ORIGINAL ARTICLE

Takotsubo syndrome and chronic kidney disease: a deadly duet in long-term follow-up

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KEY WORDS

chronic kidney disease, mortality, takotsubo syndrome

ABSTRACT

INTRODUCTION The prognosis of takotsubo syndrome (TTS) was recognized as benign. However, patients with TTS and chronic kidney disease (CKD) more often experience severe complications in the acute phase of the disease, particularly sudden cardiac arrest.

OBJECTIVES We aimed to assess the impact of CKD on early and long-term outcomes, including mortality, among 95 patients with TTS.

PATIENTS AND METHODS All patients underwent coronary angiography. Clinical, biochemical, and other medical data were recorded. Estimated glomerular filtration rate was assessed using the CKD-EPI formula.

RESULTS CKD was diagnosed in 32% of the patients. Contrast-induced acute kidney injury (CI-AKI) was not reported in any of the patients. Patients with CKD were older but had a lower prevalence of positive cardiovascular family history as well as higher creatine kinase activity and concentrations of inflammatory parameters. During hospitalization, sudden cardiac arrest was more common in CKD patients. In-hospital, 1-year, and long-term mortality rates were the highest in CKD patients, reaching 33.3% in long-term follow-up. Predictors of death in a multivariate analysis were body mass index, ejection fraction, and serum creatinine concentrations.

CONCLUSIONS CKD is a novel and still underestimated risk factor for TTS. It may trigger TTS but, more importantly, it adversely affects the outcomes. Thus, it is important to assess kidney function in all patients with TTS to evaluate the risk of morbidity and mortality in follow-up, as well as to adjust drug doses and implement preventive measures to avoid CI-AKI when coronary angiography or contrast-enhanced computed tomography is performed.

INTRODUCTION Chronic kidney disease (CKD) is a well-recognized and an independent cardiovascular risk factor.[1-3] First described by Japanese authors in the 1990s, takotsubo syndrome (TTS; also known as takotsubo cardiomyopathy) presents as an acute myocardial infarction, occurs usually in connection with a stressful situation, and is characterized by severe left ventricular dysfunction.[4-6] TTS is observed mainly in women. Generally, patients with TTS have a normal coronary angiogram and left ventricular dysfunction that recovers within days or weeks. The prognosis was recognized as benign, but a few studies have demonstrated that mortality is higher than previously thought.[4,5]

The stress factor triggering TTS may be a mental factor (primary TTS), but also a somatic one (secondary TTS), including either CKD or acute kidney injury (AKI). However, data on the association between kidney function and TTS outcomes are very limited. In recent years, it has been reported that impaired kidney function increases the risk of complications, prolonged hospital stay, and, most importantly, mortality.[7-10]

Considering all the data, the aim of the study was to assess the impact of CKD on early and long-term outcomes, including mortality, in patients with TTS.

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TABLE 1 Comparison of patients with takotsubo syndrome depending on estimated glomerular filtration rate (n = 95) (continued on the next page)

