

Perioperative changes of serum albumin are a predictor of postoperative pulmonary complications in lung cancer patients: a retrospective cohort study

Pengfei Li^{1,2#}, Jue Li^{1,2#}, Yutian Lai^{1,2}, Yan Wang^{1,2}, Xin Wang^{1,2}, Jianhua Su³, Guowei Che¹

¹Department of Thoracic Surgery, West China Hospital, ²West China School of Medicine, ³Department of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu 610041, China

Contributions: (I) Conception and design: P Li, J Su, G Che; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: J Li, Y Wang; (V) Data analysis and interpretation: Y Lai, X Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Guowei Che. Department of Thoracic Surgery, West China Hospital, Sichuan University, Guoxuexiang No. 37, Chengdu 610041, China. Email: guowei_che@yahoo.com.

Background: A decrease in serum albumin is commonly observed after lung cancer surgery, however, whether it is associated with postoperative outcomes is unknown. The objective of this study was to evaluate whether the reduction of serum albumin (Δ ALB) on postoperative day one could serve as a predictor of postoperative pulmonary complications (PPCs) after thoracoscopic anatomical resection in lung cancer patients.

Methods: Patients characteristics were compared between groups of whether they experienced PPCs or not. The cutoff value of Δ ALB was examined by receiver operating characteristic curve to find out the threshold value of Δ ALB in predicting PPCs. Logistic regression analysis was conducted to identify potential risk factors for PPCs.

Results: Totally 533 patients were included into analysis, and among them, 52 experienced PPCs. The Δ ALB was significant in the PPCs group than in the non-PPCs group ($P < 0.001$), and Δ ALB was observed an independent risk factor for PPCs (OR = 2.268, 95% CI: 1.153–4.460). The cutoff value of Δ ALB in predicting PPCs was 14.97%. Patients with Δ ALB \geq 14.97% were more likely to have PPCs ($P < 0.001$).

Conclusions: A reduction of serum albumin with a cut-off value of 14.97% can be served as a predictor to identify patients at high risk of developing PPCs following thoracoscopic anatomical lung cancer surgery.

Keywords: Lung cancer; postoperative pulmonary complications (PPCs); serum albumin; risk factor

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Introduction

Since the introduction of video-assisted thoracoscopic surgery (VATS), it has rapidly developed to become a major method in treating operable non-small cell lung cancer (NSCLC). Though the surgical techniques and the perioperative management levels developed rapidly, postoperative complications are still important factors that trouble both patients and physicians. Postoperative

complications may prolong the length of hospital stay, increase the in-hospital cost and influence the recovery of patients' function status (1). Postoperative pulmonary complications (PPCs) are the most common complications after lung cancer surgery.

As a nutritional status indicator and inflammatory factor, the role of perioperative albumin levels and postoperative outcomes has been explored (2). Several previous studies

have demonstrated that preoperative serum albumin was significantly associated with postoperative complications in malignancies including colorectal, gastric, and gynecologic cancer and non-cancer patients (3-6). Likewise, the relationship between postoperative hypoalbuminemia and poor postoperative outcomes has been discussed (7). Increasing evidence also indicated that the decrease of albumin after surgery was associated with surgery outcomes (8-11).

However, whether perioperative albumin is related with postoperative short-term morbidity after lung cancer resection is still unknown. The objective of this study was to define how the postoperative decrease of serum albumin (Δ ALB) was related with PPCs for lung cancer patients who underwent VATS anatomical resection.

Methods

Patients

This is a retrospective cohort study from a single center. Consecutive patients underwent VATS lobectomy or segmentectomy for NSCLC at the Department of Thoracic Surgery, West China Hospital, between May 1, 2015 and December 30, 2016 were retrospectively examined. Finally, a total of 533 patients were enrolled in the study.

Patients' inclusion criteria: (I) a defined diagnosis of primary NSCLC confirmed by pathology; (II) underwent VATS lobectomy or segmentectomy. Exclusion criteria: (I) transfusion of albumin during the perioperative period; (II) underwent neoadjuvant therapy; (III) a history of surgery within 3 months preoperatively; (IV) patients with signs of infection and those combined with disease which may affect the serum albumin; (V) data incomplete or could not be obtained.

