Peri-operative Takotsubo syndrome after non-cardiac surgery: a retrospective nested case–control study

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Abstract

Aims  Takotsubo syndrome (TTS) is an acute reversible cardiac dysfunction that may occur during the peri-operative period and among patients with serious illness. We aimed to evaluate the clinical characteristics, peri-operative management, and prognosis of peri-operative TTS (pTTS) and explore the factors associated with pTTS.

Methods  We conducted a retrospective nested case–control study using the database of patients who underwent in-hospital non-cardiac surgeries between January 2017 and December 2020 in Peking University Third hospital. Cases were adult patients diagnosed TTS at discharge who were matched with four controls based on operative types. Multivariable conditional logistic regression was used to identify the factors associated with pTTS. The area under the curve (AUC) was used to evaluate the diagnostic efficacy.

Results  Among the 128,536 patients underwent non-cardiac surgery, 20 patients with pTTS and 80 patients without were enrolled in this study. The incidence of pTTS was about 0.016% in our centre. The median age of patients with pTTS was 52.5 (38.25, 76.25) years, although 90% of them were female. Fifty per cent (9 cases) of female patients were pre-menopausal. Caesarean section has the highest proportion of pTTS (30% of the pTTS cases) with the incidence of caesarean section-related pTTS of 0.06% in our centre. A high prevalence of non-apical ballooning pattern of regional wall motion abnormality (seven cases, 35%) and a high mortality (two cases, 10%) were observed. Left ventricular ejection fraction (LVEF) of patients with pTTS was significantly decreased (41.7 ± 8.8%). In the acute phase, supportive treatments aiming to reduce life-threatening complications were main treatment strategies. After receiving systematic treatment, significant improvements were observed in LVEF (63.1 ± 13.5%), with median recovery time of LVEF of 7.48 days. Leucocyte count [odds ratio (OR): 4.59; 95% confidence interval (CI): 1.10–19.15], haemoglobin (HGB) (OR: 10.52; 95% CI: 1.04–106.36), and the revised cardiac risk index (RCRI) score (OR: 6.30; 95% CI: 1.05–37.88) were the factors significantly associated with pTTS. The RCRI score performed poorly in the prediction of pTTS (AUC: 0.630; 95% CI: 0.525–0.735). After adding leucocyte count and HGB into the RCRI score, the AUC was significantly improved (AUC: 0.768; 95% CI: 0.671–0.865; P = 0.001).

Conclusions  Patients with pTTS have some differences compared with common TTS, including higher proportion of pre-menopausal female, higher prevalence during caesarean section, higher prevalence of non-apical ballooning pattern of regional wall motion abnormality, and higher mortality. The RCRI score performed poorly in the evaluation of pTTS. Adding HGB and leucocyte count into the RCRI score could significantly improve its predictive performance.

Keywords  Peri-operative Takotsubo syndrome; Caesarean section; Revised cardiac risk index; Leucocyte; Haemoglobin; Nested case–control study

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**Introduction**

Takotsubo syndrome (TTS), also known as stress cardiomyopathy, has emerged as an important form of acute reversible myocardial injury characterized by transient regional systolic left ventricular (LV) dysfunction, which often leads to circumferential dysfunction of the ventricular segments involved.\(^1\) The presence of acute transient LV regional wall motion abnormalities characteristically extending beyond a single epicardial coronary artery distribution defines the syndrome, which is often triggered by psychological or physiological stress.\(^1,2\) The typical pattern of regional LV wall motion abnormality is the apical hypokinesia (apical ballooning) with basal hyperkinesis.\(^1\) Post-menopausal women are the most vulnerable group.\(^1\)

Surgery is also an important trigger for TTS, which appreciably contributed to the peri-operative adverse cardiac events.\(^3\) Although TTS is usually considered to represent a benign syndrome due to its self-limiting clinical course, there is a substantial risk of mortality, not dissimilar to that of the acute coronary syndrome.\(^4\) The broader scope of surgical trauma, the longer operation time, and the more apparent sympathetic activation that patients encounter, the higher incidence of peri-operative TTS (pTTS) will be.\(^3\) In a number of TTS case series, 3–23% of cases appeared to be triggered or precipitated by surgical procedures.\(^5\) The pTTS was always occurred in the context of surgical, interventional, or anesthetic procedures, which was different from the common TTS that occurred in the context of an acute medical illness or critical condition.\(^6\) The pTTS has some specific clinical features that were different from common TTS. As revealed by the related research results, compared with common TTS cases, patients with pTTS were more commonly male and younger, less likely to have an obvious precipitating factor, and less likely to present with chest pain.\(^5,7\) In addition, pTTS had a lower left ventricular ejection fraction (LVEF) and was prone to higher mortality.\(^5,7\)

TTS occurred in about 2–9/100,000 persons in the general population annually and may occur in up to 1 in 6700 (0.015%) cases during peri-operative period.\(^5\) However, few studies have reported the clinical characteristics of pTTS. In this study, we aimed to evaluate the clinical characteristics, peri-operative management, and prognosis of pTTS and explore the factors associated with pTTS in the setting of non-cardiac surgery.

