

MRI findings in patients with acute coronary syndrome and unobstructed coronary arteries

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PURPOSE

The underlying diagnosis in patients with acute coronary syndrome (ACS) and unobstructed coronary arteries remains a diagnostic challenge. We analyzed the value of magnetic resonance imaging (MRI) in this clinical setting.

METHODS

A total of 213 patients with ACS and unobstructed coronary arteries underwent MRI within a median of 2 days after initial presentation. Clinical, laboratory, and MRI data were analyzed. A consensus diagnosis was established for each case by an independent panel after reviewing the individual clinical, laboratory, and MRI data. Standardized interviews to determine patient outcomes were carried out after a median follow-up of 24 months. Clinical events were defined as a composite of death, stroke, myocardial infarction or recurrence of Takotsubo syndrome (TTS), new onset of heart failure with a left ventricular ejection fraction (LVEF) <30%, and occurrence of a new left ventricular thrombus formation.

RESULTS

Final diagnoses included acute myocardial infarction (AMI) (40%), acute myocarditis (24%) and TTS (33%). In 3% of patients, nonspecific findings lead to an indeterminate diagnosis. Patients with TTS showed a significantly impaired LVEF during the index event (50% vs. 60% in AMI and 60% in myocarditis, $P = 0.001$). The extent of myocardial edema was most pronounced in patients with TTS ($13.4\% \pm 11.4$ vs. $4.6\% \pm 7.9$ in AMI and $1.8\% \pm 2.7$ in myocarditis, $P < 0.001$). TTS patients had the highest event rate (16.9%).

CONCLUSION

Our study emphasizes the diagnostic utility of timely MRI in patients with ACS and unobstructed coronary arteries. We found a high prevalence of TTS patients, who had poorer outcomes compared with patients with a final diagnosis of AMI or myocarditis.

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In a small proportion of patients presenting with acute coronary syndrome (ACS), as suggested by chest pain and elevated biomarkers for myocardial necrosis such as high-sensitivity troponin T, coronary angiography reveals unobstructed coronary arteries. The prevalence of patients with ACS and unobstructed coronary arteries has been reported to range from 1% to 14% (1). Finding a certain diagnosis for these patients still remains a challenge. Troponin elevations are known to occur in many clinical scenarios besides ACS. Small studies have suggested that cardiovascular magnetic resonance imaging (MRI) can be of value in such patients (2–6). Potential underlying causes that can be detected with MRI include acute myocarditis, acute myocardial infarction (AMI) due to recanalized thrombotic occlusion, or Takotsubo syndrome (TTS) (6–8).

TTS is an acute but mostly reversible heart failure syndrome. Yet, its precise incidence is not clearly known. However, increasing awareness and more widespread access to early coronary angiography have led to a more frequent recognition of TTS. Data on patient outcome is mixed. Previous studies reported a benign outcome (9–11). Lately, mortality in TTS was found to be comparable to patients with non-ST-elevated myocardial infarction (12, 13). In a recently published study, patients with prior TTS had persistent long-term heart failure changes with modifications in myocardial structure and metabolism despite normal left ventricular ejection

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fraction (LVEF) and cardiac biomarkers (14). Interestingly, studies examining prognosis after TTS are based on comparisons to patients with “true” myocardial infarction secondary to an identifiable culprit lesion. Data comparing MRI and patient outcome in TTS versus in other patients with elevated biomarkers and unobstructed coronary arteries but other diagnoses are lacking.

We therefore aimed to evaluate the outcome of patients with TTS as compared with patients with AMI and with other causes for ACS in the presence of unobstructed coronary arteries and to analyze the diagnostic value of MRI in a larger cohort of these ACS patients.