Parameter	EGFR <60 ml/min/1.73 m² (n = 30)	EGFR ≥60 ml/min/1.73 m² (n = 65)	*P* value
Clinical characteristics			
Age, y, mean (SD)	74.8 (10.3)	64.2 (14.5)	<0.005
Female sex, n (%)	26 (86.7)	59 (90.8)	0.54
BMI, kg/m², mean (SD)	25.8 (5.49)	25.9 (4.72)	0.93
Previous myocardial infarction, n (%)	3 (10.0)	1 (1.54)	0.06
History of malignancy, n (%)	1 (3.33)	3 (4.62)	0.77
History of hypertension, n (%)	22 (73.3)	35 (53.8)	0.06
Hyperlipidemia, n (%)	7 (23.3)	28 (43.1)	0.06
Smoking, n (%)	4 (13.3)	16 (24.6)	0.21
Family history of coronary artery disease, n (%)	3 (10)	20 (30)	0.03
Chronic obstructive pulmonary disease, n (%)	4 (13.3)	7 (10.8)	0.72
Anxiety/depression, n (%)	2 (6.67)	6 (9.2)	0.68
Thyroid disorders, n (%)	3 (10)	18 (27.7)	0.05
Hypothyroidism, n (%)	1 (3.33)	7 (10.8)	0.22
Hyperthyroidism, n (%)	0.0	9 (13.8)	0.03
Euthyroid goiter, n (%)	2 (6.67)	2 (3.1)	0.21
Echocardiography			
LVEF on admission, %	39.4 (9.73)	40.1 (10.2)	0.75
LVEF after a mean of 4 days, n (%)	47.2 (10.4)	49.3 (9.86)	0.35
Coronary angiography			
No coronary atherosclerotic lesions, n (%)	7 (23.3)	35 (53.8)	0.005
Insignificant stenoses <50%, n (%)	23 (76.7)	30 (46.2)	0.005
Rhythm on admission			
Sinus rhythm, n (%)	25 (83.3)	63 (96.9)	0.02
Atrial fibrillation, n (%)	4 (13.3)	1 (1.54)	0.02
Pacemaker rhythm, n (%)	1 (3.33)	1 (1.54)	0.58
Conduction disorders			
LBBB, n (%)	3 (10)	1 (1.5)	0.056
ST-segment elevation, n (%)	18 (60)	39 (60)	–
ST-segment depression, n (%)	2 (6.67)	3 (4.62)	0.68
T-wave inversion, n (%)	7 (23.3)	17 (26.2)	0.76
Deep T-wave inversion (after a few days), n (%)	20 (66.7)	56 (86.2)	0.03
QTc interval on admission, ms, mean (SD)	486.4 (38.8)	462.8 (37.3)	0.007
QTc interval after a few days, ms, mean (SD)	488.3 (26.8)	472.9 (96.5)	0.24
Laboratory parameters			
Hemoglobin, g/dl, mean (SD)	13.46 (2.13)	13.30 (1.37)	0.66
White blood cell count, × 10⁹/µl, mean (SD)	10.6 (4.81)	9.33 (3.39)	0.19
Platelet count, × 10³/µl, lmean (SD)	247.2 (105.1)	244.8 (88.3)	0.91
Creatinine, mg/dl, mean (SD)	1.29 (0.39)	0.72 (0.14)	<0.001
EGFR (CKD-EPI), ml/min/1.73 m², mean (SD)	44.9 (11.2)	88.2 (20.8)	<0.001
AST, IU/l, mean (SD)	52.1 (43.7)	46.8 (29.1)	0.55
ALT, IU/l, mean (SD)	28.5 (27.2)	33.3 (38.1)	0.49
CK, IU/l, mean (SD)	806.6 (1590)	269.8 (312.7)	<0.001
CK-MB, IU/l, mean (SD)	45.7 (47.4)	52.0 (81.1)	0.64
Troponin (significant increase), n (%)	27 (90)	50 (76.9)	0.13
Troponin I concentration, ng/ml, mean (SD)	7.56 (17.5)	5.77 (14.19)	0.63
Glycemia on admission, mmol/l, mean (SD)	7.22 (3.17)	6.97 (2.37)	0.71
Total cholesterol, mmol/l, mean (SD)	4.56 (1.06)	4.76 (1.07)	0.38
LDL cholesterol, mmol/l, mean (SD)	2.61 (0.99)	2.95 (0.97)	0.12
HDL cholesterol, mmol/l, mean (SD)	1.41 (0.56)	1.33 (0.41)	0.49

TABLE 1 Comparison of patients with takotsubo syndrome depending on estimated glomerular filtration rate (n = 95) (continued from the previous page)

Parameter	EGFR <60 ml/min/1.73 m² (n = 30)	EGFR ≥60 ml/min/1.73 m² (n = 65)	*P* value
Triglycerides, mmol/l, mean (SD)	2.73 (1.52)	2.48 (1.27)	0.43
Fibrinogen, g/l, mean (SD)	4.81 (2.4)	3.803 (1.02)	0.03
CRP, mg/l, mean (SD)	55.8 (78.6)	21.6 (23.7)	0.03