**Methods**

**Study design**

We conducted a retrospective review of all patients who underwent in-hospital non-cardiac surgeries by a medical record system in the Peking University Third Hospital between January 2017 and December 2020, forming the retrospective cohort. Non-cardiac surgeries contained the operations conducted on organs except for the heart and its appendages (the details were showed in *Table S1*). We then performed a retrospective, nested case–control study using the retrospective cohort among which patients with age younger than 18 years were excluded. The International Classification of Diseases, Tenth Revision (ICD-10), has been used to extract the target population who were diagnosed TTS (I42.8) at discharge. And we used InterTAK Diagnostic Criteria to identify TTS (*Table S2*). Patients were defined as cases if all of the following criteria applied: (i) The age of the individual was over 18 years; (ii) the individual was diagnosed as TTS after surgery.

The control group covered patients who did not develop TTS during the peri-operative period. Patients in the control group underwent 1:4 matching based on the operative type (*Table S1*). All clinical information of patients was collected by the medical record system.

This study was conducted in accordance with the Declaration of Helsinki and with the approval from the ethics committee of Peking University Third Hospital (No. M2018258).

**Data collection**

The following patient information was collected: (i) demographic data including age and gender; (ii) surgical information including classification of operation (endoscopic operation, weekend operation, night-time operation, and emergency operation), anaesthesia method (including local anaesthesia, intrathecal anaesthesia, and general anaesthesia), intra-operative blood loss, blood transfusion (during operation), and operative risk (including high risk, moderate risk, and low risk; *Table S2*); (iii) chronic co-morbidities including cardiac diseases [including chronic heart failure (HF), chronic coronary disease, severe aortic stenosis, severe aortic regurgitation, severe mitral valve stenosis, severe mitral valve regurgitation, atrial fibrillation, and patients with pacemaker/implantable cardioverter defibrillator], hypertension, diabetes mellitus, stroke (haemorrhagic stroke and/or ischaemic stroke), bronchial asthma, chronic kidney disease, and cancer; (iv) laboratory evaluations including leucocyte count, haemoglobin, platelet, alanine aminotransferase, aspartate aminotransferase, serum creatinine, potassium, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, D-dimer, cardiac troponin I (cTnl), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and creatine kinase isoenzyme (CK-MB); and (v) examination results: electrocardiogram (ECG) and echocardiography results.

The revised cardiac risk index (RCRI) score was calculated at the day before surgery. The onset symptoms, ECG performance, and the trend of NT-proBNP, cTnl, and...
echocardiogram results were also collected after the diagnosis of TTS was confirmed.

**Statistical analysis**

Descriptive statistics were done for all variables. Continuous variables conformed to the normal distribution were expressed as the mean ± standard deviation (SD), and t-test was used for comparison between two groups, whereas median (interquartile range) and Wilcoxon tests were used for continuous variables not conform to normal distribution. Categorical variables were presented as percentages with chi-squared test or Fisher’s exact test for comparison between two groups. Univariable conditional logistic regression analysis was performed to investigate the unadjusted association between the case group and the control group. We selected the variables with P < 0.1 in univariate analysis and age (set 65-year-old as cut-off value), which was clinically considered to be closely related to the occurrence of TTS, to be included in multivariate analysis. Conditional logistic regression was used to identify factors associated with pTTS in non-cardiac surgery by estimating odds ratios and 95% confidence intervals (CI). The restricted cubic spline curve was used to evaluate the relationship between continuous variables and pTTS, whereas the receiver operating characteristic (ROC) curve as well as the area under the curve (AUC) were used to evaluate the diagnostic efficacy of continuous variables. The Delong test was used to evaluate whether the difference between the two ROC curves was statistically significant. All analyses were performed using R 4.0.3.

**Results**

**Study population and baseline characteristics**

After the preliminary screening period, 20 out of 128 536 patients undergoing non-cardiac surgery experienced pTTS (0.016%), of which 90% (18 cases) were women. Fifty percent (9 cases) of these female patients were pre-menopausal, and 30% (six cases) occurred during caesarean section. The hospital mortality of pTTS was 10%. The specific screening process was shown in Figure 1.

Patients in the case and the control group were similar in demographic characteristics, with slightly more elderly and female patients in the case group. There was no significant difference between the case and the control group in classification type, operative risk, and anaesthesia methods. Intra-operative bleeding did not have between-group difference, whereas the proportion of blood transfusion in the case group was slightly higher than the control group (30% vs. 12.5%, P = 0.084).

