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Article

Risk Factors for Early HALT after Transfemoral TAVI

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Abstract

Objective: To investigate the risk factors of hypoattenuated leaflet thickening (HALT) in the early stage after transfemoral transcatheter aortic valve implantation (TAVI). **Methods**: Patients who underwent transfemoral TAVI in the Affiliated Hospital of Qingdao University from January 2021 to June 2023 were selected. According to the results of four-dimensional computed tomography (4DCT), patients were divided into HALT group and non-HALT group. The perioperative data of the two groups were collected to find the risk factors of HALT in the early postoperative period. **Results**: A total of 100 patients underwent TAVI operation via femoral artery, 2 died after operation, 1 discharged due to cerebral complication, and 2 patients had incomplete 4DCT data. The data of 95 patients were completely collected, including 56 males and 39 females, with an average age of (72.0 $\pm$ 6.7) years and a body mass index of (24.0 $\pm$ 3.7) kg/m^2. 10 patients had HALT, the incidence was 10.5%. 85 patients were in the non-HALT group, including 52 males (61.2%). 10 patients were in the HALT group, 4 cases were male (40%). There were no significant differences in age, sex, body mass index (BMI), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), brain complications, coronary heart disease, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF) and operation time between the two groups. And the differences between the two groups in perioperative white blood cell, neutrophil, lymphocyte and platelet counts, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and creatinine were not significant. Compared with the non-HALT group, patients in the HALT group had a higher proportion of isolated aortic insufficiency, a lower proportion of post dilatation after valve release, and a higher proportion of valves with skirts. **Conclusion**: Isolated aortic insufficiency, without post dilatation after valve release, and use of valves with skirt are associated with early HALT after transfemoral TAVI.

Keywords

transcatheter aortic valve implantation; hypoattenuated leaflet thickening; computed tomography

Introduction

Since 2002, when Cribier *et al.* [1] first used transcatheter aortic valve implantation (TAVI) for high-risk aortic stenosis patients, this technology has gained rapid popularity and development all over the world in the past 20 years. Subclinical leaflet thrombosis (SCLT) after TAVI was reported in a case report in 2013 [2]. Now studies show SCLT is a common phenomenon after TAVI, which manifests as hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM or RELM) on the four-dimensional computed tomography (4DCT) [2,3]. And HALT and RLM are different stages of the same phenomenon, which may accelerate valve dysfunction [4]. There is still debate about the impact of HALT on valve hemodynamics, durability, and clinical outcomes [5]. Meta-analysis showed that clinical leaflet thrombosis or SCLT was not associated with an increased risk of death. However, patients with clinical valve thrombosis have a higher risk of stroke [6]. Chakravarty *et al.* [7] showed that valve thickening may be associated with an increased risk of transient ischemic attack (TIA). Makkar *et al.* [8] found that HALT did not have any significant association with individual end points of death, myocardial infarction, or stroke, but did see an association with an increased incidence of combined thromboembolic events of stroke, TIA, and retinal artery occlusion. Furthermore, studies showed there is a relationship between valve thrombus and early calcification and degeneration of valves [9], and HALT/RLM also represents a potential mechanism of biological valve degeneration [4]. It was reported that the rate of SCLT formation after TAVI was 15%, and the rate of clinical valve thrombosis was 3% [10]. Many factors