Data collection

Data including: age, gender, body mass index (BMI), smoking history, American Society of Anesthesiologists (ASA) grade, preoperative comorbidities, surgical procedures (surgical approach, type of resection), pathology and American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging (the eighth edition) were collected.

Usually, blood tests were performed within 7 days preoperatively and on the morning of postoperative day 1 (POD1) in our institution, so serum albumin levels were obtained and Δ ALB were calculated according to previous studies (8-12).

Definition of outcomes

The primary outcome of our study was the incidence of PPCs that occurred within 30 days postoperatively. PPCs were defined including: pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), pulmonary embolism, re-intubation. The criteria used to define PPCs were according to the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons joint definitions (13). Hypoalbuminemia was defined as a serum albumin level less than 35 grams per liter (g/L).

Statistical analysis

According to whether they experienced PPCs, patients were divided into two groups (the PPCs group and non-PPCs group). Clinicopathologic characteristics were compared between the two groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal threshold Δ ALB value to predict PPCs. The optimal cut-off value of Δ ALB was estimated using the Youden index (sensitivity + specificity-1) which is a common summary measure of the ROC curve. Patients were categorized and compared based on the cut-off value identified by the ROC curve analysis. Binomial logistic regression analysis was conducted to identify potential preoperative risk factors for PPCs and to examine the associations between Δ ALB with PPCs. Firstly, univariate analysis was conducted, and then variables with P value <0.1 were included into the adjusted multivariable analysis. The results of regression analysis were reported as odds ratio (ORs) and 95% confidence interval (95% CI).

Continuous normally distributed data were expressed as mean \pm standard deviation (SD) and non-normal data as medians with interquartile range (IQR) (25th and 75th percentiles). Student *t*-test was used to compare normally distributed continuous variables, and non-normal data were tested with Mann-Whitney U test. Categorical variables are expressed as absolute frequencies and proportions (%) and between group difference were compared using the χ^2 or Fisher's exact tests. All significance tests were two tailed with P<0.05 considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 23.

Results

Study population and baseline characteristics

A total of 533 female and male patients who underwent

VATS anatomical resection for lung cancer were identified for eligibility this study. The baseline characteristics are summarized in *Table 1*. The mean age was 61.63 ± 8.64 years. Nearly half of the patients (50.7%) had a history of smoking. The preoperative mean albumin level was 42.39 ± 4.12 g/L. Only 16 patients (3%) with a preoperative albumin level less than 35 g/L were defined with hypoalbuminemia. While on POD1, the mean ALB level was decreased to 37.63 ± 4.93 g/L, and more patients (131, 24.6%) were at hypoalbuminemia status. Four hundred patients (75%) underwent lobectomies and 133 patients (25%) underwent segmentectomies.

On POD1, the mean value of albumin level in the PPCs groups was significantly lower than in the non-PPCs group (34.94 ± 4.61 vs. 37.92 ± 4.88 , $P < 0.001$), and more patients had hypoalbuminemia status in the PPCs group than in the non-PPCs group [23 (44.2%) vs. 108 (22.5%), $P = 0.001$]. Patients who experienced PPCs were at higher rate of ALB decrease after surgery [0.16 (0.09–0.21) vs. 0.12 (0.06–0.16), $P < 0.001$]. Patients in the PPCs group tended to have higher rate of comorbidities of chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD), while there was no difference regarding hypertension, diabetes and history of malignant neoplasm. There was no difference regarding baseline characteristics including age, gender, smoking history, preoperative albumin level, the rate of preoperative hypoalbuminemia and oncological characteristics including TNM stage, extent of resection, and pathology in the PPCs group compared to the non-PPCs group (*Table 1*).

ROC curve analysis of Δ ALB in predicting PPCs

Based on the ROC curve analysis, the Δ ALB of 14.97% was found the cut-off value in predicting PPCs. The area under the value (AUC) was 0.655 (95% CI: 0.578–0.732, $P < 0.001$), with the specificity of 69.6% and sensitivity of 57.7% (*Figure 1*).