Methods

Study design

As part of this retrospective study, medical records from January 2005 to January 2017 were reviewed for patients who presented with ACS in our chest pain unit but whose coronary angiogram demonstrated no significant stenosis (no stenosis $\geq 50\%$) and who underwent contrast-enhanced MRI (<30 days after index event). ACS was defined as chest pain, elevated high-sensitivity cardiac troponin, and new ST-changes on electrocardiogram. Upon admission to our chest pain unit, a detailed physical examination and past medical history were recorded. Excluded from our record review were patients <18 years old or those with a past history of myocardial infarction, coronary bypass surgery, or congenital heart disease.

Since the definition of TTS changed over time, we used the current definition for all cases. A diagnosis of TTS was assigned to cases with acute heart failure with or without apical ballooning or wall motion abnormalities that extended beyond a single epi-

cardial vascular distribution in accord with the current ESC position statement criteria on TTS and the Mayo Clinic Diagnostic Criteria (11, 15). Additionally, TTS was defined by absence of the typical late gadolinium enhancement (LGE) pattern seen in myocarditis or AMI on MRI. Acute myocarditis was diagnosed in patients fulfilling typical clinical and diagnostic criteria according to the current ESC position statement on myocarditis and presenting with a typical mid-wall to subepicardial LGE pattern for myocarditis on MRI (16–19). AMI was diagnosed in cases fulfilling clinical criteria according to the current ESC guidelines and in cases with myocardial edema or LGE with the typical ischemic pattern that matched a single epicardial vascular distribution (5, 20).

Major adverse cardiac events (MACE) were defined as a composite of death, stroke, myocardial infarction or recurrence of TTS, admission due to new onset of heart failure with a left ventricular ejection fraction (LVEF) <30% and occurrence of a new left ventricular (LV) thrombus formation.

Follow-up data for this study was obtained from the patients by standardized telephone interviews with the patients or their treating physicians after a median of 24 months (range, 0–138.5 months).

The local ethics committee approved this study, and patients were contacted for written informed consent. The standardized telephone interviews were also approved by the local ethics committee.

Cardiac catheterization

All patients were evaluated according to the standardized diagnostic protocol for ACS in our certified chest pain unit and underwent cardiac catheterization within a median of 16 hours after presentation (interquartile range [IQR], 3–32). All received standard of care therapy for ACS according to the current guidelines. Patients with unobstructed coronary arteries either had normal coronary artery perfusion or mild atherosclerosis (<50% stenosis) without unstable atherosclerotic plaques.

Laboratory parameters

Blood samples were taken at the time of admission and daily or as required thereafter to measure high-sensitivity troponin T and creatine kinase (CK) values until normalization. Plasma samples for C-reactive protein (CRP) and glomerular filtration rate (GFR) values were also evaluated at admission and as part of the daily routine. Peak values of

high-sensitivity troponin T, CK, and CRP and the lowest GFR were recorded. The normal values for these laboratory tests at our institution are: troponin T <100 pg/mL, CK-MB <24U/L, CK <140U/L, CRP <0.5 mg/dL, and GFR 90–150 mL/min/1.73m².

MRI protocol and image analysis

MRI was performed on a 1.5 Tesla scanner (Intera Achieva, Philips). The MRI protocol provided an analysis of left ventricular function and wall motion and provided a quantitative assessment of myocardial edema and LGE. A state of the art standard steady-state free precession technique (2D turbo gradient-echo sequence) in short axis, four-chamber, two-chamber, and three-chamber views of the entire left ventricle were used for the left ventricular function analysis. Myocardial or pericardial edema was evaluated with T2-weighted black blood turbo-spin-echo sequences (with and without fat saturation pre-pulse) in the short axis and covering the complete left ventricle. This sequence has previously been used and validated for the assessment of myocardial edema (21–23).

To analyze LGE, a 3D inversion-recovery turbo gradient echo sequence was used to obtain images of the left and right ventricles 10 min after injection of 0.2 mmol/kg of gadoteridol (Prohance®, Bracco-Imaging). LGE image acquisition covered the entire left and right ventricles in multiple slices without gaps with views in the short axis and four-, two-, and three-chamber long axis.