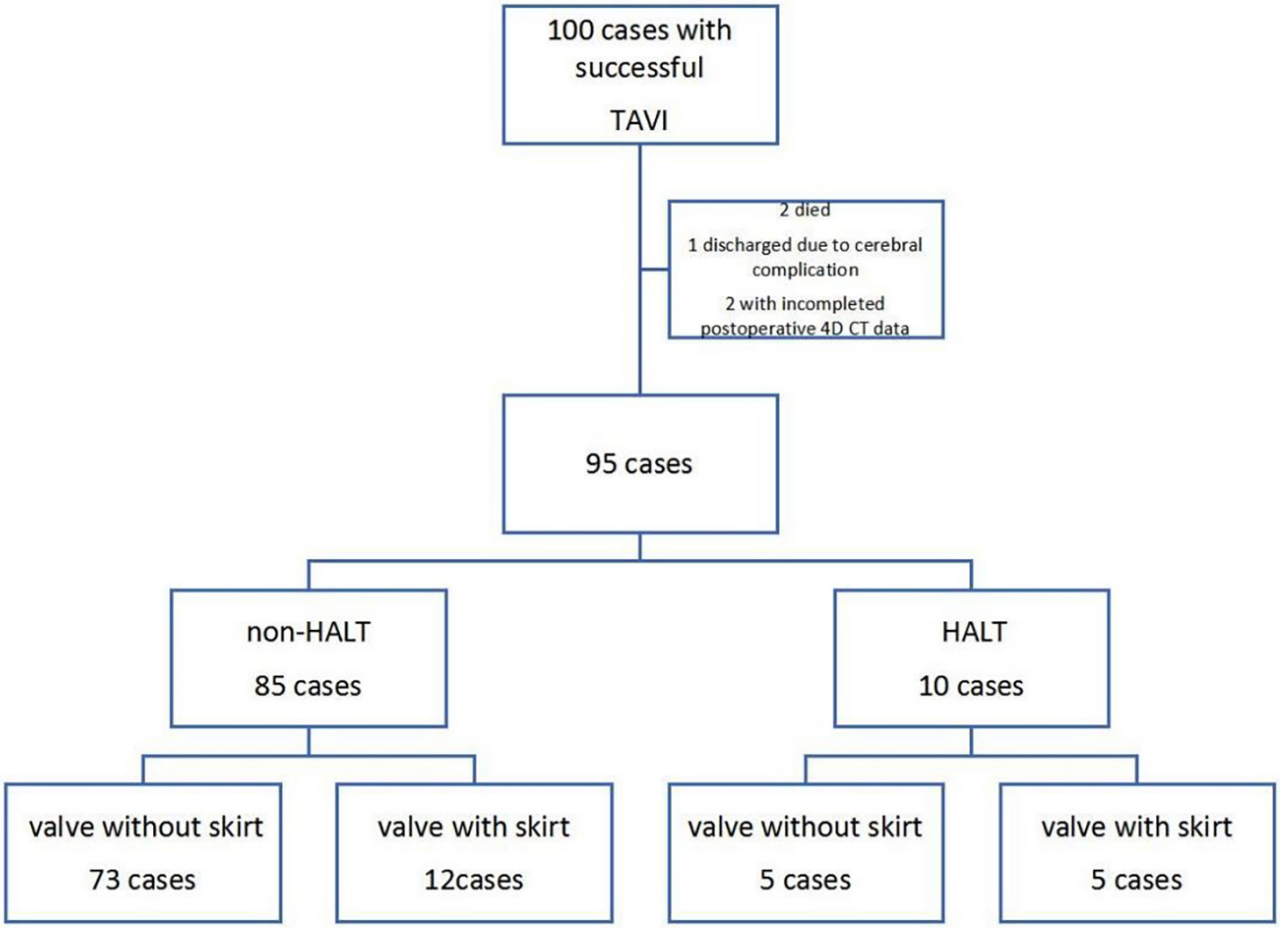

Fig. 1. Flowchart of the patients in this study. TAVI, transcatheter aortic valve implantation; 4DCT, 4 dimensional computed tomography; HALT, hypoattenuated leaflet thickening.

were shown to be related with HALT, such as implant duration, hypertension, large and balloon-expandable prostheses, severe prosthesis-patient mismatch, para-valvular leakage, *etc*. [11–13]. In most studies, the TAVI surgical approach included the transfemoral and transapical approach. This study investigated the risk factors associated with early HALT after transfemoral TAVI solely, which maybe helpful in preventing the complications caused by HALT.