**Factors associated with pTTS**

We used restricted cubic spline curves to evaluate the relationship between continuity variables, including leucocyte count and HGB and pTTS (Figure 2). The results showed that pTTS was positively correlated the increase of leucocyte count, but was negatively correlated with the increase of HGB.

We selected the variables with P < 0.1 in baseline analysis and age, which were clinically considered to be closely related to the occurrence of TTS, to be included in the multivariate analysis. In order to reduce the impact of multicollinearity on the results, we converted the continuity variables into categorical ones. We set 65-year-old as the cut-off value of age because it was reported that the mean age of TTS was about 65 years old. For other consecutive variables, we chose the upper or lower limit of the normal value as the cut-off value. The results of the univariate logistic regression analysis were shown in Table 2, which were similar to those of baseline analysis except for HCT (P = 0.203). Finally, the multiple regression analysis showed that the variables of leucocyte count (>10 × 10⁹/L), HGB (<120 g/L), and the RCRI score (≥1) were independently associated with pTTS for patients who underwent non-cardiac surgery.

**New indicators improved the predictive performance of the RCRI**

The RCRI score was the most widely validated and used model for predicting the risk of cardiovascular events in non-cardiac surgery. Therefore, we calculated every patient’s RCRI score and verified the predictive ability of the model in our population. The results showed that the AUC for the ROC curve of the RCRI score was poor (AUC: 0.630; 95% CI: 0.525–0.735). The AUCs of leucocyte count (AUC: 0.734; 95% CI: 0.597–0.871) and HGB (AUC: 0.644; 95% CI: 0.512–0.777) were both higher than RCRI score, although the difference was not significant. However, after adding leucocyte count and HGB into RCRI score, the AUC was significantly improved (AUC: 0.768, 95% CI: 0.671–0.865; P < 0.05), which meant that these two indicators might help the RCRI score become a superior predictor for the prediction of pTTS. Details were shown in Figure 3.
Clinical manifestation of pTTS

There were 20 patients diagnosed as pTTS, among whom two patients (10%) died. One patient died of ventricular fibrillation, and the other died of severe HF. Among all the operative types, caesarean section had the highest proportion (6; 30%). During the study period, 9852 caesarean sections were performed in our centre, with the incidence of caesarean section-related pTTS of 0.06%. The median time of onset was 1 day after operation, and so was the median diagnosed time. The most common symptoms at onset were dyspnoea (10; 50%) and chest pain (5; 25%), whereas other patients (5; 25%) were sedated at the time of onset with no chief complaint. ECG tests showed that five of 20 patients had T-wave inversion, while 10% (2 cases) of patients had anterior wall ST-segment elevation. Fifty per cent (10 cases) patients had no ST-T changes. Atrial fibrillation occurred in 15% (three cases) of patients, ventricular tachycardia occurred in 10% (two cases) of patients, and ventricular fibrillation occurred in 5% (one case) of patients, respectively (Table 3).

The pTTS was often accompanied by an increase in myocardial injury biomarkers. Our results indicated that NT-proBNP increased significantly in patients with pTTS, whereas cTnI and CK-MB were slightly increased, respectively. The level of NT-proBNP peaked on the first day after symptom onset and then began to decline rapidly. With respect to cTnI and CK-MB, they peaked on the day after the onset of symptoms and decreased rapidly (Figure 4).

All patients had normal preoperative LVEF (mean ± SD: 67.8 ± 2.9%). LVEF decreased in 90% (18 cases) of patients (mean ± SD: 41.7 ± 8.8%), whereas LV end-diastolic diameter was not increased significantly (mean ± SD: 45.95 ± 3.44 mm). The mean degree of decline in LVEF was 38.5% (SD: 9.8%). The most common type of anatomical variant was apical ballooning, which accounted for 65% (13 cases) of TTS patients in this study. Basal type and mid-ventricular type accounted...
Table 1 Baseline characteristics of study population

