Clinical Features and Outcomes of Takotsubo Syndrome at a University Hospital

Características clínicas y evolutivas del síndrome de Takotsubo en un hospital universitario

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ABSTRACT

Background: Takotsubo syndrome (TS) is a reversible cardiomyopathy with many different forms of presentations. There is no local data of TS published so far.
Methods: One hundred and fifteen patients with either primary or secondary TS were retrospectively studied at Hospital Italiano de Buenos Aires from 2005 to 2017. The purpose of the study was to assess the clinical features of this population during hospitalization.
Results: Median of age was 78 years (64-84); 90 % of patients were female, and 22% had associated coronary artery disease. Fifty-seven percent of cases were primary TS, 31 % experienced an emotional trigger and 44 % had a physical origin. The presentation syndrome was as follows: 9 % shock, 12 % heart failure, 70 % mimicking acute coronary syndrome, 5 % stroke/peripheral embolism and 4 % arrhythmias. Median ejection fraction at admission was 40 % (36-50) and recovery from admission to discharge [median hospital stay: 4 days (3-8)] was 20 %, p <0.001.
In-hospital mortality was 4/115 cases (3.48 %). In univariate analysis, shock compared with other forms of presentation (p=0.0035) and secondary TS (p=0.020) were associated with higher in-hospital mortality. There was a direct relationship between in-hospital mortality and maximum NT-pro-BNP levels (p= 0.0082) and white cell count (p=0.0101).
In addition, in-hospital mortality was inversely associated with hematocrit (p=0.0084) and with ECG abnormalities at admission; i.e. patients who died during hospitalization had more frequently normal ECG at admission, (p<0.001).
Conclusion: Compared with international registries, this single center population had more comorbidities, but similar in-hospital mortality rates.

Key words: Takotsubo Cardiomyopathy - Acute coronary syndrome - Heart failure.

RESUMEN

Introducción: El síndrome de Takotsubo (ST) es una miocardiopatía reversible que tiene diversas formas de presentación. Hasta el momento no se han publicado datos de ST en nuestro medio.
Métodos: Desde el 2005 al 2017 se incluyeron a 115 pacientes con diagnóstico de ST primario o secundario en el Hospital Italiano de Buenos Aires. El objetivo fue evaluar las características clínicas del ST durante la internación.
Resultados: La mediana de edad de la población fue de 78 años (64-84), el 90 % eran mujeres, y el 22% presentó enfermedad coronaria asociada. El 57% eran ST primarios, 31% tuvieron un gatillo emocional y 44%, físico. El síndrome de presentación fue como *shock*: 9%, insuficiencia cardiaca 12%, "tipo SCA" 70%, ACV/embolia 5% y, arritmias, 4%. La mediana de Fey al ingreso fue del 40% (36-50) y su recuperación, desde el ingreso al alta (mediana de internación de 4 días, 3-8), fue del 20%, *p < 0.001*.
La mortalidad hospitalaria fue de 4/115 (3,48%). En el análisis univariado, las variables asociadas a mayor mortalidad fueron: shock respecto a otras formas de presentación (*p = 0.0035*) y ST secundario respecto al primario, p = 0.020. Además, existió una relación directa entre la mortalidad y los niveles de NT-pro-BNP máximo (*p = 0.0082*) y glóbulos blancos (*p = 0.0101*).
Asimismo, la mortalidad hospitalaria mostró una relación inversa con el hematocrito (*p = 0.0084*) y con las alteraciones en el ECG de ingreso; es decir, que los pacientes que fallecieron durante la internación tuvieron ECG normal al ingreso con mayor frecuencia (*p < 0.001*).
Conclusión: En este registro unicéntrico se observó que los pacientes tuvieron más comorbilidades y similar mortalidad respecto a registros internacionales.

Palabras clave: Síndrome de Takotsubo - Miocardiopatía por estrés - Síndrome coronario agudo - Insuficiencia cardíaca aguda

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Abbreviations

ACS	Acute coronary syndrome	**CMR**	Cardiac magnetic resonance
CA	Coronary angiography	**NT-proBNP**	Amino terminal pro brain natriuretic peptide
CAD	Coronary artery disease	**TS**	Takotsubo síndrome
EF	Ejection fraction	**UST**	Ultra-sensitive troponin