Association between threshold Δ ALB and perioperative parameters

The demographic differences between patients with Δ ALB $\geq 14.97\%$ and patients with Δ ALB $< 14.97\%$ were summarized in *Table 2*. Compared with patients with Δ ALB $\geq 14.97\%$, patients with Δ ALB $< 14.97\%$ were older, had lower BMI.

Association between threshold Δ ALB and the development of postoperative complications

The incidence of common complications including pulmonary complications and surgery related complications is summarized in *Table 3*. In our cohort, the most frequent pulmonary complication was postoperative pneumonia (6.2%), followed by atelectasis (3.4%), pulmonary embolism (0.9%), ARDS (0.4%) and reintubation (0.4%).

The overall incidence of PPCs of patients with Δ ALB $\geq 14.97\%$ was significantly higher than that of patients with Δ ALB $< 14.97\%$ [30 (17.0%) vs. 22 (6.2%), $P < 0.001$]. Compared with patients with Δ ALB $< 14.97\%$, patients with Δ ALB $\geq 14.97\%$ had higher rate of postoperative pneumonia [23 (13.1%) vs. 10 (2.8%), $P < 0.001$] and pulmonary embolism [4 (2.3%) vs. 1 (0.3%), $P = 0.043$], while no significant difference was found in the other PPCs between these two groups.

Predictive factors for PPCs

The results of univariate and multivariate analysis are summarized in *Table 4*. Potential risk factors were included into analysis. From the univariate analysis, postoperative hypoalbuminemia (OR = 0.365, 95% CI: 0.203–0.657, $P = 0.001$), Δ ALB $\geq 14.97\%$ (OR = 3.129, 95% CI: 1.746–5.608, $P < 0.001$) and FEV1 (OR = 0.556, 95% CI: 0.349–0.855, $P = 0.013$) were found to be significantly associated with PPCs. Then a multivariate analysis model was conducted to identify the independent predictive factors for PPCs. Δ ALB $\geq 14.97\%$ (OR = 2.268, 95% CI: 1.153–4.460, $P = 0.018$) and FEV1 (OR = 0.596, 95% CI: 0.369–0.963, $P = 0.034$) were maintained in the model after adjustment (*Table 4*).

Discussion

The serum albumin level indicating the nutrition status is regarded as an acute phase protein. Both pre- and postoperative albumin levels have been proven to be significantly related with perioperative morbidity (3–7,14). However, if we focus on only pre- or postoperative albumin levels, we might not perceive the dynamic change of serum albumin during the perioperative period and its relationship with postoperative outcomes. To our knowledge, no studies have investigated the meaning of serum albumin change postoperatively in predicting postoperative morbidity in lung cancer patients who underwent anatomical resection.

Table 1 Characteristics of two group patients divided by PPCs

Characteristic	PPCs		P
	Yes (n=52)	No (n=481)	
Age (years), mean \pm SD	59.67 \pm 7.98	61.84 \pm 8.69	0.086
Gender (female), n (%)	19 (36.5)	206 (42.8)	0.460
BMI (kg/m ²), mean \pm SD	23.62 \pm 3.29	23.29 \pm 2.96	0.456
Current or former smokers, n (%)	30 (57.7)	240 (49.9)	0.309
Preoperative ALB (g/L)	41.80 \pm 4.90	42.46 \pm 4.03	0.273
Preoperative hypoalbuminemia, n (%)	3 (5.8)	13 (2.7)	0.198
Postoperative ALB (g/L), mean \pm SD	34.94 \pm 4.61	37.92 \pm 4.88	<0.001
Postoperative hypoalbuminemia, n (%)	23 (44.2)	108 (22.5)	0.001
Δ ALB, median (95% CI)	0.16 (0.09–0.21)	0.12 (0.06–0.16)	<0.001
Blood loss (mL), median (95% CI)	100 (32.5–127.5)	80 (40–150)	0.302
ASA score, n (%)			<0.001
2	45 (86.5)	384 (79.8)	
3	7 (13.5)	90 (18.7)	
4	0	7 (1.5)	
Perioperative morbidity, n (%)			
COPD	13 (25.0)	111 (23.1)	0.732
Hypertension	16 (30.8)	120 (24.9)	0.402
Diabetes	3 (5.6)	51 (10.6)	0.341
CHD	2 (3.8)	26 (5.4)	1.000
Previous malignancy	5 (9.6)	38 (7.9)	0.596
Pulmonary function (L), mean \pm SD			
FEV1	2.13 \pm 0.62	2.47 \pm 2.22	0.276
TNM stage, n (%)			0.595
I	39 (75)	340 (70.7)	
II	7 (13.5)	74 (15.4)	
III	4 (7.7)	58 (12.1)	
IV	2 (3.8)	9 (1.9)	
Extent of resection, n (%)			0.866
Lobectomy	40 (76.9)	360 (74.8)	
Segmentectomy	12 (23.1)	121 (25.2)	
Pathology, n (%)			0.815
Adenocarcinoma	36 (69.2)	342 (71.1)	
SCC	10 (19.2)	97 (20.2)	
Others	6 (11.5)	42 (8.7)	