Image analysis was performed with commercially available software (Extended MR Workspace 2.6.3.4, Philips Medical Systems and CVI 42, Version 4.0, Circle Cardiovascular Imaging Inc.). LVEF was calculated by assessment of the volumes of the endocardial contours in diastole and systole. Therefore endocardial contours were manually drawn in the four- and two-chamber slices. Area of myocardial edema was considered to have a signal intensity of >2 standard deviations (SD) above remote, normal myocardium in T2-weighted sequences (24). The extent of the myocardial edema was expressed as percentage of the total LV mass. Left ventricular mass was assessed by endocardial and epicardial contours drawn manually in the short axis of the entire left ventricle.

LGE was determined by semi-automated quantification in each short axis slice. LGE was defined as an area of hyperenhancement with a signal intensity ≥ 5 SD above

Main points

- MRI had high diagnostic value in patients with acute coronary syndrome and unobstructed coronary arteries.
- Timely MRI increased the diagnosis of Takotsubo syndrome (TTS) in this patient population.
- TTS had a poorer prognosis compared with acute myocardial infarction (AMI) with unobstructed coronary arteries and myocarditis.
- Left ventricular function in the acute phase of the disease was most impaired in TTS compared with AMI with unobstructed coronary arteries and myocarditis.

the signal intensity of a region of normal “nulled” myocardium (25). The extent of LGE was expressed as a percentage of LV volume and was calculated by taking the sum of the volume of LGE regions for all slices and dividing that by the sum of the total LV myocardial volume. Two cardiologists with ESC MRI Level III certification independently reviewed MRI studies.

Statistical analysis

Categorical data were described by frequencies, and continuous data were expressed as mean \pm SD or median with either minimum and maximum or lower and upper interquartile (Q1, Q3). To compare the three groups with respect to gender, age, cardiovascular risk factors, laboratory and MRI parameters multinomial logistic regression (Wald test) was used. All *P* values are age-adjusted with the exception of age. The rate of patients without events was estimated with the Kaplan-Meier estimator and presented in a Kaplan-Meier survival graph. All statistical tests were two-sided. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using STATA/IC 14.2 software (Stat Corp, LP).

Results

A total of 213 patients were included; of these, 136 were female (63.2%). The mean age of the study population was 59.6 ± 17.5 years. Cardiovascular risk factors included arterial hypertension in 50 (23.5%), diabetes mellitus in 23 (10.8%), current smoking in 49 (23%), hyperlipidemia in 50 (23.5%) and a family history of myocardial infarction in 49 (23%). Median body mass index of the study population was 26 kg/m^2 (range, 16–47 kg/m^2). Peak values of myocardial biomarkers were elevated with high-sensitivity troponin T, 345 pg/mL (range, 15–9908 pg/

mL); CK-MB, 37 U/L (10–858 U/L); CK, 256 U/L (21–10610 U/L). Median CRP was 1.5 mg/dL (0–32.6 mg/dL) in the study population and median GFR was 78 mL/min per 1.73 m^2 (26–144 mL/min per 1.73 m^2).

MRI was performed a median of 2 days (IQR, 1–4 days) after cardiac catheterization. The median LVEF of the study population during the index events was decreased to 56% (range, 18%–77%). The mean myocardial edema volume was elevated at 0% (0%–43%). LGE was detected in 92 patients (43.2%).

A final diagnosis was found in 206 patients (96.7%) (Fig. 1). The diagnosis or underlying cause remained unclear in 7 patients only. Final diagnosis was AMI in 84

patients (39.4%), TTS in 71 patients (33.3%), and myocarditis in 51 patients (23.9%). Demographic findings, laboratory and MRI data of the different groups are presented in Table 1. Patients with TTS had the most myocardial edema (13% [0%–43%] vs. 0% [0%–38%] in AMI vs. 0% [0%–9%] in myocarditis, $P < 0.001$; Fig. 2). During the index event, patients with TTS had the lowest median LVEF (50% [25%–73%] vs. 60% [18%–77%] in AMI vs. 60% [45%–71%] in myocarditis, $P = 0.001$). The LGE pattern differed among the three groups (Fig. 3). Patients with AMI had the most LGE (1% [0%–26%] vs. 1% [0%–5%] in myocarditis vs. 0% [0%–0%] in TTS, $P < 0.001$; Fig. 2). There was a trend towards a shorter time lapse between