INTRODUCTION

Takotsubo syndrome (TS) or stress cardiomyopathy is a reversible cardiomyopathy that can present as acute coronary syndrome (ACS), as acute heart failure syndrome or as systemic embolism. (1, 2) Although its mechanism is not clearly known, the most accepted hypothesis is associated to a discharge of endogenous or exogenous catecholamines. (3-5) Although emotional or physical triggers are recognized to develop TS, it may sometimes present in their absence. (1) The modified Mayo Clinic diagnostic criteria, including absence of a plaque accident and/or severe lesion of an epicardial coronary artery are currently used to diagnose it. (6) At present, there is no specific treatment for this syndrome, except hemodynamic support in cases of circulatory collapse, management of heart failure and anticoagulation in cases of embolism. Several registries in the world have evaluated hospitalization and long-term outcome and have even compared it with the evolution of ACS. (1-2, 7-8) So far, these aspects have not been explored in our setting. It is possible that both the clinical features of TS: age, prevalence of coronary artery disease (CAD), triggers and outcomes (mortality, recurrences) are different from those reported by other authors. The purpose of this study was to describe the clinical features and outcomes of patients hospitalized with TS at a university hospital.

METHODS
Study population

From January 2005 to June 2016, patients with primary or secondary diagnosis of TS (main discharge diagnosis or main discharge diagnosis other than TS, respectively) were consecutively included in the study at Hospital Italiano de Buenos Aires. Data was taken from the electronic clinical history of the institution, using the following keywords in the epicrisis as search criteria: "Takotsubo syndrome" or "Stress cardiomyopathy." Patients with pheochromocytoma, myocarditis or severe coronary lesions corresponding to the same territory of the regional ventricular motility disorder were excluded from the study.

Statistical analysis

Continuous variables were reported as mean and standard deviation in case of normal distribution or as median and interquartile range for non-normal distribution. Categorical variables were expressed as absolute and relative frequency. Univariate analysis was performed to identify variables associated with in-hospital mortality. A ROC curve was built considering maximum NT-proBNP values to establish the best cut-off point to identify in-hospital mortality patients. Statistical analysis was performed with STATA 13 statistical software package. A p-value <0.05 was considered statistically significant.

Study definitions

The modified Mayo Clinic criteria was applied to diagnose TS, except in cases of secondary TS.(6) Cardiovascular risk factors, type of triggers (emotional vs. physical), type of TS (primary vs. secondary) (1), neurological or psychiatric history, electrocardiographic data, echocardiogram, cardiac magnetic resonance (CMR) and coronary angiography (CA) data were recorded. In addition, maximum NT-proBNP value, ultrasensitive troponin (UST), and NT-proBNP /UST ratio were reported as cardiac biomarkers.

Ethical considerations

The study was approved by the ethics committee of Hospital Italiano de Buenos Aires.

RESULTS

Median population age was 78 years (IQR 64-84) and 90% were women. Coronary angiography was performed in 87% of patients and 22% had associated coronary artery disease (Table 1).

The presentation syndrome was shock in 9% of cases, heart failure in 12%, mimicking ACS in 70%, stroke/peripheral embolism in 5%, and arrhythmias in 4%. Primary TS was present in 57% of patients and emotional and physical triggers occurred in 31% and 44% of cases, respectively. Table 2 shows the different triggers identified during hospitalization.

The most frequent electrocardiographic findings at admission and before discharge were the presence of negative T waves in 67% and 97% of the patients, respectively, and the absence of any abnormality in the V1 lead in 85% and 88% of the patients, respectively. The rest of the findings are shown in Figure 1.

Median ejection fraction (EF) at admission was 40%, IQR (36-50) and 20% of patients had severe ven-

Table 1. Baseline population characteristics, n=115

Female gender	104 (90)
Age,years	78 (64-84)
Hypertension	77 (67)
Dyslipidemia	64 (56)
Diabetes	9 (8)
Smoking	12 (11)
Previous infarction	3 (2.6)
Psychiatric history	29 (25)
Neurological history	15 (13)