Study Population

Patients with symptomatic severe aortic stenosis or insufficiency that had a successful transfemoral TAVI procedure were recruited. We excluded those patients that had a valve-in-valve procedure, or died before the obtaining of 4DCT, or had incomplete postoperative 4DCT data. A total of 100 patients who underwent TAVI via femoral artery in the Affiliated Hospital of Qingdao University from January 2021 to June 2023 were consecutively selected. And all the patients were operated by the same experienced doctor. Among them, two patients died (1 died because of postoperative aspiration and one died because of postoperative pulmonary infection), and one patient was discharged due to cerebral complications during postoperative recovery treatment. The above 3 patients did not undergo 4DCT after operation. All the rest 97 patients underwent 4DCT examinations for the detection of HALT before discharge. 2 patients did not follow the standard procedure for scanning, and had incomplete postoperative 4DCT data, leading to unable to judge whether HALT existed. Thus, a total of 5 patients were excluded. 95 patients were included in the analysis, including 56 males and 39 females, with an average age of (72.0 $\pm$ 6.7) years and body mass index (BMI) of (24.0 $\pm$ 3.7) kg/m^2. According to the existence of HALT in 4DCT imaging, the patients were divided into HALT group (10 cases) and non-HALT group (85 cases). Fig. 1 shows the flowchart of the patients. The preoperative characters, operation time, type of valve used during operation and whether to perform post dilatation after valve release were collected. Meanwhile, the counts of white blood cells, neutrophils, lymphocytes and platelets were collected at the following time points: after admission, the day after surgery, the first day after surgery, before discharge. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. The dif-

ferences of the above indexes were compared. The study protocol was approved by the Committee for the Protection of Human Subjects at the Affiliated Hospital of Qingdao University.

TAVI Procedure and Postoperative Anticoagulation Protocol

All patients were carefully evaluated by our cardiac team and were determined to be suitable for TAVI surgery according to clinical guidelines. The size and type of valve were determined by the team based on 4DCT imaging and surrounding blood vessels, combined with the patient's anatomy. Patients treated with balloon-expandable valves were implanted with SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA), and patients treated with self-expanding valves were implanted with Venus-A (Qiming Company, hangzhou, China) or TaurusElite (Peijia Medical Limited, suzhou, China). The procedure was performed via femoral artery using a percutaneous safe guidewire technique and a Prostar XL (Abbott vascular, Redwood City, CA, USA) vessel closure device. Post dilatation was performed when esophageal ultrasound showed irregular valve morphology, transvalvular pressure gradient greater than 10 mmHg, and mild to moderate paravalvular leakage after valve release. The operation time was from the puncture of the femoral artery to the completion of the suture of the femoral artery. All patients underwent general anesthesia with tracheal intubation. Heparin was used to maintain the activated clotting time greater than 250 s. Dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) was started three days before surgery, and continued for 6 months after surgery, then single antiplatelet therapy (clopidogrel 75 mg) was continued. The anticoagulation strategy was changed to warfarin or rivaroxaban if the patient has HALT.

Acquisition of 4DCT and Analysis for HALT

According to the literature [14], we conducted the 4DCT scanning, and the evaluations for HALT was judged by two experienced imaging specialists in at least 2 different diastolic phases and the entire systolic phases.

Statistical Analysis

Measurement data were expressed as mean ± standard deviation. When the distribution was normal, a *t*-test was used. Shapiro-Wilk test was used to test the normality of continuous variables between each group, and Mann-Whitney test was performed when abnormal distribution was found. Pearson chi-square test was performed for count data. The primary effect estimate is expressed with its 95% confidence interval. Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 19.0, IBM Corp., Armonk, NY, USA). A p value of less than 0.05 was considered statistically significant.