SI conversion factors: to convert C-reactive protein to nmol/l, multiply by 9.524; hemoglobin to g/l multiply, by 10.0; creatinine to μmol/l, by 88.4; platelet count to $\times 10^9$/μl, by 1.0.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CK, creatine kinase; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; CK-MB, creatine kinase–MB fraction; CRP, C-reactive protein; EF, ejection fraction; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LBBB, left bundle branch block; LDL, low-density lipoprotein; QTc, corrected QT interval

PATIENTS AND METHODS

This was a retrospective study, in which data of 101 patients with a diagnosis of TTS were collected in 5 cardiology centers in Podlasie Province in Poland. In 95 patients, TTS was confirmed according to the Mayo Clinic criteria.[6] There were no exclusion criteria in the study. All the patients were admitted to the invasive cardiology department for coronary angiography due to suspicion of acute myocardial infarction. In all cases, creatinine concentrations were measured on admission and after coronary angiography to check for the presence of contrast-induced AKI (CI-AKI).

CKD (defined as an estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m²) was classified according to Kidney Disease Improving Global Outcomes criteria.[11] For further analyses, patients were divided into 2 groups according to eGFR levels (calculated by the CKD-EPI formula): 30 patients (32%) with eGFR of less than 60 ml/min/1.73 m² and 65 patients (68%) with eGFR of 60 ml/min/1.73 m² or higher. The endpoint was all-cause mortality.

The study protocol was approved by the local ethics committee. Patients gave their written informed consent to participate in the study. The mean follow-up duration was 3.2 years, and its completion was possible owing to the database of Podlaski Urząd Wojewódzki (Podlasie Province Office).

Statistical analysis

Data distribution was tested with the Shapiro–Wilk test. Quantitative data were compared with the *t* test and Mann–Whitney test, and qualitative data were analyzed by the χ^2 test and Fisher exact test. Survival analysis was performed with the Kaplan–Meier method. The multifactor analysis was conducted with the logistic regression method. In the multivariate analysis, factors of significant prognostic importance in patients after acute coronary syndromes were included (age, sex, hypertension, hyperlipidemia, family history, sudden cardiac arrest, body mass index, hemoglobin, creatine kinase, leukocytes, creatinine, and eGFR). A *P* value of less than 0.05 was considered significant. The statistical analysis was performed using the STATISTICA 13.1 program (Tulsa, Oklahoma, United States).

RESULTS

The eGFR values in the study group were as follows: 3% of patients had eGFR values below 30 ml/min/1.73 m² (CKD stage 4); 29%, between 30 and 59 ml/min/1.73 m² (CKD stage 3); 44%, between 60 and 89 ml/min/1.73m² (CKD stage 2); and 24%, of 90 ml/min/1.73 m² or higher (CKD stage 1). The demographic, clinical, and biochemical data of patients are shown in **TABLE 1**. CI-AKI was not observed in any of the patients.

Compared with patients without CKD, those with CKD stages 3 and 4 were older but less often had a positive family history of cardiovascular disease and did not have hyperthyroidism (**TABLE 2**). On coronary angiography, CKD patients more frequently had insignificant coronary atherosclerotic lesions. On electrocardiography, they more often had atrial fibrillation and significantly longer QTc interval on hospital admission, but there was no difference in ST-segment elevation between groups. However, after a few days of hospitalization, pronounced negative T waves were observed less frequently in patients with CKD than in those without. CKD patients had significantly higher creatine kinase activity and concentrations of fibrinogen and C-reactive protein.

During hospitalization, sudden cardiac arrest was diagnosed significantly more frequently in patients with CKD than in non–CKD population. In-hospital, 1-year, and 3-year mortality rates were significantly higher in patients with CKD (**FIGURE 1**).