Table 2. Forms of presentation of Takotsubo syndrome

	n=115, %
Trigger	86 (75)
Emotional Trigger	36 (31)
Emotional Trigger categories	
Interpersonal conflict	16 (44)
Fear/panic	8 (22)
Suffering/loss	5 (14)
Frustration	1 (3)
Others	6 (17)
Physical Trigger	50 (44)
Physical Trigger categories	
Infection	14 (27)
Postoperative	10 (20)
Neurological	9 (18)
Respiratory failure	7 (15)
Cancer	4 (9)
Others	6 (11)
Presentation syndrome, "mimicking" ACS	80 (70)
CHF	14 (12)
Shock	10 (9)
Stroke/embolism	6 (5)
Arrhythmia	5 (4)
CA, (n=100)	(87)
Normal coronary arteries, (n=78)	(78)
Coronary lesions, (n=22)	
Coronary lesions, Mild	(59)
Moderate	(32)
Severe	(9)
EF at admission; median IQR 25-75	40 (36-50)
CMR, (n=28)	(24)
CMR imaging of edema, (n=25)	(89)
CMR late gadolinium enhancement, (n=9)	(32)
Ultra-sensitive troponin (pg/ml), median IQR 25-75	353 (130-700)
NT-proBNP (pg/ml), median IQR 25-75	5000 (1800-12000)
NT-proBNP/UST ratio, median IQR 25-75	15 (5-55)

ACS: Acute coronary syndrome. CHF: Congestive heart failure. CA: Coronary angiography. EF: Ejection fraction. CMR: Cardiac magnetic resonance. UTS: Ultrasensitive troponin

tricular function impairment. The recovery during the hospitalization period was 20%, p <0.001. Median maximum UST was 353 pg/ml, IQR (130-700), NT-proBNP 5000 pg/ml, IQR (1800-12000) and NT- proBNP/UST ratio 15, IQR (5-55).

In-hospital mortality occurred in 4/115 patients (3.48%) and median hospital stay was 4 days (3-8). In univariate analysis, the variables associated with higher mortality were shock compared to other forms of presentation (p=0.0035) and secondary TS in 4/50 patients (8%) vs. primary TS in 0/65 patients, p=0.020. In addition, there was a direct relationship between

mortality and maximum NT-proBNP levels: OR 1.12, 95% CI (1.02-1.22), p=0.0082, per 1000 ng/l; and between mortality and white blood cell count: OR 1.15 (95% CI 1.01-1.30, p=0.0101) per 1000 mm3 (see Figure 2). Similarly, in-hospital mortality showed an inverse relationship with the hematocrit: OR 0.79 (95% CI 0.65- 0.96, p=0.0084) and with ECG abnormalities at admission, i.e. the patients who died during hospitalization had a higher rate of normal ECG at admission: 29% vs.1.85%, p<0.001. Patients who maintained microvoltage in the ECG during hospitalization had a tendency to higher mortality, p=0.066. Consid-
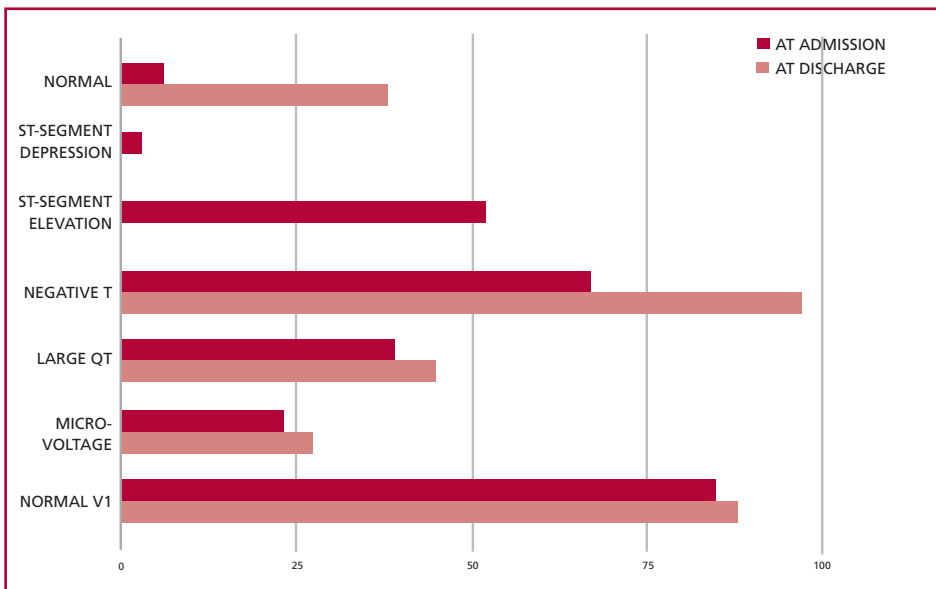
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Fig. 1. ECG at admission and before discharge