Results

A total of 95 patients were included in the study, 85 in the non-HALT group and 10 in the HALT group. As shown in Table 1, there were no significant differences in gender (male, 61.8% *vs*. 40%, $p = 0.308$), age (71.9 ± 6.5 *vs*. 71.1 ± 8.5, $p = 0.717$), BMI, and preoperative comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease between the two groups. There were no significant differences in preoperative creatinine, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF) and pulmonary artery systolic pressure (PASP), and no significant differences were found in the count of white blood cells, neutrophils, lymphocytes and platelets, hematocrit, NLR, PLR at all the time points. There was no significant difference in operation time between the two groups. Compared with the patients in the non-HALT group, patients in the HALT group had a lower rate of post dilatation after valve release (60% *vs*. 88.8%, $p = 0.033$), a higher rate of isolated aortic insufficiency (50% *vs*. 9%, $p = 0.033$) and the use of valve with skirt (50% *vs*. 13.5%, $p = 0.012$), and the difference was statistically significant. The incidence of HALT was not associated with the use of a large valve (50% *vs*. 38.2%, $p = 0.509$) or reimplantation (0 *vs*. 10.1%, $p = 0.590$) (see Table 1). As shown in Table 2, in the isolated aortic insufficiency group, the proportion of patients undergoing post-dilatation after valve release was lower (15.4% *vs*. 96.5%, $p = 0$), while the use of valve with skirt was higher (38.5% *vs*. 14%, $p = 0.044$). However, the significant differences were not found in multivariate regression analysis (as shown in Table 3). After three months of anticoagulant therapy, HALT disappeared in the 10 patients.

Discussion

This study retrospectively analyzed the risk factors for early HALT after transfemoral TAVI. The main findings of our study can be summarized as follows. First, the incidence of early HALT after transfemoral TAVI was 10.5%. Second, the incidence of HALT was higher in patients without post-dilatation after the valve release, or with isolated aortic insufficiency, or using valve with skirt.

Now TAVI is not only used to treat high-risk patients with severe aortic stenosis, but also has been extended to moderate to low risk patients [15], and even the aortic insufficiency. HALT is a common phenomenon after TAVI. Although there is still debate about the impact of HALT, there are studies showing that HALT can increase the risk of TIA [7,16] or represents a potential mechanism of biological valve degeneration. So we think we still need to pay attention to the HALT, early detection and treatment are particularly important. Pache *et al*. [17] observed that

Table 1. Perioperative characters of the two groups.

	non-HALT (85 cases)	HALT (10 cases)	*p* value
Sex (male, cases)	55 (61.8%)	4 (40%)	0.308
Age (years)	71.9 ± 6.5	71.1 ± 8.5	0.717
BMI (kg/m^2)	23.7 ± 3.6	24.8 ± 5.2	0.407
Hypertension (cases, %)	43 (48.3%)	6 (60%)	0.525
Diabetes (cases, %)	27 (30.3%)	5 (50%)	0.285
COPD (cases, %)	7 (7.9%)	1 (10%)	0.587
Cerebrovascular disease (cases, %)	16 (18.0%)	1 (10%)	1
LVEDD (cm)	5.0 ± 0.7	5.4 ± 0.6	0.132
LVESD (cm)	3.4 ± 0.8	3.8 ± 0.8	0.168
LVEF (%)	54.7 ± 11.1	50.2 ± 11.2	0.232
PASP (mmHg)	35.6 ± 13.2	36.8 ± 14.7	0.794
Preoperative index			
Creatinine (μmol/L)	83.0 ± 89.1	73.8 ± 29.1	0.746
White blood cell count (×10^9)	6.1 ± 1.5	7.0 ± 3.5	0.440
Neutrophils count (×10^9)	3.7 ± 1.3	4.4 ± 2.7	0.413
Lymphocytes count (×10^9)	1.8 ± 0.6	1.9 ± 0.8	0.487
Platelets count (×10^9)	187.8 ± 48.1	202.2 ± 62.5	0.386
Hematocrit (%)	39.1 ± 5.3	38.3 ± 5.0	0.673
NLR	2.5 ± 2.3	2.4 ± 1.3	0.948
PLR	119.3 ± 54.0	122.7 ± 58.7	0.852
Operation time (min)	81.3 ± 27.9	98.0 ± 44.5	0.097
Index in the day after surgery			
White blood cell count (×10^9)	8.4 ± 3.1	10.0 ± 4.4	0.154
Neutrophils count (×10^9)	7.2 ± 3.0	8.5 ± 3.7	0.212
Lymphocytes count (×10^9)	0.9 ± 0.3	1.2 ± 0.7	0.257
Platelets count (×10^9)	159.3 ± 43.2	156.8 ± 63.0	0.867
Hematocrit (%)	34.9 ± 5.0	32.4 ± 5.9	0.146
NLR	9.6 ± 5.9	9.5 ± 6.4	0.978
PLR	209.6 ± 103.3	205.0 ± 202.0	0.945
Index in the first day after surgery			
White blood cell count (×10^9)	10.5 ± 3.1	10.1 ± 3.4	0.676
Neutrophils count (×10^9)	8.7 ± 2.9	8.2 ± 3.0	0.592
Lymphocytes count (×10^9)	1.0 ± 0.4	1.1 ± 0.6	0.544
Platelets count (×10^9)	152.5 ± 45.8	131.1 ± 61.4	0.181
Hematocrit (%)	34.3 ± 5.4	31.5 ± 6.2	0.127
NLR	9.5 ± 5.0	8.8 ± 5.8	0.655
PLR	167.8 ± 93.3	139.4 ± 86.0	0.359
Index before discharge			
Creatinine (μmol/L)	81.4 ± 90.8	76.5 ± 23.8	0.867
White blood cell count (×10^9)	7.1 ± 2.4	8.0 ± 3.0	0.284
Neutrophils count (×10^9)	4.9 ± 2.3	5.6 ± 2.4	0.420
Lymphocytes count (×10^9)	1.3 ± 0.4	1.5 ± 1.1	0.629
Platelets count (×10^9)	165.9 ± 56.0	188.3 ± 45.1	0.225
Hematocrit (%)	33.5 ± 5.0	33.5 ± 5.0	0.977
NLR	4.5 ± 3.3	5.0 ± 3.3	0.672
PLR	143.0 ± 67.6	165.1 ± 78.3	0.336
Balloon dilatation followed valve release (cases, %)	79 (88.8%)	6 (60%)	0.033
Valve reimplantation (cases, %)	9 (10.1%)	0 (0)	0.592
Large valve implantation (size ≥29) (cases, %)	34 (38.2%)	5 (50%)	0.509
Valve with skirt (cases, %)	12 (13.5%)	5 (50%)	0.012
Isolated aortic insufficiency (cases, %)	8 (9.0%)	5 (50%)	0.003