The pharmacological treatment did not differ significantly between groups. Patients with CKD more often used fondaparinux, whereas acetylsalicylic acid and β-blockers were administered less frequently than in non–CKD population. The remaining data are presented in **TABLE 3**.

In the multivariate analysis in the logistic regression model, the predictors of death were as follows: low body mass index (OR, 0.694; 95% CI, 0.558–0.8630; *P* = 0.001), low left ventricular ejection fraction (OR, 0.889; 95% CI, 0.807–0.980; *P* = 0.02), and elevated serum creatinine levels (OR, 13.813; 95% CI, 1.8–105.9; *P* = 0.01).

DISCUSSION

TTS was first described less than 30 years ago. Its pathomechanism has not yet been fully elucidated. For years, TTS was believed to be a benign disease with favorable outcomes.

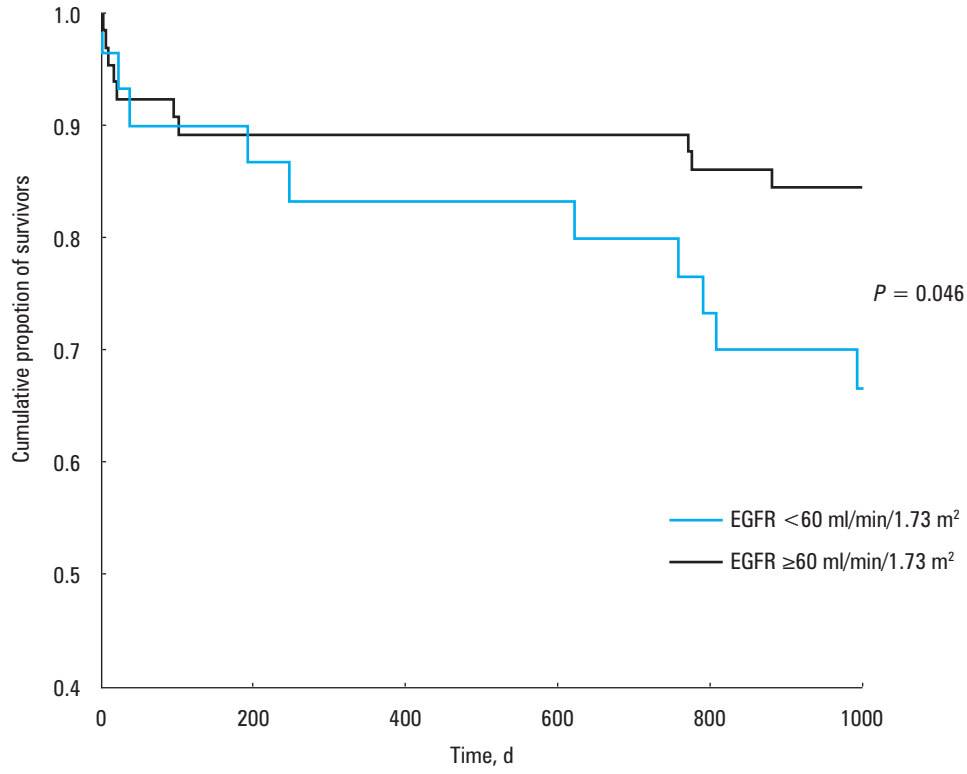

FIGURE 1 Kaplan–Meier survival curves in patients with takotsubo syndrome (n = 95)

TABLE 2 Clinical course of takotsubo syndrome in study groups divided according to estimated glomerular filtration rate