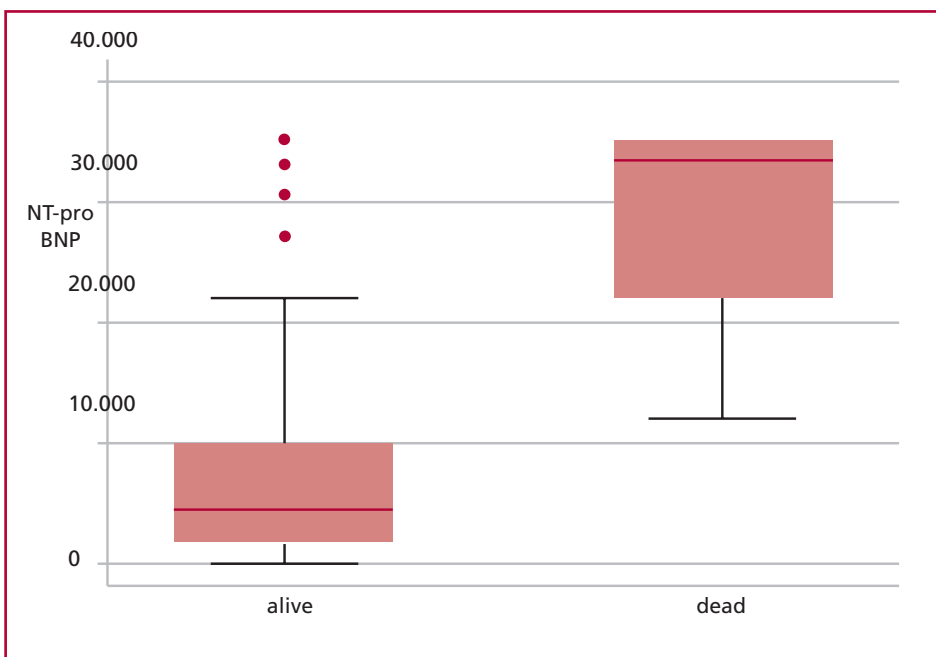Normal V1 refers to absence of any pathological dysfunction in said lead.

Fig. 2. Maximum NT-proBNP levels according to in-hospital mortality Patients who died presented higher maximum NT-proBNP levels: 33500 ng/l (22000-35000) vs. those who survived 4642 ng/l (1800-10033), *p=0.0082*.

ering all the variables explored, NT-proBNP was the one that best identified the patients who died during hospitalization (Figure 3). A cut-off point ≥12000 ng/l, had a sensitivity of 100%, specificity of 76%, L+ of 4.23 and LR- of 0 to identify patients who died during hospitalization. The echocardiographic variables [EF, CMR (presence of edema and gadolinium) and maximum UST] were not associated with higher in-hospital mortality. With respect to the use of diagnostic CA, patients who did not undergo this procedure had a lower prevalence of diabetes (p=0.004), pathological ECG at admission (p=0.016), shock (p=0.004), and

primary TS (p<0.001), lower use of CMR (p=0.018), higher white blood cell count (p=0.032) and higher in-hospital mortality (p<0.001).

Cardiac magnetic resonance imaging was performed in 24% of patients, 89% of which had myocardial edema and 32% late gadolinium enhancement (Table 2). The rate of CMR was 46% in patients with primary TS and 2% in patients with secondary TS, p<0.001. Patients who presented with edema had higher white blood cell count than those without edema: 9660 mm3 (7665-11000) vs. 6000 mm3 (5790-7500), p=0.030. Patients who had late gadolinium en-

Fig. 3. Discrimination capacity of maximum NT-proBNP on hospital mortality.