| Variable                                      | Control group (n = 80) | pTTS group (n = 20) | P value |
|-----------------------------------------------|------------------------|---------------------|---------|
| Age (years)                                   | 42.5 (36, 61.25)       | 52.5 (38.25, 76.25) | 0.186   |
| Gender (female, %)                            | 59 (74%)               | 18 (90%)            | 0.212   |
| Medical history                               |                        |                     |         |
| Basic cardiac disease (%)                     | 6 (70%)                | 3 (15%)             | 0.541   |
| Coronary artery disease (%)                   | 3 (4%)                 | 1 (5%)              | 1.000   |
| HF (%)                                        | 0 (0%)                 | 1 (5%)              | 0.451   |
| AF (%)                                        | 1 (1%)                 | 0 (0%)              | 1.000   |
| HT (%)                                        | 21 (26%)               | 6 (3%)              | 0.955   |
| DM (%)                                        | 9 (11%)                | 4 (2%)              | 0.503   |
| Insulin use (%)                               | 1 (1%)                 | 2 (10%)             | 0.187   |
| Stroke (%)                                    | 2 (3%)                 | 2 (10%)             | 0.372   |
| CKD (%)                                       | 4 (5%)                 | 2 (10%)             | 0.752   |
| Malignancy (%)                                | 9 (11%)                | 4 (20%)             | 0.503   |
| Asthma (%)                                    | 1 (1%)                 | 0 (0%)              | 1.000   |
| Endoscopic operation (%)                      | 13 (16%)               | 5 (25%)             | 0.558   |
| Weekend operation (%)                         | 15 (19%)               | 4 (20%)             | 1.000   |
| Nocturnal operation (%)                       | 13 (16%)               | 6 (30%)             | 0.279   |
| Emergency operation (%)                       | 25 (31%)               | 10 (50%)            | 0.190   |
| Intra-operative bleeding (mL)                 | 98 (10 202)            | 83 (10 350)         | 0.489   |
| Blood transfusion (%)                         | 6 (30%)                | 10 (12.5%)          | 0.084   |
| Classification of operative risk (%)          |                        |                     | 0.592   |
| High cardiac risk                             | 28 (35%)               | 7 (35%)             |         |
| Moderate cardiac risk                         | 44 (55%)               | 11 (55%)            |         |
| Low cardiac risk                              | 8 (10%)                | 2 (10%)             |         |
| Anaesthesia (%)                               |                        |                     | 0.278   |
| Local anaesthesia                             | 12 (15%)               | 3 (15%)             |         |
| Intra-spinal anaesthesia                      | 26 (33%)               | 3 (15%)             |         |
| General anaesthesia                           | 42 (52%)               | 14 (70%)            |         |
| Medications (%)                               |                        |                     |         |
| ACEi/ARB                                      | 5(6.3%)                | 1(5%)               | 1.000   |
| Beta blocker                                  | 3(3.8%)                | 2(10%)              | 0.261   |
| Calcium channel blocker                       | 9(11%)                 | 2(10%)              | 1.000   |
| Metformin                                     | 3(3.8%)                | 2(10%)              | 0.261   |
| Statin                                        | 4(5%)                  | 0(0%)               | 0.581   |
| Laboratory test                               |                        |                     |         |
| Leucocyte (10⁹/L)                             | 7.43 (5.84, 8.56)      | 9.27 (7.88, 14.36)  | 0.001*  |
| Haemoglobin (g/L)                             | 128 ± 18               | 117 ± 20            | 0.041*  |
| Haematocrit                                   | 0.38 (0.35, 0.43)      | 0.36 (0.32, 0.39)   | 0.046*  |
| Platelet (10⁹/L)                              | 228 (172, 276.5)       | 235.5 (168, 254.75) | 0.846   |
| Alanine aminotransferase (U/L)                | 14 (11, 25)            | 17.5 (8.75, 24)     | 0.935   |
| Aspartate aminotransferase (U/L)              | 19 (16,25)             | 22 (14,29)          | 0.604   |
| Lactate dehydrogenase (U/L)                   | 188 (174.75, 206)      | 194.5 (179, 220.25) | 0.384   |
| Blood urea nitrogen (mmol/L)                  | 4.27 (3.72, 5.3)       | 5.15 (3.97, 6.18)   | 0.108   |
| Serum creatinine (µmol/L)                     | 62 (52.75, 77)         | 61 (48.5, 76)       | 0.477   |
| Estimated glomerular filtration rate (mL/min/1.73m²) | 99 (89.75, 116.5) | 98.5 (81.75, 112.5) | 0.793   |
| Cholesterol (mmol/L)                          | 4.89 (4.11, 6.33)      | 4.74 (4.49, 7.23)   | 0.599   |
| High-density lipoprotein (mmol/L)             | 1.27 (1.14, 1.51)      | 1.23 (1.13, 1.39)   | 0.425   |
| Low-density lipoprotein (mmol/L)              | 2.89 ± 0.84            | 2.89 ± 0.73         | 0.963   |
| Hs-CRP (mg/L)                                 | 3.04 (1.09, 4.81)      | 5.98 (3.76, 9.19)   | 0.003*  |
| Potassium (mmol/L)                            | 3.98 (3.84, 4.27)      | 3.93 (3.7, 4.03)    | 0.148   |
| Glucose (mmol/L)                              | 5.3 (4.6, 6.06)        | 5.62 (5.17, 6.28)   | 0.299   |
| Fibrinogen (g/L)                              | 3.53 ± 0.94            | 3.45 ± 1.23         | 0.766   |
| D-dimer (µg/mL)                               | 0.8 (0.41, 1.88)       | 2.22 (0.7, 4.62)    | 0.010*  |
| Creatine kinase isoenzyme (U/L)               | 9 (7, 11)              | 8.05 (5.75, 13.01)  | 0.986   |
| Echocardiography                              |                        |                     |         |
| Left atrial area (mm²)                        | 17 (16, 18.25)         | 17.5 (16.75, 18)    | 0.538   |
| LVEDD (mm)                                    | 46.45 (45.08, 48.35)   | 45.95 (44.98, 47.28) | 0.236   |
| LVESD (mm)                                    | 28 (26.67, 29.22)      | 28 (26.9, 28.55)    | 0.727   |
| Sm (cm/s)                                     | 11 (10, 12)            | 11.5 (11, 12)       | 0.343   |
| Em (cm/s)                                     | 12 (11, 14)            | 11 (9, 13.25)       | 0.367   |

