G Model
JJCC-1555; No. of Pages 9

ARTICLE IN PRESS

Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Clinical characteristics of patients with Takotsubo syndrome diagnosed without coronary artery evaluation: A retrospective nationwide study

Toshiaki Isogai (MD, MPH)[a,b,*], Hiroki Matsui (MPH)[a], Hiroyuki Tanaka (MD, PhD)[b], Kiyohide Fushimi (MD, PhD)[c], Hideo Yasunaga (MD, PhD)[a]

[a] Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan
[b] Department of Cardiology, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan
[c] Department of Health Policy and Informatics, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 7 June 2017
Received in revised form 8 September 2017
Accepted 15 September 2017
Available online xxx

Keywords:
Takotsubo syndrome
Coronary angiography
Coronary computed tomography angiography
Mortality
Comorbidity

ABSTRACT

Background: Although the current diagnostic criteria require that culprit coronary artery disease be ruled out before the diagnosis of Takotsubo syndrome (TTS) is made, performing coronary artery evaluation (CAE) in patients with serious backgrounds is sometimes challenging.

Methods: We conducted a retrospective cohort study using the Diagnosis Procedure Combination database in Japan. We identified patients in whom TTS was diagnosed at Japanese Circulation Society board-certified teaching hospitals from April 2011 to March 2014 and divided eligible patients into those who underwent CAE (coronary angiography or coronary computed tomography angiography) during hospitalization and those who did not. We compared the patient characteristics and in-hospital mortality between the groups.

Results: TTS was diagnosed in 5274 patients; 3255 (61.7%) underwent CAE and 2019 (38.3%) did not. Patients who did not undergo CAE were older; were more often male; showed higher proportions of an underweight status, impaired activities of daily living, and impaired consciousness; and showed higher proportions of several comorbidities (malignancy: 16.1% versus 5.7%; pneumonia: 15.0% versus 6.7%; and cerebrovascular disease: 13.7% versus 4.0%; all $p < 0.001$) but lower proportions of coronary risk factors than patients who underwent CAE. Multivariable logistic regression analysis showed that older age [adjusted odds ratio: 0.98 (95% confidence interval: 0.97–0.98)], underweight [0.77 (0.65–0.91)], impaired consciousness [0.25 (0.18–0.35)], several comorbidities, and early requirement for surgery [0.13 (0.08–0.21)] were significantly associated with a lower likelihood of undergoing CAE. Crude in-hospital mortality was significantly higher in patients without than with CAE (12.8% versus 4.9%; $p < 0.001$). However, propensity score-matching analysis revealed no significant difference in in-hospital mortality between the two groups (8.8% versus 7.2%; $p = 0.252$).

Conclusions: Among patients diagnosed with TTS, CAE was less likely to be performed in patients with more serious backgrounds. CAE itself may not be associated with in-hospital mortality in patients with TTS.

Introduction

Takotsubo syndrome (TTS) is a unique cardiac disorder characterized by reversible ventricular dysfunction [1,2]. As the clinical presentation of TTS mimics that of acute coronary syndrome (ACS), coronary angiography (CAG) is considered the gold standard for differentiating TTS from ACS [1,2]. Indeed, the current diagnostic criteria require the presence of a culprit coronary artery disease to be ruled out before the diagnosis of TTS is made [2–7]. However, patients occasionally receive the diagnosis of TTS on the basis of clinical findings without coronary artery evaluation (CAE) in real-world clinical practice. Large-scale observational studies in the USA suggested that 35–43% of patients with a diagnosis of TTS received the diagnosis without undergoing CAG [8,9]. However, the clinical characteristics of such TTS patients who did not undergo CAE have been poorly investigated.

* Corresponding author at: Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
E-mail address: toisogai-circ@umin.ac.jp (T. Isogai).

https://doi.org/10.1016/j.jjcc.2017.09.007
0914-5087/© 2017 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.

A substantial proportion of patients develop TTS secondary to acute diseases (e.g. infection or cerebrovascular disease), after surgery, or in the presence of chronic diseases (e.g. malignancy or chronic pulmonary disease) [10–12]. It may be challenging to perform CAG in patients with serious backgrounds due to the invasive nature of the procedure. We therefore aimed to compare the clinical characteristics between patients with TTS who underwent CAE and those who did not in a real-world clinical setting using a large-scale national inpatient database in Japan.

