsraten im Vergleich zu Patienten ohne VHF.
2) VHF ist ein unabhängiger Prädiktor für eine erhöhte Langzeitmortalität.
3) Ungefähr ein Drittel der Patienten hatte ein neudiagnostiziertes VHF zum Zeitpunkt des TTS Events.
4) TTS Patienten mit vorbekanntem VHF und solche mit neu diagnostiziertem VHF haben vergleichbare Kurz- und Langzeitprognosen.

Bei Spitaleintritt wiesen 7% der untersuchten TTS Patienten ein VHF auf. Vorhergehende Studien haben über ähnliche Ergebnisse berichtet (12, 13, 14). Jedoch wurde in diesen Studien keine Unterteilung in bekanntes und erstmals im Rahmen des TTS Events aufgetretenem VHF vorgenommen. In der vorliegenden Studie hatten 42% der Patienten bei ihrem

TTS Indexevent kein vorbekanntes VHF. Daher ist es wahrscheinlich, dass diese Patienten ein VHF im Zusammenhang mit dem TTS Ereignis entwickelten. Die TTS Patienten mit VHF zeigten signifikant höhere Entzündungsparameter (C-reaktives Protein, Leukozyten) und präsentierten sich häufiger mit klassischen TTS Typen im Sinne einer apikalen Ballonierung und einer niedrigeren linksventrikulären Ejektionsfraktion. Diese Parameter könnten unter anderem Faktoren sein, die zur Entstehung eines VHF führen und somit eine schlechtere Prognose begünstigen. Akuter emotionaler Stress kann zu einer Aktivierung des sympathischen Nervensystems und zu einer Katecholaminfreisetzung führen. Dies wiederum könnte zu elektrophysiologischen Veränderungen des linken Vorhofes (15, 16), zu oxidativem Stress und zu einer Inflammation auf zellulärer sowie molekularer Ebene führen und somit ein VHF auslösen (17, 18, 19, 20, 21, 22, 23). Das Vorhandensein von VHF könnte somit einen Marker für eine stärkere Katecholaminausschüttung in TTS Patienten darstellen. TTS Patienten mit VHF benötigten häufiger eine akute kardiologische Behandlung (Einlage einer intraaortale Ballonpumpe sowie die Gabe von Katecholaminen), erlitten vermehrt kardiogenen Schock und hatten eine höhere Mortalität als TTS Patienten ohne VHF. Ähnliche Observationen wurden bei Patienten mit ACS und VHF gemacht (24, 25). Es ist daher anzunehmen, dass VHF einen signifikanten Einfluss auf eine funktionelle Genesung und auf die Prognose von TTS Patienten hat. Daher sollten die Therapie des VHF bei TTS Patienten gemäss aktueller Richtlinien erfolgen (26).

3.5. Eigenleistung

Mein Aufgabenbereich bei der Studie umfasste unter anderem die Datenerhebung der Patientencharakteristika, welche ich mittels vorhandener Patientenakten des InterTAK-Registers, dem internen elektronischen Patientenaktensystem des USZ (KISIM) sowie durch telefonische Follow-up Befragungen der Patienten erfasste. Das Patientengut konnte ich differenzieren mittels demographischer Parameter, klinischem Bild des TTS und dessen Trigger, Symptomatik der Patienten bei Aufnahme, laborchemisch gemessenen kardialen Biomarkern, Entzündungsparametern beim TTS Ereignis, Herzfrequenz, systolischem und diastolischem Blutdruck, linksventrikulärer Ejektionsfraktion, linksventrikulärem enddiastolischem Druck, sowie mit anamnestischen Daten der kardialen Risikofaktoren und Komorbiditäten. Ich war bei der Analyse der Elektrokardiogramme bei Eintritt beteiligt, wobei ich Arrhythmien wie VHF (paroxysmal, persistent, permanent) und andere pathologische Elektrophysiologien des Herzens beurteilte und unterteilte. Zudem war ich an der Erhebung der Medikation (ACE-Inhibitoren, Angiotensin-Rezeptor Blocker, Beta-Blocker, Statine, Aspirin, Orale Antikoagulation) beteiligt. Dabei wurde der Schwerpunkt auf die Analyse der Antikoagulation gelegt (Rivaroxaban, Apixaban, Vitamin-K Antagonisten). Um eine prognostische Aussage zu treffen, sammelte und analysierte ich Daten zum akuten kardiologischen Management, intrahospitalen Komplikationen, sowie zum Outcome nach 5 Jahren (MACCE, Tod). Des Weiteren beteiligte ich mich an der statistischen Auswertung und erstellte in Zusammenarbeit mit dem Team die Abbildungen.

Das Manuskript befindet sich aktuell unter Revision im Journal of the American Heart Association. Dabei habe ich für die Beantwortung der Fragen der Gutachter die Hospitalisationsdauer des Patientenguts aus Table 2 berechnet, den CHA2DS2-VASc-Score der TTS Patienten mit sowie ohne VHF verglichen und eine Einteilung der Risikofaktoren nach einer Klassifikation von Sharkey et al durchgeführt (27).