(Continues)
for 20% (four cases) and 15% (three cases) of patients with pTTS, respectively. The median time for recovery of LVEF was 7.48 days (Table 3). It was noteworthy that there was no statistical difference in the incidence of pTTS in pre-menopausal female patients between the case group and the control group (50% vs. 42.4%, P = 0.765), which indicated that pTTS was also common in post-menopausal women (Figure 5).

**Treatments for pTTS**

In the acute phase, supportive treatments aiming to reduce life-threatening complications were mainly current treatment strategies. The main medication treatment options included vasopressors (14; 70%), cardiac inotropes (6; 30%), diuretics (18; 90%), nitrate esters (18; 90%), and beta-blockers (10; 50%). Nineteen (95%) patients were treated with varying degrees of analgesic and sedative treatments. Fourteen (70%) patients were performed with mechanical ventilation, one case with intra-aortic balloon pumping (IABP), one case with extracorporeal membrane oxygenation (ECMO), and five cases with continuous renal replacement therapy. Twenty patients (100%) received antibiotics for therapeutic or preventive strategies. In the stable stage, eight patients (40%) were prescribed with beta-blocker, and six patients (30%) with anti-anxiety and depression drugs. Details were outlined in Table 4.

**Discussion**

Cardiovascular complications are the most important causes of mortality in patients who underwent non-cardiac operation. In previous studies, the major adverse cardiac events (MACEs) broken out in peri-operative period usually referred to acute myocardial infarction, HF, and sudden cardiac death.
And our study showed that pTTS was another adverse cardiovascular event that could not be ignored. Our study showed that the incidence of pTTS in our centre was about 1/6400. This is similar to the incidence of 1/6700 predicted in the review by Hessel, but somewhat higher than 1/15000 reported by Garcia Guzzo et al. However, according to our clinical experience, the incidence rate of pTTS may be under-estimated. Firstly, we used ICD-10 to extract the target population who were diagnosed TTS (I42.8) at discharge, which was likely to under-estimate its incidence rate. Secondly, there was no agreement on the diagnostic criteria of pTTS. Mayo Clinic diagnostic criteria, Heart Failure Association of the European Society of Cardiology diagnostic criteria for Takotsubo syndrome, and the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) are the commonly used diagnostic criteria for TTS. The Mayo Clinic diagnostic criteria regarded existence of coronary heart disease as one of the exclusion criteria. However, our study found that 5% of patients were complicated with coronary artery diseases, which was consistent with the results of previous studies. Therefore, we used InterTAK Diagnostic Criteria as diagnostic criteria for pTTS.

There were many clinical manifestations of pTTS, varying from acute HF to sudden cardiac death. Our study showed that five of 20 (25%) sedated patients suffered from pTTS, emphasizing the importance of peri-operative management. The diagnosis can be missed, and the patient can be mismanaged because of insufficient knowledge. Considering the tremendous harm (two of 20 patients in the case group died), precise measures for preoperative identification of patients at risk for pTTS are essential in clinical routine. To our knowledge, there is no comprehensive study incorporating TTS into MACEs or describing its clinical features in non-cardiac operation. Moreover, the clinical factors associated with pTTS were not mentioned in the previous study, which were of great importance for the evaluation of pTTS before non-cardiac operation. Our study found that there was a significant relationship between leucocyte counts, as well as HGB levels, and pTTS.

Although the exact pathophysiological mechanisms remained unclear, acute cardiac sympathetic eruption and noradrenaline seethe and spillover were proposed to play an important role in causing TTS in predisposed patients. Circulating inflammatory factors were causally involved in the sympathetic activation. Stress response on the non-cardiac surgery, such as haemorrhage, dehydration, trauma, and traction of organs and the nerves system, were always accompanied with significant immunomodulatory and inflammatory changes, resulting in sympathetic disruption or excessive surge of noradrenaline that might cause life-threatening cardiovascular complications. It was reported that high levels of leucocyte counts, natural killer cells, and classical and intermediate monocytes, as well as reduced levels of non-classical monocytes and regulatory T cells, were correlated with MACEs and had the ability to