Methods

Study design and data source

This was a retrospective cohort study conducted in Japan using the Diagnosis Procedure Combination (DPC) database, a nationwide inpatient database containing hospital administrative claims information and discharge abstracts. The details of the DPC database and its data have been described elsewhere [12–15]. A unique advantage of the DPC system is that attending physicians are required to provide diagnostic data in abstracts entered throughout each hospitalization until discharge or death [15]. The DPC database includes up to 12 diagnoses, including main diagnosis, admission-precipitating diagnosis, most resource-consuming diagnosis, second most resource-consuming diagnosis, comorbidities already identified on admission, and complications occurring after admission, in its discharge abstracts [14]. The diagnoses are recorded in Japanese text and using International Classification of Diseases, Tenth Revision (ICD-10) codes. Although the database includes data on the timing of laboratory tests, investigations, and interventions [e.g. cardiac biomarkers, electrocardiography, echocardiography, CAG, and coronary computed tomography angiography (CCTA)], the results are not recorded. This study was approved by the Institutional Review Board of The University of Tokyo. The requirement for informed consent was waived due to the anonymous nature of the data.

Patient selection and study setting

We identified TTS cases using both the Japanese text-based diagnosis of TTS and the relevant ICD-10 code (Supplementary Table 1) as in our previous studies [12,13]. We then selected patients admitted for TTS from April 2011 to March 2014. This study did not include patients who developed TTS after admission. We excluded patients who: (i) were aged <20 years, (ii) underwent coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) during hospitalization; (iii) had pheochromocytoma or acute myocarditis; (iv) had a history of myocardial infarction; and (v) were discharged on the day of admission (day 1) or day 2.

Supplementary Table 1 related to this article can be found, in the online version, at doi:10.1016/j.jjcc.2017.09.007.

The Japanese Circulation Society provides two types of board-certification (class A and class B) for hospitals that provide training to physicians seeking board-certification in cardiology [15–17]. In order to focus on patients with TTS who received their diagnosis from experienced cardiologists, this study enrolled only those patients hospitalized at (i) Japanese Circulation Society board-certified teaching institutions; (ii) institutions at which ≥90 patients with acute myocardial infarction were hospitalized during the study period; and (iii) institutions at which ≥3 TTS cases were diagnosed by CAE during the study period.

For the purpose of this study, CAE included CAG and CCTA. All CCTAs identified in this study were performed with a ≥64-slice multi-detector scanner. Eligible patients were classified into two groups: those who underwent CAE during hospitalization [the CAE (+) group] and those who did not [the CAE (−) group].

Baseline variables

We obtained data on the following baseline variables: age, sex, ambulance use, body mass index (BMI), status of activities of daily living, which can be used for calculation of the Barthel Index [18], consciousness level on admission as measured using the Japan Coma Scale [19], comorbidities and coronary risk factors already identified on admission (Supplementary Table 1), initial treatment on day 1, surgery under general anesthesia on day 1 or 2, and hospital characteristics (academic status and type of board-certification). Comorbidities were selected in line with our previous studies (Supplementary Table 1) [12,13]. Initial treatment included inotropic/mechanical circulatory support, mechanical ventilation, renal replacement therapy, and red blood cell transfusion. We also obtained data on when the CAE was performed as well as data on cardiac magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) performed during hospitalization.

Outcomes

The primary outcome was in-hospital all-cause mortality. The secondary outcomes were 30-day in-hospital mortality, 7-day in-hospital mortality, and length of hospital stay. Thirty-day and 7-day in-hospital mortality were defined as in-hospital all-cause deaths within 30 days and 7 days after admission, respectively.

Statistical analyses

Categorical variables are shown as numbers and proportions, and were compared using the Fisher's exact test. Continuous variables are shown as the mean and standard deviation or the median and interquartile range, and were compared using the Student *t*-test or the Mann–Whitney *U* test.

To determine the factors associated with the likelihood of undergoing CAE, we performed a multivariable logistic regression analysis with adjustments for baseline characteristics. To account for within-hospital clustering, we fitted the logistic regression analysis with a generalized estimating equation using a unique hospital identifier as a subject variable. We used multiple imputation and created 20-copy datasets wherein missing data for BMI, Barthel Index, and smoking history were imputed by chained equations [20,21]. We then obtained the pooled results of the odds ratios and their 95% confidence intervals (CIs) from the 20-copy datasets using Rubin's rules [20].

To examine the association between CAE and outcomes after adjusting for baseline characteristics, we performed 1:1 propensity score-matching analysis. The day of CAE varied from early to late during the index hospitalization, and all patients who underwent CAE were alive when CAE was performed (that is, they were "immortal" during the interval from admission to the day of CAE). Thus, we excluded patients who underwent CAE on day 3 or later from this propensity score-matching analysis to avoid immortal time bias [22] [all patients in both the CAE (+) and CAE (−) groups were alive within 2 days after admission due to the eligibility criteria in this study]. We estimated a propensity score for CAE (−) using a logistic regression model including baseline characteristics as covariates. Each patient in the CAE (−) group was matched to one patient in the CAE (+) group with the closest propensity score within a caliper (≤0.20 of the standard deviation of propensity scores) by nearest neighbor matching without replacement. We then compared the outcomes between the CAE (−) and CAE (+) groups in the propensity score-matched cohort.