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4. Paper

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Impact of Atrial Fibrillation on Clinical Outcome in Takotsubo Syndrome: Data from The International Takotsubo Registry

El-Battrawy *et al.* Atrial Fibrillation in Takotsubo Syndrome

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ABSTRACT

Background: Atrial fibrillation (AF) is a major risk factor for mortality. The prevalence, clinical correlates, and prognostic impact of AF in takotsubo syndrome (TTS) has not yet been investigated in a large patient cohort.

Methods and Results: TTS patients were enrolled from the International Takotsubo Registry, which is a multinational network with 26 participating centers in Europe and the United States. Patients were dichotomized according to the presence or absence of AF at the time of admission. Of the 1,584 TTS patients enrolled, 112 (7.1%) had AF. The mean age was higher (73.8±12.2 years vs. 66.1±13.0 years; P<0.001) and there were fewer women (84.8% vs. 90.6%; P = 0.046) in the AF than in the non-AF group. The left ventricular ejection fraction was significantly lower (37.2±11.1% vs. 41.3±11.8%; P=0.001) and cardiogenic shock was more often observed (20.0% vs. 8.8%; P<0.001) in the AF group. Both in-hospital (P<0.001) and long-term mortality (P=0.006) were higher in the AF group. Multivariable Cox-regression analysis revealed AF was independently associated with higher long-term mortality (hazard ratio, 2.31; 95% confidence interval: 1.50–3.55; P<0.001). Among patients with AF on admission, 42% had no known history of AF before the acute TTS event, and such patients had comparable in-hospital and long-term outcomes, as compared to those with a history of AF.

Conclusions: In patients presenting with TTS, AF on admission is significantly associated with increased in-hospital and long-term mortality. Whether antiarrhythmics and/or cardioversion is beneficial in TTS with AF should thus be tested in a future trial.

Clinical Trial Registration: ClinicalTrials.gov number, NCT01947621

INTRODUCTION

Takotsubo syndrome (TTS) is characterized by acute left ventricular (LV) dysfunction.(28) This syndrome has historically been considered a benign disease, as the LV dysfunction recovers spontaneously within a few weeks.(29) However, recent data show that TTS is associated with a substantial risk of adverse events both during the acute phase and in the long-term, with complication rates comparable to those of acute coronary syndrome (ACS).(5, 30) The occurrence of complications in TTS patients is associated with poor and even fatal outcomes. For example, TTS patients can experience concurrent arrhythmias, severe heart failure with or without pulmonary edema, and LV free-wall rupture.(31, 32, 33) A recent international consensus document on TTS reported that cardiac arrhythmias are a major determinant of clinical outcomes in TTS patients.(34)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its presence has been associated with a 5-fold increase in the incidence of stroke and a 2-fold increase in mortality.(35, 36) In small series, AF among TTS patients has been reported, but estimates of its prevalence ranged from 5% – 25% .(12, 37) In addition, the impact of a history of AF versus newly diagnosed AF in the context of an acute TTS event has not been properly evaluated. To overcome this drawback, we analyzed data from the *International Takotsubo Registry* (*InterTAK Registry*), which is the largest available cohort of TTS patients, to determine the prevalence, clinical correlates, and prognostic impact of AF in TTS patients.

METHODS

Study population

The study design of the *InterTAK* Registry has been comprehensively outlined in previous reports.(5, 38) The inclusion criteria were the *InterTAK* Diagnostic Criteria:(39) (I) transient left ventricular LV wall motion abnormality presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. The wall motion abnormality usually extends beyond a single epicardial coronary artery distribution; rare cases, (focal TTS) can exist where the wall motion abnormality is identical to a single coronary artery territory; (II) an emotional, physical, or combined stress can precede the TTS event, but this is not mandatory. (III) neurologic disorders as well as pheochromocytoma may serve as triggers of TTS; (IV) new electrocardiographic (ECG) abnormalities; however, but not mandatory; (V) moderate elevations of cardiac biomarkers (troponin and/or creatine kinase), usually significant elevation of brain natriuretic peptide; (VI) coexisting significant coronary artery disease which is not related to the wall motion abnormality is not a contradiction in TTS; and (VII) the absence of infectious myocarditis. TTS patients who died during the acute phase before complete recovery of LV wall motion were also included.

Data collection

Data on the patients' clinical characteristics were collected through a review of their medical records and included demographics, cardiovascular risk factors, comorbidities, triggering factors, symptoms at admission, laboratory profile, electrocardiographic findings, imaging features, and management. Outcome data were collected from clinical visits, personal telephone interviews, or medical charts. Patients were dichotomized according to the presence or ab-

sence of AF as assessed using 12-lead surface ECG on admission, and we compared clinical characteristics and in-hospital and long-term outcomes between the two groups. Furthermore, in a subanalysis, patients with AF on admission were categorized into two groups based on the presence or absence of known history of AF before TTS events, and baseline features and outcomes were compared. Patients without complete information for this categorization were excluded from this subanalysis.