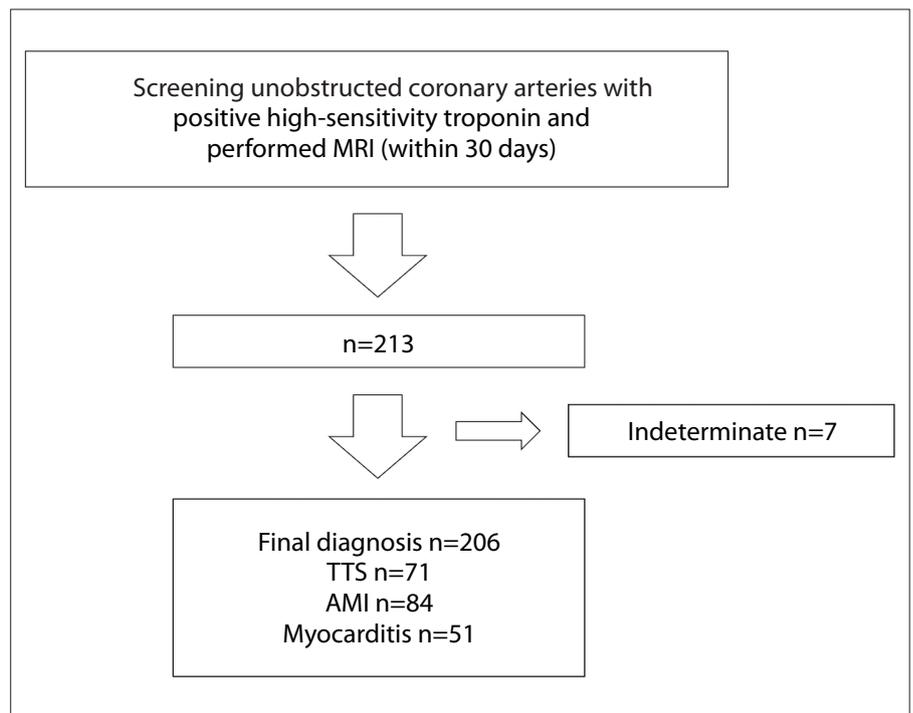


Figure 1. Study flow chart.

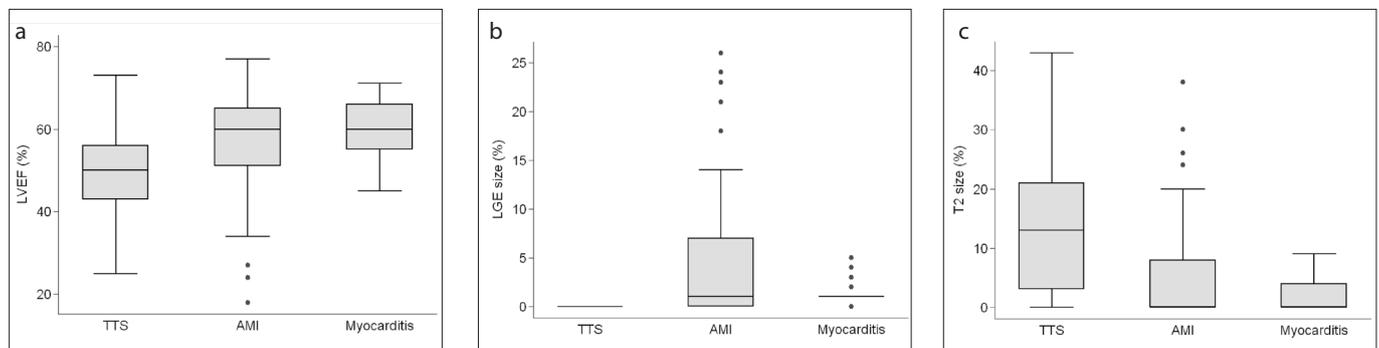


Figure 2. a–c. Comparison of MRI parameters between patients with Takotsubo Syndrome (TTS), acute myocardial infarction (AMI) and myocarditis: (a), left ventricular ejection fraction (LVEF); (b), late gadolinium enhancement (LGE); (c), myocardial edema (T2).