### Table 2 Univariate and multivariate logistics regression of related factors

| Variables                  | Univariate logistics regression | Multivariate logistics regression |
|----------------------------|---------------------------------|----------------------------------|
|                           | OR                              | 98% CI                           | P value | OR                              | 95% CI                           | P value |
| Age (>65 years)           | 1.86                            | 0.61–5.63                        | 0.274   | 1.31                            | 0.33–5.17                        | 0.698   |
| Leucocyte (>10 × 10⁹/L)   | 5.26                            | 1.70–16.31                       | 0.004*  | 4.59                            | 1.10–19.15                       | 0.036*  |
| HGB (<120 g/L)            | 0.97                            | 0.95–0.99                        | 0.033*  | 10.52                           | 1.04–106.36                      | 0.046*  |
| Haematocrit (<0.35)       | 2.00                            | 0.69–5.78                        | 0.203   | 0.64                            | 0.16–2.56                        | 0.526   |
| Hs-CRP (>3 mg/L)          | 2.85                            | 0.95–8.60                        | 0.062   | 0.74                            | 0.18–3.04                        | 0.740   |
| D-dimer (>1 μg/mL)        | 3.10                            | 1.11–8.62                        | 0.031*  | 2.48                            | 0.71–8.60                        | 0.154   |
| Blood transfusion         | 3.00                            | 0.94–9.60                        | 0.064   | 2.25                            | 0.54–9.42                        | 0.267   |
| RCRI (≥1)                 | 11.00                           | 2.46–49.22                       | 0.002*  | 6.30                            | 1.05–37.88                       | 0.044*  |

HGB, haemoglobin; h<sub>s</sub>-CRP, high-sensitivity C-reactive protein; RCRI, revised cardiac risk index. *P values that indicate significant differences (P < 0.05) between pTTS and control group.
MACEs after non-cardiac surgery. HGB level was an independent related factor.

HGB can cause tissue ischaemia and hypoxia. Hypoxia was a potent stimulus to the cardiopulmonary system in humans that can increase sympathetic nerve activity. In addition, the elevation in sympathetic outflow can persist up to 1 h beyond the period of exposure.\textsuperscript{22,23}

The RCRI score was the most commonly used prediction model of peri-operative MACEs, which was recommended by the current guidelines.\textsuperscript{24,25} Our study showed that the performance of the RCRI score was poor in the evaluation of pTTS (AUC: 0.630; 95% CI: 0.525–0.735). However, after adding HGB and leucocyte count to the RCRI score, the performance of the model was significantly improved (0.768, 95% CI: 0.671–0.865; \(P < 0.05\) compared with RCRI). Therefore, our study suggested that HGB and leucocyte count might become cost-effective predictors of pTTS in the setting of non-cardiac surgery.

The median time of onset of pTTS was the first day after operation in our study. Post-emergence can be a particularly vulnerable period due to intravascular volume expansion on anaesthetic withdrawal and acute increases in intrathoracic pressure with coughing.\textsuperscript{3} The culmination can cause elevated ventricular filling pressures and acute pulmonary oedema, which can rapidly lead to clinical deterioration in susceptible patients. Hypertensive crisis occurring during this period can also precipitate pTTS. Therefore, vigilance to quickly identify physiologic disturbance and consideration for pTTS as a differential diagnosis are the key issues.

In our study, although most of the patients in the event group were women, the only two male patients underwent pTTS died, indicating that the mortality rate of male patients with pTTS might be higher than that of female patients. This was confirmed by a cohort study including 24 701 patients with TTS in which male patients had a higher mortality rate than females (8.4% vs. 3.6%, \(P < 0.001\)).\textsuperscript{26} Hessel reviewed 131 patients with pTTS, and the results showed that compared with non-peri-operative cases, this population involved more males (20 vs. 80%).\textsuperscript{3} The age of pTTS was also significantly lower than that of common TTS.\textsuperscript{27} There were other researches showed that emotional stress or the absence of identifiable triggers was more common in women, whereas a physical stressful triggering event such as surgical procedures,\textsuperscript{5} shock, or resuscitation on presentation was more common in men.\textsuperscript{6}

It was worth noting that caesarean section had the highest percentage (6; 30%) among all types of non-cardiac surgeries of patients who suffered pTTS. A narrative review including 131 pTTS cases also showed that caesarean section, accounting for 13% in all surgeries, was one of the most common surgical procedures, which was second only to gastrointestinal (16%) and orthopaedic (15%) surgeries.\textsuperscript{5} In another systematic review of 102 cases of pTTS, Agarwal \textit{et al.} reported that 12% of their cases were associated with caesarean section.\textsuperscript{27} Currently, there were still few cases of TTS after caesarean section reported in the literature.\textsuperscript{28}

Previous studies have shown that TTS had a strong susceptibility for post-menopausal women,\textsuperscript{1} which meant that age and gender may be important risk factors for the