The study protocol was reviewed by the local ethics committee or investigational review board at each collaborating site. Due to the partly retrospective nature of the study, the ethics committees of most study centers waived the need for informed consent. At centers in which the ethics committees or investigational review boards required informed consent or in which patients were included prospectively, formal written consent was obtained from the patients or their surrogates. The study was registered at www.ClinicalTrials.gov (registration number, NCT01947621).

Statistical analysis

Categorical variables are presented as frequencies (%) and continuous parameters are expressed as mean ± standard deviation or as median and interquartile range (IQR). Group comparisons were conducted using the chi-square test or Fisher exact test for categorical variables and the Student t-test or Mann–Whitney U-test for continuous variables. The Kaplan–Meier method was used to assess the long-term mortality and major adverse cardiac and cerebrovascular events (MACCE; a composite of a recurrence of TTS, myocardial infarction, stroke or transient ischemic attack, or death from any cause) rate and the log-rank test was used to compare Kaplan–Meier curves, as well as a landmark analysis with a landmark set at 60 days. Cox regression analysis was conducted to determine the hazard ratio (HR) and 95% confi-

dence intervals (CI) of AF on admission for long-term outcome. To account for possible differences in clinical characteristics and comorbidities between patients with and without AF, a multivariable adjustment analysis including covariates which had a significant difference in the baseline comparison was performed in a Cox regression model. Missing data on covariates were completed with multiple imputations prior to multivariable Cox regression. All tests were two-sided and $P < 0.05$ indicated statistical significance. Statistical analyses were performed using SPSS v25.0 and GraphPad v7.0 was used for figure preparation.

RESULTS

Patient characteristics

Of a total of 1,750 potentially eligible patients, 1,584 TTS patients with complete information on AF on admission were enrolled in the present study. Among these, 112 (7.1%) had AF on admission as determined by ECG. Compared with TTS patients without AF, those with AF were less frequently females (84.8% vs. 90.6%; P = 0.046) and were significantly older (73.8 ± 12.2 years vs. 66.1 ± 13.0 years; P < 0.001). Physical triggering factors were more common among those with AF than among those without AF (44.6% vs. 33.8%; P = 0.020). Notably, patients with AF more often had the apical TTS type (89.3% vs. 81.4%; P = 0.036), presented with significantly higher levels of brain natriuretic peptide, and had a lower left ventricular ejection fraction (LVEF; 37.2±11.1% vs. 41.3±11.8%; P = 0.001) than patients without AF. Additionally, C-reactive protein (CRP) level and white blood cell (WBC) counts on admission were higher in TTS patients with AF than in TTS patients without AF (**Table 1**). Pre-existing comorbidities such as hypertension (86.1% vs. 63.9%; P < 0.001), diabetes mellitus (25.7% vs. 13.0%; P < 0.001), and coronary artery disease (22.4% vs. 15.2%; P = 0.049) were more common among those with AF than among those without AF. Angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARB) (52.2% vs. 37.3%, P = 0.005) and beta-blockers (48.9% vs. 31.6%, P = 0.001) had been more frequently prescribed to patients with AF before admission (**Table 1**).

In-hospital management and outcomes

Acute cardiac care measures such as intra-aortic balloon pump insertion (6.3% vs. 2.3%; P = 0.011), cardiopulmonary resuscitation (19.8% vs. 7.3%; P < 0.001), invasive or non-invasive

ventilation (27.0% vs. 14.9%; P = 0.001), or catecholamine administration (20.7% vs. 10.8%; P = 0.002) were more often required in patients with AF than in patients without AF in relation to a significantly higher incidence of cardiogenic shock (20.0% vs. 8.8%; P < 0.001) (**Table 1**). Moreover, in-hospital mortality was significantly higher among patients with AF compared to those without AF (14.3% vs. 3.1%; P < 0.001).

Long-term outcomes

Kaplan-Meier analyses demonstrated that patients with AF had significantly worse long-term MACCE and mortality rates compared to those without AF (**Table 1**). In addition, a landmark analysis showed a substantially higher mortality rate in patients with AF than in those without AF within the first 60 days (P < 0.001, **Figure 1**). After 60 days up to 5 years, a significant difference on mortality between patients with and without AF still existed (P = 0.006, **Figure 1**). A multivariable analysis demonstrated that AF on admission was independently associated with long-term mortality (hazard ratio, 2.31; 95% confidence interval: 1.50 – 3.55; P < 0.001, **Figure 2**).

Comparison of a history of AF vs newly diagnosed AF

Of the patients with AF on admission, previous AF episodes were identified in 58% (48/83) of patients, while in the remaining 42% with AF the episode was considered the first in the patients' history. Main patient characteristics between two groups are summarized in **Table 2**. No significant differences in clinical characteristics were observed except for heart rate on admission (87.0 ± 23.6 bpm vs. 103.4 ± 15.9 bpm, P = 0.002). There were no significant differences on cardiovascular risk factors and coexisting medical conditions. 57.1% of the patients with preexisting AF were on oral anticoagulation therapy upon presentation, while one

patient with newly diagnosed AF was prescribed such an agent before admission. Of note, acute intensive care measures including intra-aortic balloon pump, catecholamine use, invasive or noninvasive ventilation, and cardiopulmonary resuscitation were required equally often in patients with preexisting or newly diagnosed AF, respectively. Furthermore, in-hospital mortality rates were similar between two groups (18.8% vs. 14.3%, P = 0.59). Kaplan-Meier analyses with log-rank tests demonstrated that there were no significant differences on long-term MACCE (P = 0.53) and mortality (P = 0.48) between patients with preexisting AF or newly diagnosed AF, respectively (**Table 2**).