PPCs, postoperative pulmonary complications; BMI, body mass index; ALB, albumin; Δ ALB, postoperative decrease in serum albumin; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; FEV1, forced expiratory volume in 1 second; SCC, squamous cell carcinoma.

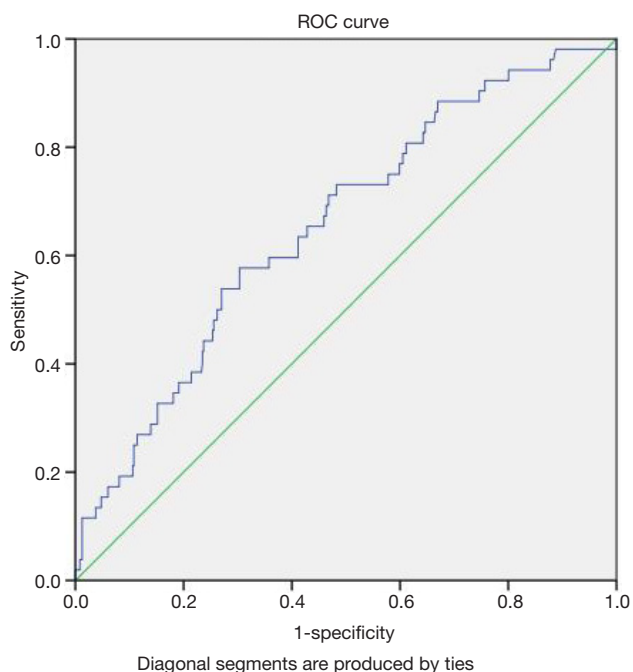


Figure 1 Receiving operator curve of Δ ALB in predicting PPCs. PPC, postoperative pulmonary complication.

Our results revealed that Δ ALB was an independent risk factor in predicting PPCs after anatomical resection in lung cancer patients. And a Δ ALB of 14.97% was found to be the threshold value to predict PPCs. The rates of PPCs including postoperative pneumonia and pulmonary embolism, were significant higher in the high Δ ALB group than in the low Δ ALB group. No such relation was discovered regarding surgery related complications.

Our results agree with several previous studies that investigated the relationship between the Δ ALB and perioperative outcomes. Liu *et al.* (9) investigated the relationship between Δ ALB and short-term complications after gastric cancer resection. They found that a Δ ALB value of 14.0% was the cut-off value in predicting postoperative complications after gastrectomy and patients whose serum ALB levels were reduced by >14.0% should be identified by physicians for complications. Ge *et al.* (10) retrospectively analyzed 626 patients who underwent colorectal surgery, and the authors discovered that a Δ ALB value of $\geq 15\%$ after 2 days postoperatively was an independent risk factor for overall complications. Though their studies were not focused on lung cancer patients, their results were quite similar to ours regarding the Δ ALB cut-off value in predicting postoperative complications. Another study revealed that the serum albumin

dropped rapidly and a definite decrease of serum albumin was significantly associated with postoperative complications and prolonged hospital stay (8,11).