Table 3 Clinical manifestation of pTTS

| Features | Description |
|----------|-------------|
| Symptoms (%) | Dyspnoea 10 (50%) | Chest pain 5 (25%) |
| Electrocardiogram (%) | Anterior wall ST segment elevation 2 (10%) | Anterior wall ST segment depression 1 (5%) |
| | Inferior wall ST segment elevation 1 (5%) | Inferior wall ST segment depression 1 (5%) |
| | T-wave inversion 5 (25%) |
| Arrhythmia (%) | Ventricular fibrillation 1 (5%) | Ventricular tachycardia 2 (10%) |
| | Atrial fibrillation 3 (15%) |
| Laboratory test\textsuperscript{4} | NT-proBNP (pg/mL) 19 772 (9630, 28 211) | Cardiac troponin I (μg/L) 0.71 (0.11, 2.24) |
| | Creatine kinase isoenzyme (U/L) 50.5 (17.5, 107.5) |
| Echocardiography | LAA (mm\textsuperscript{2}) 19.4 ± 4.8 | LVESD (mm) 45.95 ± 3.44 |
| | LVEDD (mm) 35.88 ± 5.15 | Sm (cm/s) 9 (7, 11) |
| | Em (cm/s) 9.5 (7.8, 12.3) | LAP (mmHg) 10.5 (8.8, 13.3) |
| | LVEF (%) 41.7 ± 8.8 |
| TTS type\textsuperscript{6} | Basal type (%) 4 (20%) | Mid-ventricular type (%) 3 (15%) |
| | Apical type (%) 13 (65%) |
| Clinical features | Post-operative onset time of pTTS (days) 1.00 (0.75, 1.25) | Post-operative diagnosis time of pTTS 1.00 (1.00, 2.25) |
| | Recovery time of LVEF (days) 7.48 (5.75, 10.00) | LVEF before operation (%) 67.8 ± 2.9 |
| | LVEF after operation (%) 41.7 ± 8.8 | LVEF recovery (%) 63.1 ± 13.5 |
| | The degree of decline in LVEF (%) 38.5 ± 9.8 |

Em, peak motion velocity in early diastolic mitral annulus; LAA, left atrial area; LAP, left atrial pressure; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NT-proBNP: N-terminal pro-B-type natriuretic peptide; pTTS, peri-operative Takotsubo syndrome; Sm, peak systolic mitral annulus velocities. Values are mean ± standard deviation, n (%), or median (interquartile range).

\textsuperscript{4}The test results were collected at first time after onset of symptoms.

\textsuperscript{5}Classification is based on echocardiographic imaging.

Predict cardiovascular events in peri-operative period. Our study further confirmed that leucocyte counts were of great significance in predicting pTTS, with leucocyte counts over \(10 \times 10^7/L\) being an independent related factor.

We also found that HGB had a negative correlation with pTTS. This result was consistent with previous studies, which have shown that lower HGB values were associated with MACEs after non-cardiac surgery.\textsuperscript{20,21} HGB level was an indirect measure of oxygen-carrying capacity, whereas decreased HGB can cause tissue ischaemia and hypoxia. Hypoxia was a potent stimulus to the cardiopulmonary system in humans that can increase sympathetic nerve activity. In addition, the

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pathogenesis of this disease. This may be explained by the cardio-protective effects of oestrogen against catecholamine-induced stress through modulation of cardiac contractility and calcium uptake.29,30 However, TTS has been observed in post-menopausal women despite hormone replacement therapy,31 and an explanation for the low incidence of the disease in males is lacking, indicating our current understanding is incomplete. Similarly, in our study, although the female patients accounted for a considerable proportion in pTTS group (18; 90%), there were no statistical difference in the median of age and the ratio of female between the pTTS group and the control group. And we also found no statistical difference in the proportion of post-menopausal women between the pTTS group and the control group. Hence, age, gender, and menopausal status may not be mandatory features for the onset of pTTS. Ruling out the diagnosis of TTS completely for the patients who lack the above risk factors is inappropriate. The established point of view that TTS has relative preponderance among post-menopausal women may need to be reconsidered in the context of peri-operative non-cardiac operation. The youth and middle-aged perinatal women who underwent non-cardiac surgery could also suffer the risk of having pTTS.