DISCUSSION

In this by far largest cohort of TTS patients we investigated the impact of AF on the clinical outcomes and found the following: (1) TTS patients with AF on surface ECG at admission had a more eventful in-hospital course and significantly higher mortality rates compared to those without AF; (2) AF on admission was independently associated with a higher long-term mortality; (3) approximately one-third of patients had no known history of AF before their TTS index event, suggesting that these patients may have developed new-onset AF; and finally (4) TTS patients with preexisting AF and newly diagnosed AF had comparable in-hospital and long-term outcomes.

Among the 1,584 TTS patients, the prevalence of AF upon admission was 7%. Previously reported studies reported a prevalence ranging between 5% – 25% among TTS patients, suggesting that their numbers are unreliable due reporting bias and low patient numbers.(12, 37, 40) Furthermore, these studies did not provide information a possible previous history of AF. Interestingly, in our study almost half of the patients (42%) who presented with AF during the index TTS event did not have a known prior history for AF. Therefore, it is likely that in the majority of such TTS patients new-onset AF was indeed related to TTS. In this context, it is of interest that patients with AF more commonly presented with apical ballooning and a lower ejection fraction, both conditions known to be associated with left ventricular increased filling pressures and as a consequence increased left atrial pressures. Furthermore, TTS patients with AF had signs of inflammation such as higher levels of CRP and WBC. Taken together, these may be the most likely mechanisms leading to AF during an acute TTS event.

Acute AF is known to impair hemodynamics. Thus, it is of note that TTS patients with AF on admission developed more often cardiogenic shock and required more commonly acute

cardiac care measures including catecholamine administration and intra-aortic balloon pump insertion as compared to those without AF. Additionally, in-hospital mortality was significantly higher among TTS patients with AF than among those without it. Our findings in our large TTS cohort are in line with observations in ACS patients, in whom AF is associated with a higher rate of complications such as cardiogenic shock and life-threatening ventricular tachyarrhythmias, and poorer overall outcomes.(41, 42) The observed association between the presence of AF on admission and mortality in patients with TTS is likely related to the adverse hemodynamic effects of AF, such as loss of atrial contraction and the resultant loss of atrioventricular synchronicity, rhythm irregularity and rapid ventricular rates.(43) All these aspects contribute further to the reduced LVEF and cardiac output. In addition, there is evidence demonstrating that TTS and AF might be associated with inflammation.(44, 45) Interestingly, TTS patients with AF had a greater degree of inflammatory markers (CRP and WBC) than those without AF in the present study. Therefore, it is conceivable that a strong inflammatory response might lead to a more eventful outcome in TTS patients with AF. Furthermore, AF is known to increase the risk of cardioembolic events in patients with TTS.[46] Such risk might be more pronounced in TTS patients, given the severe hypokinesia/akinesia of the ventricular wall in apical ballooning during the acute phase of the disease.

Besides ACS and TTS reported here, AF has been reported as a predictor of poor long-term prognosis in patients with other cardiac conditions such as dilated cardiomyopathy and congenital heart disease.(47, 48, 49) Furthermore, in patients with chronic coronary syndromes, AF has been associated with significantly higher rates of thromboembolic stroke, heart failure, and long-term mortality, regardless of the time of AF onset. Interestingly, although global LV ejection fraction is normalized within a few weeks in TTS, we demonstrated by landmark analysis that the long-term mortality rate was still significantly higher in the AF group than in the non-AF group after excluding the strong influence of the acute phase. In

addition, AF emerged as an independent predictor of long-term mortality in TTS. Taken these observations together, we may suggest that preexisting or new-onset AF may have a significant impact of functional recovery and adversely affect long-term outcomes. Thus, all TTS patients with AF on admission need to be managed appropriately according to the established guidelines for AF.(50)

Both TTS and AF are distinct clinical entities, which may occur due to a large spectrum of clinical conditions associated with increased catecholamine states. Left atrial dysfunction occurring due to TTS may contribute to AF initiation.(51) On the other hand, acute mental stress and other medical conditions may result in left atrial electrophysiologic changes leading to AF.(52),(53) Thus, besides acute atrial dysfunction, AF in TTS patients may occur also due to direct mechanisms of acute stress and the underlying catecholamine release.(23) Indeed, massive activation of the sympathetic nervous system as occurs in TTS may lead to increased oxidative stress and inflammation at the cellular and molecular level and impaired myofibrillar energetics, and thereby may trigger AF.(54, 55, 56, 57, 58, 59) The presence of AF might be a marker of a greater severity of the underlying catecholamine surge in such TTS patients.