The decrease in serum albumin can be attributed to the blood loss intraoperatively and postoperatively including the hemodilution during fluid transfusion and capillary permeability into the interstitial space (15). However, in our study, we did not find a relationship between blood loss and PPCs, and in the regression analysis blood loss was not an independent risk factor for PPCs. This may be explained by the fact that most of the albumin decrease after surgery was on account for the redistribution (11). For pulmonary resection patients, the lung injure from the operation and single lung ventilation during the procedure could increase the inflammatory response (16,17).

Unlike traditional inflammatory factors of C-reactive protein (CRP) and IL-6, IL-8 and IL-10, serum albumin is a negative acute phase protein, where its level drops in response to inflammation and surgery trauma. Studies demonstrated that the response of serum albumin might occur earlier than CRP to surgical stress, and this may be attributed to its quicker kinetics than CRP (10,18-20). The relationship between CRP and albumin during the perioperative period had been studied (20), and the authors found that the antecedent CRP levels could predict hypoalbuminemia to some extent in the future, which reflected the close relationship between CRP and albumin. Increased inflammatory cytokines during the perioperative period promote the degradation of the serum albumin and decrease its synthesis (20,21). This mechanism combined with the capillary permeability and fluid transfusion result in the decrease of serum albumin postoperatively.

On the other hand, the serum albumin level is the most frequently used parameter to reflect one's nutritional status (20,22). The nutritional status plays an important role in patient recovery from surgery and may account for the incidence of perioperative morbidity after surgery (23,24). However, in our study, the preoperative serum albumin was not an independent risk factor for PPCs, which was not consistent with other studies. This could be explained by the low rate of preoperative malnutrition of 3%. Despite this inconsistency, we found that the decrease of serum albumin on POD1 is an independent risk factor for PPCs, which was consistent with two other studies in gastric and colorectal resection patients (9,10).

There are some limitations in our study. This is a retrospective, observational cohort study from one single institution that only included patients who underwent

Table 2 Characteristics classified by Δ ALB cutoff value

Variables	Δ ALB <14.97% (n=357)	Δ ALB \geq 14.97% (n=176)	P
Age (years), mean \pm SD	62.53 \pm 8.47	59.80 \pm 8.72	0.001
Gender (female), n (%)	161 (45.1)	64 (36.4)	0.062
BMI (kg/m ²), mean \pm SD	22.95 \pm 2.86	24.09 \pm 3.12	<0.001
Smoking history, n (%)	180 (50.4)	90 (51.1)	0.927
ASA score, n (%)			0.393
2	290 (81.2)	139 (79.0)	
3	61 (17.1)	36 (20.5)	
4	6 (1.7)	1 (0.6)	
Perioperative morbidity, n (%)			
COPD	83 (23.2)	41 (23.3)	1.000
Hypertension	94 (26.3)	42 (23.9)	0.598
Diabetes	35 (9.8)	19 (10.8)	0.761
CHD	21 (5.9)	7 (4)	0.414
Previous malignancy	33 (9.2)	10 (5.7)	0.178
Pulmonary function (L), mean \pm SD			
FEV1	2.52 \pm 2.54	2.26 \pm 0.63	0.178
TNM stage, n (%)			0.011
I	247 (69.2)	132 (75.0)	
II	66 (18.5)	15 (8.5)	
III	39 (10.9)	23 (13.1)	
IV	5 (1.4)	6 (3.4)	
Extent of resection, n (%)			0.09
Lobectomy	276 (77.3)	124 (70.5)	
Segmentectomy	81 (22.7)	52 (29.5)	
Pathology, n (%)			0.184
Adenocarcinoma	244 (68.3)	134 (76.1)	
SCC	78 (21.8)	29 (16.5)	
Others	35 (9.8)	13 (7.4)	

BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; FEV1, forced expiratory volume in 1 second; SCC, squamous cell carcinoma.

anatomical resection, which may limit its applicability. The primary endpoint of this study was the occurrence of PPCs, and the other perioperative morbidities and mortality was not explored. We failed to assess the predictive value of Δ ALB combined with other factors that may have a close relationship with the drop of serum albumin including the amount and type of transfusion since these records were not

available. Finally, the present findings need to be further validated by large prospective cohort studies.