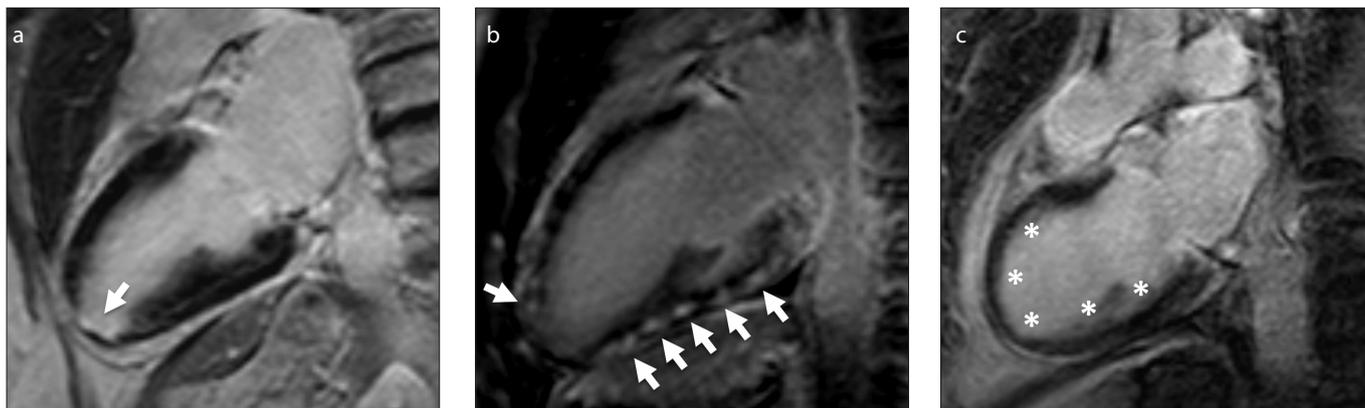


Figure 3. a–c. Different LGE patterns of AMI (a), myocarditis (b), and TTS (c). Subendocardial LGE pattern of the left ventricular apex in AMI (a, white arrow), typical epicardial LGE pattern of the inferior segments and smaller parts of the anterior segment in a patient with myocarditis (b, white arrows). No LGE, but apical to midventricular ballooning in a patient with TTS (c, white asterisks).