Limitations

Since the InterTAK Registry is a retrospective and partly prospective registry and our definition of the presence of AF was based on ECG on admission, we did not assess the prevalence of AF after admission. Furthermore, the power to account for confounding factors is limited and some residual selection bias might be present.

CONCLUSIONS

TTS patients with AF on surface ECG on admission had a more eventful in-hospital course and significantly higher mortality rates than TTS patients without AF. Furthermore, AF was independently associated with higher long-term mortality. Although some patients with AF on admission had no known prior history of AF, they had comparable in-hospital and long-term outcomes, as compared to those with preexisting AF. Thus, presence of AF on admission should alert clinicians to the prognostic implications of this rhythm. Adequate AF management as part of the overall TTS treatment strategy may improve outcomes of TTS patients with AF.

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DISCLOSURES

None

FIGURE LEGENDS

Figure 1: Short- and long-term mortality of TTS patients with and without AF

Kaplan-Meier curves with a landmark set at 60 days show a higher mortality rate in TTS patients with AF compared to TTS patients without atrial fibrillation both in short- ($P < 0.001$) and long-term ($P = 0.006$).

TTS, takotsubo syndrome; AF, atrial fibrillation

Figure 2: Multivariable Cox regression analysis of TTS patients

Multivariable Cox regression revealed that atrial fibrillation was independently associated with worse long-term mortality. Male sex, age > 70 yr, physical trigger, WBC > 10 $x10^3$ cells/µl, and LVEF < 45% also emerged as independent predictors of worse long-term mortality in TTS.

C.I. confidence interval, COPD chronic obstructive pulmonary disease, HR hazard ratio, LVEF left ventricular ejection fraction, TTS takotsubo syndrome, WBC white blood cell count. Errors bars represent 95% confidence interval. Black rhombi indicate statistically significance; grey rhombi not statistically significant.

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Table 1 Characteristics of TTS Patients with and without Atrial Fibrillation

	Atrial Fibrillation N=112	w/o Atrial Fibrillation N=1472	P Value
Demographics			
Female sex - no./total no. (%)	95 / 112 (84.8)	1334 / 1472 (90.6)	0.046
Age - yr	73.8 ± 12.2 (N=112)	66.1 ± 13.0 (N=1472)	<0.001
Takotsubo Type - no./total no. (%)			
Apical	100 / 112 (89.3)	1198 / 1472 (81.4)	0.036
Triggers - no./total no. (%)			
Physical trigger	50 / 112 (44.6)	498 / 1472 (33.8)	0.020
Emotional trigger	25 / 112 (22.3)	430 / 1472 (29.2)	0.12
Symptoms on admission - no./total no. (%)			
Chest pain	71 / 100 (71.0)	1061 / 1381 (76.8)	0.19
Syncope	5 / 103 (4.9)	104 / 1374 (7.6)	0.31
Cardiac biomarkers on admission - median (IQR)			
Troponin - factor increase in ULN *	5.60 (1.73 - 18.08) N=98	8.00 (2.50 - 24.29) N=1207	0.10
Creatine kinase - factor increase in ULN	0.82 (0.45 - 1.69) N=79	0.86 (0.54 - 1.46) N=1033	0.58
BNP - factor increase in ULN †	10.27 (0.42 - 36.21) N=40	5.25 (1.76 - 13.79) N=384	0.001
Inflammatory markers on admission - median (IQR)			
CRP - mg/l	7.10 (2.00 - 47.05) N=85	3.90 (1.20 - 10.35) N=968	0.001
WBC - 10^3/µl	10.71 (8.10 - 13.79) N=96	9.68 (7.50 - 12.57) N=1257	0.033
ECG on admission - no./total no. (%)			
ST-segment elevation	50 / 112 (44.6)	640 / 1466 (43.7)	0.84
T-wave inversion	43 / 112 (38.4)	605 / 1466 (41.3)	0.55
QTc - ms	453.2 ± 60.9 (N=81)	457.9 ± 48.6 (N=1072)	0.51
Hemodynamics - mean±SD (N)			
Heart rate - beats/min	94.5 ± 23.0 (N=96)	86.5 ± 21.1 (N=1245)	<0.001
Systolic blood pressure - mm Hg	132.1 ± 30.6 (N=92)	131.1 ± 28.7 (N=1250)	0.75
Diastolic blood pressure - mm Hg	77.6 ± 17.9 (N=92)	76.6 ± 16.9 (N=1232)	0.60
Left ventricular ejection fraction - % ‡	37.2 ± 11.1 (N=101)	41.3 ± 11.8 (N=1360)	0.001
Left ventricular end-diastolic pressure - mm Hg	21.5 ± 7.6 (N=66)	21.5 ± 7.9 (N=890)	>0.99
Cardiovascular risk factors / history - no./total no. (%)			
Hypertension	93 / 108 (86.1)	918 / 1437 (63.9)	<0.001
Diabetes mellitus	28 / 109 (25.7)	187 / 1436 (13.0)	<0.001
Current smoking	13 / 104 (12.5)	278 / 1402 (19.8)	0.07
Hypercholesterolemia	34 / 108 (31.5)	450 / 1431 (31.4)	0.99
Coexisting medical condition - no./total no. (%)			
Coronary artery disease §	24 / 107 (22.4)	207 / 1359 (15.2)	0.049
Cancer (total)	17 / 99 (17.2)	227 / 1360 (16.7)	0.90
COPD or asthma	9 / 105 (8.6)	234 / 1415 (16.5)	0.032
Medication on admission - no./total no. (%)			
ACE inhibitor or ARB	48 / 92 (52.2)	448 / 1200 (37.3)	0.005