Clinical course		EGFR <60 ml/min/1.73 m² (n = 30)	EGFR ≥60 ml/min/1.73 m² (n = 65)	*P* value
Symptoms on admission				
Retrosternal chest pain, n (%)		24 (80)	55 (84.6)	0.58
Dyspnea, n (%)		3 (10)	7 (10.8)	0.91
Sudden cardiac arrest, n (%)		4 (13.3)	1 (1.5)	0.02
Pulmonary edema, n (%)		2 (6.7)	4 (6.1)	0.91
Cardiogenic shock, n (%)		2 (6.7)	3 (4.6)	0.67
Complications				
Pneumonia, n (%)		7 (23.3)	12 (18.5)	0.59
Respiratory failure, n (%)		4 (13.3)	3 (4.6)	0.13
Urinary tract infection, n (%)		2 (6.7)	2 (3.1)	0.42
Rhythm disturbances, n (%)	Total	2 (6.7)	6 (9.2)	0.68
	Paroxysmal atrial fibrillation	1 (3.3)	5 (7.7)	0.41
	Ventricular tachycardia	1 (3.3)	1 (1.5)	0.57
AKI/CI-AKI, n (%)		0	0	–
Cardiac rupture, n (%)		2 (6.7)	1 (1.5)	0.18
Hospitalization time, d, mean (SD)		5.6 (6.43)	5.2 (3.13)	0.75
Mortality				
In-hospital mortality, n (%)		2 (6.7)	2 (3.1)	0.42
1-year mortality, n (%)		4 (13.3)	7 (10.8)	0.72
3-year mortality, n (%)		10 (33.3)	10 (15.4)	0.047

Abbreviations: AKI, acute kidney injury; CI-AKI, contrast-induced acute kidney injury; others, see TABLE 1

However, a relatively high mortality of patients with TTS in comparison with those with myocardial infarction has been reported recently.[4,5,12]

CKD is the recognized cardiovascular risk factor. It also adversely affects the prognosis of patients with cardiovascular disease.[1,13] In our study, CKD was present in 32% of the patients. Similar data were published by Bill et al,[14] based on data from 114 patients with TTS collected over 12 years. In an Italian registry by Santoro et al,[15]

TABLE 3 Pharmacological treatment of takotsubo syndrome in study groups divided according to estimated glomerular filtration rate

Treatment (pharmacological, IABP)		EGFR <60 ml/min/1.73 m² (n = 30)	EGFR ≥60 ml/min/1.73 m² (n = 65)	*P* value
Heparin	UFH	7 (23.3)	28 (43.1)	0.06
	Enoxaparin	18 (60)	32 (49.2)	0.33
	Fondaparinux	2 (6.67)	0.0	0.03
Nitroglycerin		4 (13.3)	10 (15.4)	0.79
Clopidogrel		27 (90)	51 (78.5)	0.17
ASA		28 (93.3)	65 (100)	0.03
Statin		27 (90)	58 (89.2)	0.91
β-blocker		22 (73.3)	61 (93.8)	0.005
ACEI/ARB		26 (86.7)	59 (90.8)	0.54
ACEI		24 (80)	54 (83.1)	0.71
ARB		2 (6.67)	5 (7.7)	0.86
Calcium channel blocker		3 (10)	5 (7.7)	0.71
Diuretics		17 (56.7)	30 (46.2)	0.34
PPI		22 (73.3)	49 (75.4)	0.83
Catecholamines		5 (16.7)	8 (12.3)	0.56
IABP		1 (3.33)	1 (1.5)	0.57

Data are presented as number (percentage) of patients.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; IABP, intraaortic balloon pump; PPI, proton pump inhibitor; UFH, unfractionated heparin; others, see **TABLE 1**

renal dysfunction (both CKD [19.7%] and AKI [29.5%]) developed in 49% of patients, whereas in a Korean study by Shin et al,[8] 7 of 30 patients with stress-induced cardiomyopathy had renal dysfunction (4 on hemodialysis and 3 with AKI).[16] Other studies on TTS did not assess kidney function, serum creatinine levels, or eGFR.