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Table 2. Intraoperative balloon dilatation and valve use in patients with aortic stenosis and insufficiency.

	Aortic stenosis group (n = 83)	Aortic insufficiency group (n = 12)	*p*
Balloon dilatation after valve release (cases, %)	80 (96.4%)	1 (8.3%)	0
Valve with skirt (cases, %)	12 (14.5%)	5 (41.6%)	0.037

Table 3. Multivariate logistic regression analysis for the HALT.

Variables in the equation								
	B	S.E.	Wals	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
							Lower	Upper
Balloon dilatation followed valve release	–19.578	18,177.988	0	1	0.999	0	0	
Isolated aortic insufficiency	21.521	18,177.988	0	1	0.999	2.220×10^9	0	
Valve with skirt	1.269	0.794	2.555	1	0.110	3.558	0.751	16.869
Constant	–6.219	1.508	17.002	1	0	0.002		

10% of patients developed HALT at a median interval of 5 days after TAVI. The overall incidence of HALT was found to increase from 10% at 30 days to 24% at 1 year in PARTNER 3 [8]. In our study, the incidence of early HALT after transfemoral TAVI was 10.5%, which was consistent with the above researches.

It has been reported that TAVI is more prone to produce thrombosis due to the presence of displaced primary valve leaflets, the coil of the valve leaflets during assembly which can cause damage to the valve, the trauma during valve release and expansion, and the insufficient or excessive valve expansion [18,19]. Fuchs *et al*. [18] observed that thrombosis occurs more often when the valve frame implanted via catheter cannot be fully dilated or the valve leaflet is overhanging, indicating that slow local blood flow may produce a prothrombotic environment. And Fukui *et al*. [20] found that smaller neosinus volume was independent predictor of HALT. Studies showed HALT was more frequently in those who received balloon-expandable valves compared to self-expanding valves, Bhogal *et al*. [21] and Tang *et al*. [11] thought it might be likely due to the supra-annular position of the leaflets of the self-expanding valve which lifts the neosinus above the displaced native leaflets, allowing for better neosinus washout and making the valve less prone to leaflet thrombosis [22]. And some researchers think it might be attributable to the greater interaction of the balloon with the prosthetic leaflets which potentially leading to more extensive surface injury during the procedure.