Beta-blocker	45 / 92 (48.9)	379 / 1200 (31.6)	0.001
Statin	16 / 90 (17.8)	212 / 1169 (18.1)	0.90
Acute cardiac care - no./total no. (%)			
Intra-aortic balloon pump	7 / 111 (6.3)	34 / 1466 (2.3)	0.011
Cardiopulmonary resuscitation	22 / 111 (19.8)	107 / 1466 (7.3)	<0.001
Invasive or noninvasive ventilation	30 / 111 (27.0)	218 / 1466 (14.9)	0.001
Catecholamine use	23 / 111 (20.7)	158 / 1466 (10.8)	0.002
In-hospital complications - no./total no. (%)			
Cardiogenic shock	22 / 110 (20.0)	127 / 1451 (8.8)	<0.001
Death	16 / 112 (14.3)	46 / 1472 (3.1)	<0.001
5-year outcome - no./total no. (%)			
MACCE	34 / 112 (30.4)	201 / 1472 (13.7)	<0.001
Death	28 / 112 (25.0)	121 / 1472 (8.2)	<0.001

* Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.
† Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.
‡ Data obtained during catheterization or echocardiography; if both results were available data from catheterization were used.
§ Coexisting coronary artery disease during acute hospitalization.
ACE angiotensin-converting-enzyme, ARB angiotensin-receptor blocker, BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, CRP c-reactive protein, ECG electrocardiogram, IQR interquartile range, MACCE major adverse cardiac and cerebrovascular events,QTc QT interval corrected for heart rate, SD standard deviation, TTS takotsubo syndrome, ULN upper limit of the normal, WBC white blood cell count.

Table 2 Comparison between TTS Patients with Preexisting and Newly Diagnosed AF

	Preexisting AF N=48	Newly Diagnosed AF N=35	P Value
Demographics			
Female sex - no./total no. (%)	44 / 48 (91.7)	30 / 35 (85.7)	0.48
Age - yr	76.8 ± 9.2 (N=48)	73.8 ± 11.8 (N=35)	0.20
Takotsubo Type - no./total no. (%)			
Apical	42 / 48 (87.5)	32 / 35 (91.4)	0.7
Triggers - no./total no. (%)			
Physical trigger	24 / 48 (50.0)	17 / 35 (48.6)	0.90
Emotional trigger	9 / 48 (18.8)	8 / 35 (22.9)	0.65
Symptoms on admission - no./total no. (%)			
Chest pain	29 / 41 (70.7)	21 / 32 (65.6)	0.64
Syncope	1 / 46 (2.2)	2 / 32 (6.3)	0.57
Cardiac biomarkers on admission - median (IQR)			
Troponin - factor increase in ULN *	11.50 (3.05 - 25.78) N=41	5.35 (1.03 - 16.93) N=32	0.17
Creatine kinase - factor increase in ULN	0.80 (0.47 - 1.69) N=32	0.89 (0.43 - 1.67) N=26	0.62
BNP - factor increase in ULN †	10.23 (2.32 - 25.52) N=15	10.08 (5.49 - 37.81) N=15	0.49
Inflammatory markers on admission - median (IQR)			
CRP - mg/l	9.30 (1.40 - 47.28) N=36	3.99 (1.95 - 18.20) N=26	0.64
WBC - 10^3/µl	11.35 (10.08 - 15.70) N=39	9.95 (7.60 - 11.60) N=31	0.05
ECG on admission - no./total no. (%)			
ST-segment elevation	19 / 48 (39.6)	18 / 35 (51.4)	0.28