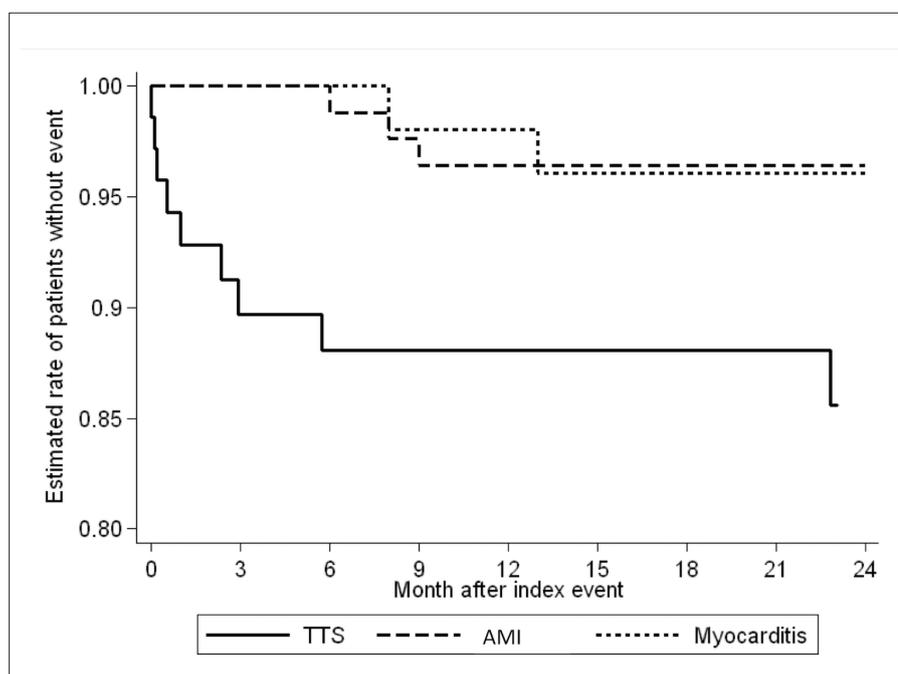


Figure 4. Kaplan-Meier survival function showing the estimated rate of patients without events within the observation period of 24 months. TTS, Takotsubo syndrome; AMI, acute myocardial infarction.

the angiogram and MRI in patients with myocarditis; however, the difference was not statistically significant.

Patients with TTS were older (69.1 ± 12.1 years vs. 58.8 ± 16.2 years in AMI vs. 47.4 ± 17.6 years in myocarditis, $P < 0.001$; Table 1) and more often female (94.4%). In terms of cardiovascular risk factors, current smoking was significantly less frequent in patients with TTS (12.7% vs. 39.3% in AMI vs. 39.2% in myocarditis, $P = 0.012$). There was a significant difference in the peak values of CK between the three groups (204 U/L [68–10610 U/L] in TTS vs. 301 U/L [25–9700 U/L] in AMI

vs. 291 U/L [21–2478 U/L] in myocarditis, $P = 0.04$). Peak troponin values were not significantly different among the three groups.

We observed 17 events (8%) in the study population within a median follow-up period of 24 months (0–138.5 months, Table 2). The mortality rate in TTS was 5.6%, with one in-hospital death and three patients who died postdischarge from noncardiac causes. There were no deaths reported in the groups with AMI and myocarditis. We found the highest MACE rate in patients with TTS (16.9%). The most common event was death, followed by stroke (4.2%; Table 2

and Fig. 4). The MACE rate in AMI patients was 3.6%, with congestive heart failure (LVEF $< 30\%$) and recurrence of myocardial infarction constituting the adverse events. In patients with myocarditis, the MACE rate was 3.9% and was due to myocardial infarction and congestive heart failure.

Discussion

Our study demonstrates the high diagnostic impact of early MRI in patients with unobstructed coronary arteries and ACS. In these patients, the use of MRI 2 days after cardiac catheterization resulted in a diagnosis in 97% of cases.

We also found that patients with TTS had the lowest initial LVEF and the greatest amount of myocardial edema compared with patients with AMI or myocarditis. Patients with TTS had the poorest outcome.

Our identified final diagnoses (TTS, AMI, and myocarditis) are in line with those previously reported in smaller studies (26). Of note though, some smaller studies evaluating ACS patients with unobstructed coronary arteries reported different frequencies for the final diagnoses. Assomull et al. (4) demonstrated in a study with a smaller cohort that MRI was a valuable diagnostic tool; however, in this study, myocarditis was the most common diagnosis. Of the 64 patients in that study population, only one patient was diagnosed with TTS. A major difference between our study and this one is the time from cardiac catheterization to MRI scan. Assomull et al. (4) reported an interval of up to 3 months between catheterization and MRI scan. In our study, we performed the MRI scans earlier, within a median of 2 days after cardiac catheterization. Previous studies have reported the time dependent

Table 1. Description and univariate global testing of categorical and continuous data between the different groups