Table 4  Treatment for pTTS

| Treatment measures                  | Description |
|-------------------------------------|-------------|
| Medication (%)                      |             |
| Vasopressorsa                        | 14 (70%)    |
| Cardiac inotropesb                   | 6 (30%)     |
| Diuretic                             | 18 (90%)    |
| Nitrate esters                      | 10 (50%)    |
| Beta blocker                         | 10 (50%)    |
| Trinoin                              | 2 (10%)     |
| Calcium gluconate                    | 14 (70%)    |
| Intravenous analgesic and sedative drug | 19 (95%) |
| Potassium chloride                   | 19 (95%)    |
| Vitamin C                            | 17 (95%)    |
| Mechanical circulatory support (%)   |             |
| Intra-aortic balloon pump            | 1 (5%)      |
| Extracorporeal membrane oxygenation  | 1 (5%)      |
| Mechanical ventilation (%)           | 14 (70%)    |
| Oxygen therapy (%)                   | 14 (70%)    |
| Continuous renal replacement therapy (%) | 5 (25%)   |
| Mechanical ventilation (%)           | 14 (70%)    |
| Oxygen therapy (%)                   | 14 (70%)    |
| Continuous renal replacement therapy (%) | 5 (25%)   |
| Antiepileptic (a)                    | 14 (70%)    |
| Intravenous analgesic and sedative drug | 19 (95%) |
| Potassium chloride                   | 19 (95%)    |
| Vitamin C                            | 17 (95%)    |
| Mechanical circulatory support (%)   |             |
| Intra-aortic balloon pump            | 1 (5%)      |
| Extracorporeal membrane oxygenation  | 1 (5%)      |
| Mechanical ventilation (%)           | 14 (70%)    |
| Oxygen therapy (%)                   | 14 (70%)    |
| Mechanical ventilation (%)           | 14 (70%)    |
| Oxygen therapy (%)                   | 14 (70%)    |
| Continuous renal replacement therapy (%) | 5 (25%)   |
| Antiepileptic (a)                    | 14 (70%)    |
| Intravenous analgesic and sedative drug | 19 (95%) |
| Potassium chloride                   | 19 (95%)    |
| Vitamin C                            | 17 (95%)    |
| Treatment for stable phasec (%)      |             |
| Beta blocker                         | 8 (40%)     |
| Diuretic                             | 6 (30%)     |
| Antibiotics                          | 20 (100%)   |
| Intraocular nutritional support       | 13 (65%)    |
| Proton pump inhibitor                | 15 (75%)    |
| Treatment for stable phasec (%)      |             |
| Beta blocker                         | 8 (40%)     |
| Diuretic                             | 6 (30%)     |
| Antibiotics                          | 20 (100%)   |
| Intraocular nutritional support       | 13 (65%)    |
| Proton pump inhibitor                | 15 (75%)    |
| Treatment for stable phasec (%)      |             |
| Beta blocker                         | 8 (40%)     |
| Diuretic                             | 6 (30%)     |
| Antibiotics                          | 20 (100%)   |
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| Antibiotics                          | 20 (100%)   |
| Intraocular nutritional support       | 13 (65%)    |
| Proton pump inhibitor                | 15 (75%)    |
| Treatment for stable phasec (%)      |             |
| Beta blocker                         | 8 (40%)     |
| Diuretic                             | 6 (30%)     |
| Antibiotics                          | 20 (100%)   |
| Intraocular nutritional support       | 13 (65%)    |
| Proton pump inhibitor                | 15 (75%)    |
However, it should be noted that our result was based on a relatively small sample size, and we will further verify it in the cohort study.

The management of pTTS remains challenging, and there are no randomized clinical trials on specific therapeutic strategies of pTTS. Many authors have emphasized the importance of avoiding psychological stress in the peri-operative period by use of psychological and pharmacologic approaches, including pre-operative deep anxiolysis, adequate level of anaesthesia during the procedure, optimal post-operative analgesia and sedation, and administration of prophylactic beta-adrenergic blocking agents. Templin et al. reported that at the time of initial episode of TTS, 18–32.5% of all types of patients who developed TTS were receiving beta-blockers. In our study, 2/20 patients used beta-blockers before operation. Although there is currently no evidence that beta-blockers were beneficial, abrupt withdrawal of adrenergic blockers may precipitate TTS. Therefore, it would seem prudent not to discontinue indicated beta-blocker therapy.

Given the reversible process of cardiac injury associated with TTS, the interim management focuses on supportive care and prevention of severe complications. Overall, the treatment results of pTTS patients in our centre were obvious. Table 4 showed a list of therapy options of our centre regarding treatment in pTTS patients, which may provide some experiences of the peri-operative management of pTTS.

There were several limitations to our study. This study was nested in a large cohort; some unknown confounding factors could have introduced a bias, even after matching for known risk factors. And as a single-centre retrospective cohort, the results may be influenced by clinical practices that were different from other institutions. The limited number of event groups who suffered TTS may indicate that some patients might be missed due to insufficient clinical data.

Conclusions

Our study found that the incidence of pTTS was about 0.016%. Fifty per cent of the female patients were pre-menopausal. High prevalence during caesarean section (30% of the cases), high prevalence of non-apical ballooning pattern of regional wall motion abnormality (35%), and high mortality (10%) were observed, confirming the results from previous studies. The RCRI score performed poorly in the evaluation of pTTS. Pre-operative HGB (<120 g/L) and leucocyte count (>10 × 10^9/L) were factors significantly associated with pTTS in patients undergoing non-cardiac surgery. Adding HGB and leucocyte count into the RCRI score could significantly improve the performance of the RCRI score.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The classification of operative type.

Table S2. International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria).

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