T-wave inversion	18 / 48 (37.5)	14 / 35 (40.0)	0.82
QTc - ms	451.0 ± 63.0 (N=36)	454.5 ± 70.4 (N=25)	0.84
Hemodynamics - mean±SD (N)			
Heart rate - beats/min	87.0 ± 23.6 (N=39)	103.4 ± 15.9 (N=30)	0.002
Systolic blood pressure - mm Hg	134.1 ± 28.8 (N=38)	125.4 ± 30.6 (N=30)	0.23
Diastolic blood pressure - mm Hg	79.6 ± 18.3 (N=38)	74.9 ± 17.5 (N=30)	0.29
Left ventricular ejection fraction - % ‡	37.6 ± 10.9 (N=44)	37.4 ± 10.8 (N=32)	0.93
Left ventricular end-diastolic pressure - mm Hg	22.0 ± 8.5 (N=30)	20.5 ± 7.1 (N=20)	0.51
Cardiovascular risk factors / history - no./total no. (%)			
Hypertension	41 / 47 (87.2)	31 / 34 (91.2)	0.73
Diabetes mellitus	14 / 47 (29.8)	7 / 33 (21.2)	0.39
Current smoking	7 / 45 (15.6)	5 / 31 (16.1)	0.95
Hypercholesterolemia	15 / 47 (31.9)	9 / 33 (27.3)	0.66
Coexisting medical condition - no./total no. (%)			
Coronary artery disease §	8 / 47 (17.0)	10 / 33 (30.3)	0.16
Cancer (total)	9 / 45 (20.0)	4 / 30 (13.3)	0.55
COPD or asthma	5 / 47 (10.6)	4 / 30 (13.3)	0.73
Medication on admission - no./total no. (%)			
ACE inhibitor or ARB	21 / 41 (51.2)	13 / 27 (48.1)	0.80
Beta-blocker	20 / 41 (48.8)	14 / 27 (51.9)	0.80
Statin	10 / 41 (24.4)	5 / 27 (18.5)	0.57
Aspirin	21 / 41 (51.2)	12 / 26 (46.2)	0.69
Oral anticoagulants	24 / 42 (57.1)	1 / 32 (3.1)	<0.001
Acute cardiac care - no./total no. (%)			
Intra-aortic balloon pump	4 / 47 (8.5)	2 / 35 (5.7)	>0.99
Cardiopulmonary resuscitation	10 / 47 (21.3)	6 / 35 (17.1)	0.64
Invasive or noninvasive ventilation	16 / 47 (34.0)	7 / 35 (20.0)	0.16
Catecholamine use	10 / 47 (21.3)	8 / 35 (22.9)	0.86
In-hospital complications - no./total no. (%)			
Cardiogenic shock	13 / 46 (28.3)	5 / 35 (14.3)	0.13
Death	9 / 48 (18.8)	5 / 35 (14.3)	0.59
5-year outcome - no./total no. (%)			
MACCE	17 / 48 (35.4)	11 / 35 (31.4)	0.53
Death	15 / 48 (31.3)	9 / 35 (25.7)	0.48

* Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.
† Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.
‡ Data obtained during catheterization or echocardiography; if both results were available data from catheterization were used.
§ Coexisting coronary artery disease during acute hospitalization.
ACE angiotensin-converting-enzyme, AF atrial fibrillation, ARB angiotensin-receptor blocker, BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, CRP c-reactive protein, ECG electrocardiogram, IQR interquartile range, MACCE major adverse cardiac and cerebrovascular events,QTc QT interval corrected for heart rate, SD standard deviation, TTS takotsubo syndrome, ULN upper limit of the normal, WBC white blood cell count.