	Description of groups			<i>P</i> ^a
	TTS (n=71)	AMI (n=84)	Myocarditis (n=51)	
Demographic findings				
Age (years), mean±SD	69.1±12.1	58.8±16.2	47.4±17.6	<0.001
Male, n (%)	4 (5.6)	36 (42.9)	33 (64.7)	<0.001
Cardiovascular risk factors				
Arterial hypertension, n (%)	49 (69.0)	54 (64.3)	19 (37.3)	0.323
Diabetes mellitus, n (%)	7 (9.9)	10 (11.9)	5 (9.8)	0.240
Current smoking, n (%)	9 (12.7)	33 (39.3)	20 (39.2)	0.012
Hyperlipidemia, n (%)	19 (26.8)	22 (26.2)	8 (15.7)	0.642
BMI (kg/m ²)	24 (16–39)	27 (18–47)	26 (20–36)	0.177
Family history for MI, n (%)	16 (22.5)	24 (28.6)	7 (13.7)	0.179
Laboratory findings				
Peak value levels				
hs troponin T (pg/mL)	415 (16–2291)	315 (21–9908)	397 (15–4620)	0.542
CK-MB value (U/L)	34 (10–159)	42 (13–858)	36 (14–198)	0.376
CK value (U/L)	204 (68–10610)	301 (25–9700)	291 (21–2478)	0.044
CRP (mg/dL)	1.1 (0.1–32.6)	1.1 (0.1–25)	3.0 (0.0–19.3)	0.549
GFR (mL/min per 1.73 m ²) lowest level	68 (26–109)	80 (36–144)	87 (45–129)	0.514
Cardiovascular MRI parameters				
LVEF (%)	50 (25–73)	60 (18–77)	60 (45–71)	0.001
LVEDVI (mL/m ²)	76 (47–112)	75 (30–206)	77 (46–106)	0.427
T2 size (%)	13 (0–43)	0 (0–38)	0 (0–9)	<0.001
LGE size (%)	0 (0–0)	1 (0–26)	1 (0–5)	<0.001
Days between angiogram and MRI	2 (0–16)	2.5 (0–20)	1 (0–12)	0.076
Age is presented as mean ± standard deviation; categorical data are presented as n (%); BMI, laboratory data and MRI parameters are presented as median (range). TTS, Takotsubo syndrome; AMI, acute myocardial infarction; SD, standard deviation; BMI, body mass index; MI, myocardial infarction; hs, high-sensitivity; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end diastolic volume index; T2, myocardial edema; LGE, late gadolinium enhancement. ^a Multinomial logistic regression (Wald test) was used. With the exception of age, all <i>P</i> values are adjusted for age.				

course of LV recovery in patients with TTS (27, 28). Thus, one explanation for the remarkably low rate of TTS in their study might be the relatively long period between symptom presentation and MRI scan, when typical signs of TTS have recovered already. In our study, there was not only a lower rate of indeterminate findings, but also a higher rate of diagnosis of TTS. Early performance

of MRI in patients with ACS and unobstructed coronary arteries might increase the diagnostic value of MRI and might increase the rate of TTS findings.

Another explanation for an indeterminate diagnosis in this patient population after MRI could be that, despite its high spatial resolution, detection of minor changes in myocardial edema and inflammation is

limited. Likewise, diffuse myocardial necrosis or microinfarctions could be missed. This highlights the importance of a multimodal diagnostic approach in these patients to enhance diagnostic accuracy.

Our data demonstrated that the initial LVEF in patients with unobstructed coronary arteries and elevated cardiac biomarkers varied depending upon the underlying cause. This had previously been suspected in smaller studies (7, 29). In our study, the initial LVEF was most severely impaired in patients with TTS compared with patients with myocarditis and AMI, which is consistent with these smaller studies (7, 29). Recent data have observed that LV function of TTS patients does not fully recover, but rather there are long-term metabolic, structural, and functional impairments as reported by Scally et al. (14).

In our study, AMI patients had the most increased extent of LGE; however, unlike the TTS patients, a normal initial LVEF. As previously reported, extent of infarct size is associated with a poorer outcome in “true” ST-elevated myocardial infarction (30). This indicates that in patients with ACS and unobstructed coronary arteries, infarct size or fibrosis seems to play a minor role in influencing the outcome.