AUC= 0.89, 95% CI (0.80-0.98)
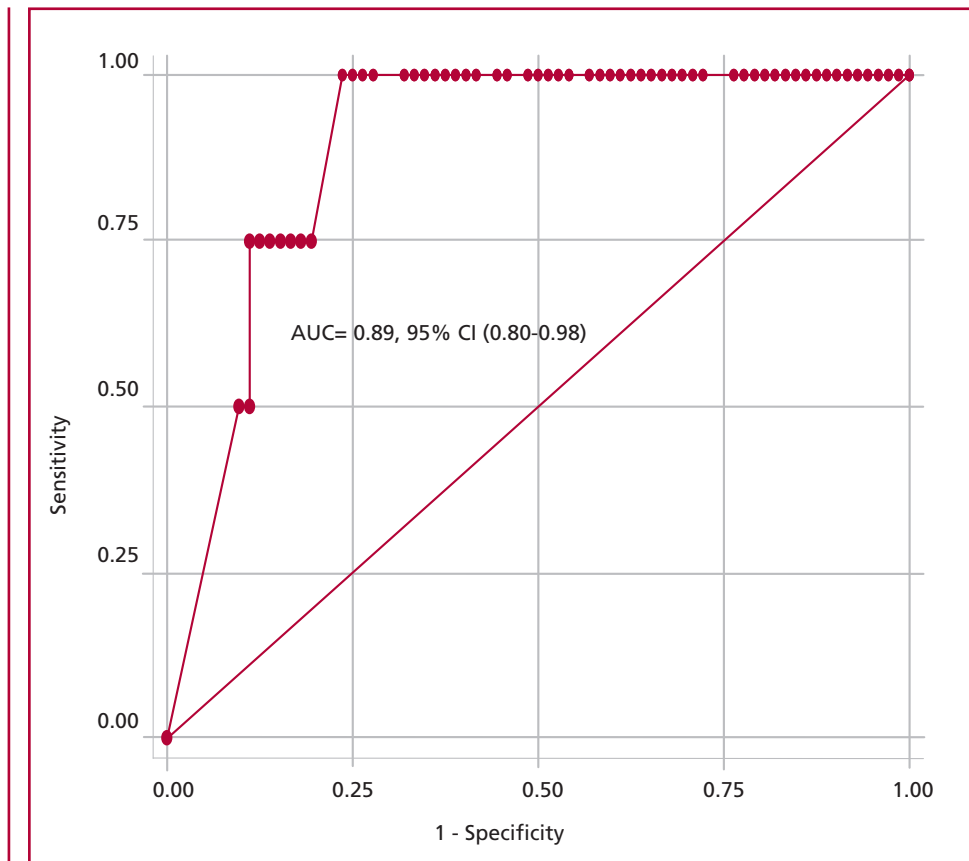
DISCUSSION

hancement had lower EF at admission compared with those who had no enhancement: 36% (35-40) vs. 40% (40-55), p=0.040.

This registry carried out in a single center reflects the usual TS practice in a high complexity hospital. Some findings deserve to be discussed in detail. Compared with international records, the patients in this sample were approximately 12 years older and had more associated CAD. (1, 2, 8) These two aspects pose greater difficulties in TS diagnosis and also have therapeutic implications. In cases in which no diagnostic CA was performed, the patients showed recovery of ventricular function. In this subgroup of patients, the highest proportion of secondary TS (septic shock, subarachnoid hemorrhage, recent major surgery) explains that CA may not provide benefit and may even add morbidity. In other studies, diagnosis of TS has been made omitting the use of CA in these populations. (9, 10)

On the other hand, patients with CAD (2 patients presenting >70% coronary artery lesions), did not show higher in-hospital mortality than the rest. Both in patients in whom CA is not considered (comorbidities or late presentation), as in those who have associated CAD, a high NT-proBNP/UST ratio and the presence of myocardial edema in CMR may favor the

diagnosis of TS. Compared with a sample of patients with AMI from our institution (unpublished data) where the NT-proBNP/UST ratio was 0.60, in this population of patients with TS it was 15. Similarly, the majority of patients who underwent CMR had diffuse myocardial edema. Several studies have reported that the BNP /UST ratio is much higher in TS than in ACS, but most of them have used non-ultrasensitive troponins. (11-14)

As in other registries, shock and secondary TS were associated with higher in-hospital mortality. (1, 15, 16) Moreover, patients with secondary TS presented higher white blood cell count and lower hematocrit (data not shown). NT-proBNP was not only associated with higher mortality in this registry, but also a position document of the European Society of Cardiology proposes to incorporate it as a diagnostic criterion and as high risk marker. (17) There is a remarkable lack of association of troponin with mortality; however, until now there is scarce information with UST in this pathology. Regarding ECG, the findings are similar to those described in the literature (1, 18, 19). The association between normal ECG at admission and higher mortality should be taken with caution since it does not present biological plausibility and is possibly confused by some other variable not analyzed or not measured.

Within the limitations of the study it is worth mentioning that a small sample size and a low rate of events precluded a multivariate model to identify predictors of poor outcome. In addition, given its retrospective nature, it was not possible to accurately establish the time to mechanical and electrical recovery. Finally, the neurological and psychiatric triggers were not coded by a neurologist or psychiatrist specialist.

CONCLUSION

In this single center registry, it was found that patients had more comorbidities and similar mortality than international registries.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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