Our study showed that HALT was more prone to occur in patients without post-dilatation after the valve release. We think it may be related to the incomplete expansion of the valve frame and the small neosinus. Therefore, when the esophageal ultrasound showed irregular valve morphology, transvalvular pressure gradient greater than 10 mmHg, and mild to moderate paravalvular leakage, we used a balloon for dilatation, which was generally equal to the size of the initial balloon in order to avoid the damage to the valve leaflets caused by excessive expansion.

We also found that the incidence of HALT was higher in patients with isolated aortic insufficiency, or the use of valve which has skirt. On the one hand, as can be seen in Table 2, the proportion of post-dilatation after valve release was lower (15.4% *vs*. 96.5%, $p = 0$) in the aortic insufficiency group, the difference was statistically significant. On the other hand, the proportion of the use of valve with skirt was higher (38.5% *vs*. 14%, $p = 0.044$) in the aortic insufficiency group, we think that it may be more likely to cause platelet adhesion and aggregation around the skirt tissue, resulting in thrombosis. We have only observed this phenomenon, and we should conduct further research to explore the specific mechanism in the future.

Koo *et al*. [12] found that hypertension was a protective factor for HALT, they thought that high blood pressure increased blood flow velocity, and associated with turbulence in the ascending aorta, the turbulence includes aortic valve washing jets, which are thought to prevent the thrombus formation in the aortic valve. In our study, we didn't find the difference was significant between the two groups in the following index such as hypertension, diabetes, COPD, cerebral vascular disease, *etc*.

Many studies show that oral anticoagulation can reduce the incidence of the HALT and RLM, such as the GALILEO trial [23], the ATLANTIS study [24] and an LRT substudy [21]. According to the 2021 ESC/EACTS guidelines for valvular heart disease, anticoagulation for HALT should be considered (Class IIa recommendation) in post-TAVI patients with reduced leaflet motion leading to elevated gradients [25].

Ruile *et al*. [26] reported the regression of HALT in all patients under anticoagulation after a median time of 86 days. Ferstl *et al*. [27] found that anticoagulation therapy resolves leaflet thickening after TAVI in most patients, non-Vitamin-K antagonists seemed to be an effective alternative to Vitamin-K antagonists. In our study, we adopted warfarin (vitamin-K antagonists) or rivaroxaban (direct oral anticoagulant, DOAC) to treat the HALT, and we found that HALT disappeared in the 10 patients 3 months after surgery.

Limitation

This study mainly investigated the incidence and risk factors of HALT in the early stage after TAVI via femoral artery. And the significant differences were not found in multivariate regression analysis, we think it is related to the small sample size. In the studies of PARTNER 3 [8] and Evolut Low-Risk [28], it was found that the HALT process was dynamic, some patients spontaneously resolved HALT within 30 days to 1 year, and some patients developed new HALT after 1 year that did not exist for 30 days, and it was pointed out that it was not entirely dependent on the concomitant use of DOAC. We did not follow up all patients in the medium and long term. Therefore, further studies are needed during the follow-up in the future.

Conclusion

In summary, HALT is a common phenomenon after TAVI, the incidence of HALT was higher in patients without post-dilatation after the valve release, or with isolated aortic insufficiency, or using valve with skirt, but the significant differences were not found in multivariate regression analysis. Further studies are needed in the future.

Availability of Data and Materials

The data are not publicly available because ethical permission was not granted, but they can be obtained from the corresponding author with reasonable grounds.

Author Contributions

WYH, JR, LWL, QZJ, WQJ, ZQZ, TGZ, ZLP, YZT, LYC and JL contributed to the conception and design of the study, and perform the study. LWL and YZT are the two experienced imaging specialists who conducted the 4DCT scanning and the evaluations for HALT. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study protocol was approved by the Committee for the Protection of Human Subjects at the Affiliated Hospital of Qingdao University (QYFY WZLL 28512). Patient consent was waived due to an anonymised data set.

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Conflict of Interest

The authors declare no conflict of interest.

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