Interestingly, initial LVEF in AMI and in patients with myocarditis was normal. One possible explanation in AMI might be that the duration of thrombotic occlusion was short enough to prevent extensive myocardial injury resulting in a relatively small infarct size. We found comparable CK peak values in AMI and in myocarditis patients suggesting that myocardial injury was similarly low in both groups.

Previous studies described a 6-month mortality of 3.1% and a 30-day mortality of 2.2% in patients without coronary artery obstruction but elevated troponins (31, 32). In our study, we found one in-hospital death and three non-cardiac deaths in patients with TTS. A long-term, multinational registry has likewise found a death rate from any cause of 5.6% per TTS patient per year (33). Conversely, we did not observe any deaths in the AMI and myocarditis group. Earlier data from TTS studies suggested a favorable prognosis (9, 34). However, more recent data have reported MACE rates in TTS comparable to patients with non-STEMI (12). Existing data on the prognosis of TTS patients are somewhat mixed, and this topic needs further evaluation. There is evidence that, despite recovery of LV function,

Table 2. Follow-up after 24-months

	TTS (n=71)	AMI (n=84)	Myocarditis (n=51)
Patients with no events, n (%)	60 (84.5)	81 (96.4)	49 (96.1)
Patients with at least one event, n(%)	11 (11.5)	3 (3.6)	2 (3.9)
Events, n (%)*	12 (16.9)	3 (3.6)	2 (3.9)
Myocardial infarction/TTS	2 (2.8)	1 (1.2)	1 (2.0)
Congestive heart failure	2 (2.8)	2 (2.4)	1 (2.0)
Stroke	3 (4.2)	0	0
Intraventricular thrombus	1 (1.4)	0	0
Death	4 (5.6)	0	0

TTS, Takotsubo syndrome; AMI, acute myocardial infarction.

*Multiple events per patient is possible. Event rate is calculated as number of events divided by the number of patients (%).

long-term changes in cardiac metabolism and structure persist after TTS (14). This leads to the hypothesis that LV dysfunction in TTS may not be transient, as earlier suspected, but persistent in terms of metabolic and structural changes. Our data with poor outcomes and a relatively high event rate in TTS might be explained by these findings. Conversely, studies on the outcomes of AMI patients with unobstructed coronary arteries have demonstrated a very low risk of cardiac events after two years of follow-up (35). It would definitely be interesting if, compared with TTS patients, the metabolic and structural changes are different in patients with AMI but unobstructed coronary arteries. These questions require further investigations.

Our study has some limitations. Due to the retrospective design of the study, the prevalence of TTS might be artificially increased. Prospective, multicenter studies examining the prevalence of TTS are currently running. Specifically, some imaging factors, which were impossible to change in this retrospective study, may have caused our study to have a high prevalence of TTS. For example, only patients who underwent MRI studies were included. Therefore patients who could not be examined in this manner, perhaps due to critical illness or other issues, were not considered in this analysis. Furthermore, the acquisition of early gadolinium enhancement sequences would have facilitated differentiation of similar LGE patterns found in a smaller proportion of AMI or myocarditis patients. However, this study focused on the combination of T2-weighted and LGE images to distinguish between the different entities. Despite its high diagnostic value, MRI

has limitations in spatial resolution. Slightly increased troponin levels due to microscopic myocardial injuries might be missed. There is always the possibility that an episode of a rapid, undetected cardiac arrhythmia or a hypertensive crisis can result in an elevation of troponin. Finally, the diagnoses in our study were not systematically confirmed by histological analyses due to our institutional guidelines that do not include unnecessary endomyocardial biopsies.

In conclusion, our study emphasizes the diagnostic utility of timely MRI in patients with ACS and unobstructed coronary arteries. Using timely MRI we found a high prevalence of TTS patients, who had poorer outcomes compared with patients with a final diagnosis of AMI or myocarditis.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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