Conclusions

The current study revealed that a decrease of serum albumin on POD1 predicted PPCs after VATS anatomical

Table 3 Main postoperative complications classified by Δ ALB cutoff value

Classification	Total	Δ ALB <14.97% (n=357)	Δ ALB \geq 14.97% (n=176)	P
Total complications, n (%)	100 (18.8)	50 (14.0)	50 (28.4)	<0.001
PPCs, n (%)	52 (9.8)	22 (6.2)	30 (17.0)	<0.001
Pneumonia	33 (6.2)	10 (2.8)	23 (13.1)	<0.001
Atelectasis	18 (3.4)	9 (2.5)	9 (5.1)	0.131
Pulmonary embolism	5 (0.9)	1 (0.3)	4 (2.3)	0.043
ARDS	2 (0.4)	2 (0.6)	0 (0.0)	1
Reintubation	2 (0.4)	2 (0.6)	0 (0.0)	1
SRCs, n (%)	56 (10.5)	33 (9.2)	23 (13.1)	0.179
BPF	1 (0.2)	0 (0.0)	1 (0.6)	0.330
Pulmonary air leak	42 (7.9)	24 (6.7)	18 (10.2)	0.173
Subcutaneous emphysema	13 (2.4)	9 (2.5)	4 (2.3)	1
Chylothorax	5 (0.9)	3 (0.8)	2 (1.1)	0.667
Pleural effusion	4 (0.8)	3 (0.8)	1 (0.6)	1

PPCs, postoperative pulmonary complications; ARDS, acute respiratory distress syndrome; SRCs, surgical related complications; BPF, bronchopleural fistula.

Table 4 Predictive factors for PPCs: univariate and Multivariable analysis

Variables	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.972 (0.940–1.004)	0.087	0.981 (0.947–1.015)	0.261
Gender (female)	0.769 (0.425–1.390)	0.384	–	–
BMI	1.037 (0.943–1.140)	0.456	–	–
Smoking history	1.369 (0.768–2.4442)	0.287	–	–
Preoperative hypoalbuminemia	0.454 (0.125–1.647)	0.230	–	–
Postoperative hypoalbuminemia	0.365 (0.203–0.657)	0.001	0.627 (0.317–1.241)	0.180
Blood loss	0.999 (0.998–1.001)	0.409	–	–
Δ ALB \geq 14.97%	3.129 (1.746–5.608)	<0.001	2.268 (1.153–4.460)	0.018
ASA score	0.601 (0.273–1.322)	0.206	–	–
Hypertension	1.337 (0.716–2.496)	0.362	–	–
Diabetes	0.516 (0.155–1.716)	0.281	–	–
Previous malignancy	1.240 (0.466–3.303)	0.667	–	–
COPD	1.111 (0.573–2.155)	0.755	–	–
CHD	0.700 (0.161–3.037)	0.634	–	–
FEV1	0.556 (0.349–0.855)	0.013	0.596 (0.369–0.963)	0.034
TNM stage	0.922 (0.628–1.353)	0.677	–	–
Extent of resection	1.120 (0.569–2.205)	0.742	–	–
Pathology	1.114 (0.727–1.707)	0.620	–	–

OR, odds ratio; CI, confidence interval; BMI, body mass index; Δ ALB, postoperative decrease in serum albumin; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; FEV1, forced expiratory volume in one second.

lung cancer resection. An Δ ALB of 14.97% was confirmed as the cut-off value in predicting PPCs, and patients with albumin levels decrease $\geq 14.97\%$ were at higher risk of developing PPCs. Surgeons are advised to monitor the change of serum albumin after lung cancer anatomical resection to detect potential pulmonary complications.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethics Committee of West China Hospital, Sichuan University, Chengdu, China (No. 2017-403) and written informed consent was waived due to the retrospective nature.

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