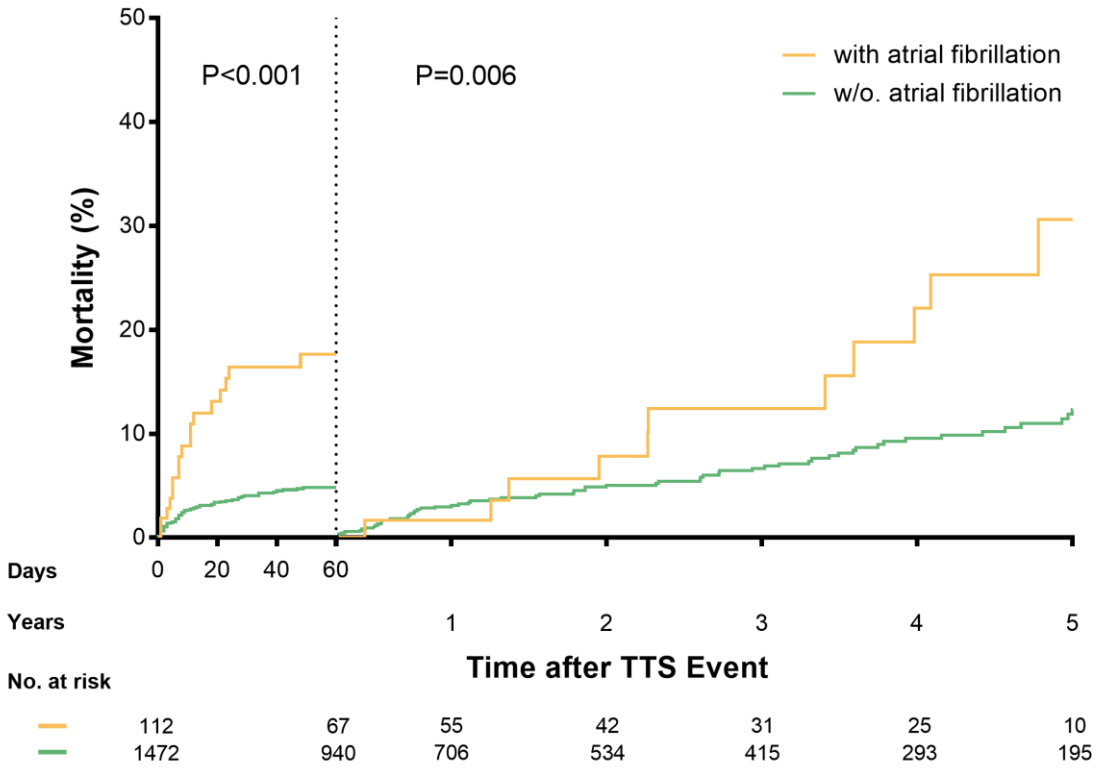

Figure 1: Short- and long-term mortality of TTS patients with and without AF

Kaplan-Meier curves with a landmark set at 60 days show a higher mortality rate in TTS patients with AF compared to TTS patients without atrial fibrillation both in short- ($P < 0.001$) and long-term ($P = 0.006$).

TTS, takotsubo syndrome; AF, atrial fibrillation

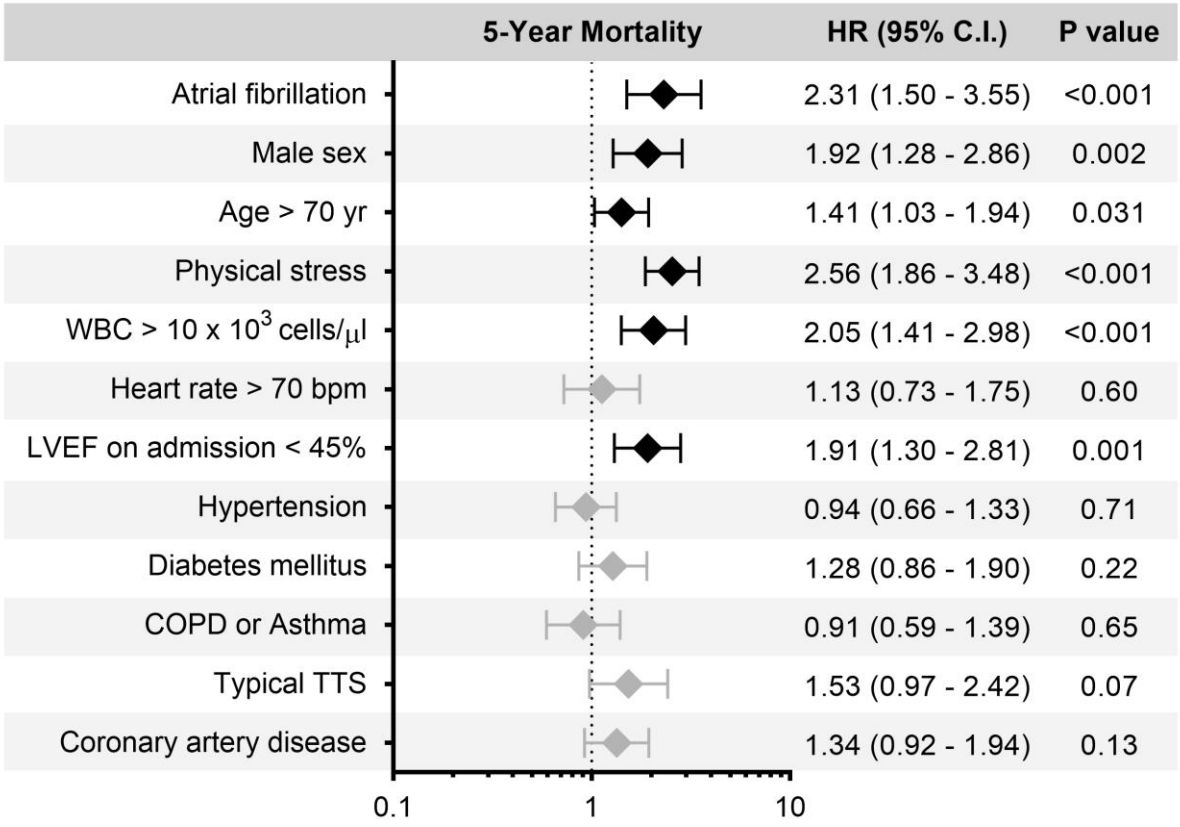

Figure 2: Multivariable Cox regression analysis of TTS patients

Multivariable Cox regression revealed that atrial fibrillation was independently associated with worse long-term mortality. Male sex, age > 70 yr, physical trigger, WBC > 10 x10^3 cells/µl, and LVEF < 45% also emerged as independent predictors of worse long-term mortality in TTS.

C.I. confidence interval, COPD chronic obstructive pulmonary disease, HR hazard ratio, LVEF left ventricular ejection fraction, TTS takotsubo syndrome, WBC white blood cell count. Errors bars represent 95% confidence interval. Black rhombi indicate statistically significance; grey rhombi not statistically significant.

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Ich erkläre ausdrücklich, dass es sich bei der von mir im Rahmen des Studiengangs

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Ich bestätige mit meiner Unterschrift die Richtigkeit dieser Angaben.

Datum: Zürich, 19.11.2019

Name: Rossi Vorname: Aurelio

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