Of note, mortality in our CKD population with TTS was high and reached 33.3% during long-term follow-up (mean, 3.2 years). CKD proved to be the strongest predictor of mortality, outweighing low left ventricular ejection fraction. Bill et al[14] reported that 5-year mortality was 43.7% for patients with TTS and an eGFR of less than 60 ml/min/1.73m² in comparison with 22.3% for those with an eGFR of 60 ml/min/1.73 m² or higher. However, they found no differences in baseline characteristics between patients with and without kidney dysfunction, no differences in the rates of life-threatening arrhythmias, cardiogenic shock, cardiopulmonary resuscitation, and thromboembolic events. In our study, we presented much more detailed characteristics of patients. Importantly, although CKD patients had a lower prevalence of positive family history of cardiovascular disease, mortality rates were significantly higher at long-term follow-up. In addition, sudden cardiac arrest was more common in the CKD population. All studied patients underwent coronary angiography, but none of them developed CI-AKI. This finding has not been reported by previous studies.[14-17]

Ando et al[16] showed that renal dysfunction in TTS was associated with the development of severe heart failure and ventricular arrhythmias, as well as with higher in-hospital mortality. In their study, 65.5% of patients underwent coronary angiography. Patients with renal dysfunction more frequently required mechanical ventilation, catecholamine administration, intra-aortic ballon contrapulsation or extracorporeal membrane oxygenation. Similar results were obtained by Murakami et al.[17] In the study of Santoro et al,[15] TTS patients with CKD required prolonged hospitalization; in addition, patients with CKD stage 4 had higher mortality rates, more frequent recurrence of TTS, and more frequent hospitalizations for other causes.

It should be emphasized that TTS is no longer considered a benign disease. Both short- and long-term mortality rates are much higher than those in patients with ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI).[18-22] In-hospital mortality of patients with TTS and CKD in our study was 6.7%, while in NSTEMI patients with CKD treated with percutaneous coronary intervention in the United States, the in-hospital mortality rate was only 2%.[18] In patients aged over 75 years with STEMI and CKD, long-term mortality (mean follow-up, 898 days) was 9%, while in the group aged 75 to 85 years, it was 31%.[19] In our study, the mean age of patients with TTS and CKD was 75 years, with female predominance (87%). It was in contrast to the STEMI and NTEMI populations. In Chinese patients with TTS and CKD undergoing primary percutaneous coronary intervention, 30-day mortality was 4.08%, 1-year mortality was 7.95%, and

long-term mortality (mean follow-up, 335 days) was 16.33%, which was comparable with mortality of CKD patients in our study.[20]

Margolis et al[21] reported that long-term mortality (mean follow-up, 1170 days) in STEMI patients with CKD was 17.6%, as compared with 2.7% in patients without CKD. In Polish Registry of Acute Coronary Syndromes, the mortality rate for STEMI patients with CKD was 6.9% at 1 year and 24.5% at 3 years; in the NSTEMI population, the mortality was 6.1% at 1 year and 13.9% at 3 years.[22] It clearly shows that TTS, particularly in patients with impaired kidney function, is a fatal disease.

Both the pathogenesis of TTS and effect of impaired kidney function on the outcomes of TTS patients have not been fully explained so far. It may be speculated that elevated catecholamine concentrations in CKD could contribute to the development of secondary TTS, and it may also have an adverse effect on TTS prognosis.[23,24]

The main limitation of our study is the small number of patients; however, we collected data for all available patients in north-eastern Poland in the last years. Another limitation is the retrospective study design. In an observational study, information about the causes of deaths was not collected, so all-cause mortality was accepted as the main endpoint.

In conclusion, CKD is a novel and still underestimated risk factor for unfavorable TTS outcomes. It may not only be a trigger of TTS, but, more importantly, it has a major adverse impact on prognosis. It should also be stressed that CKD is the strongest predictor of mortality in TTS. Thus, the assessment of kidney function is important in all patients with TTS, not only to assess the risk of short-and long-term morbidity and mortality but also to adjust drug doses and implement preventive measures to avoid CI-AKI when coronary angiography or contrast-enhanced computed tomography is scheduled.

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CONTRIBUTION STATEMENT MZ-A, JM, HB-G, and SD designed the study. MZ-A performed statistical analysis. MZ-A, JM, AT-K, MK, PK, and SD contributed to the interpretation of data. MZ-A and JM drafted the manuscript. All authors edited and approved the final version of the manuscript.

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