

ORIGINAL ARTICLE

Body surface area as a novel risk factor for chylothorax complicating video-assisted thoracoscopic surgery lobectomy for non-small cell lung cancer

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Keywords

Body surface area; chylothorax; lobectomy; non-small-cell lung cancer; video-assisted thoracoscopic surgery.

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Received: 15 August 2018;

Accepted: 19 September 2018.

doi: 10.1111/1759-7714.12896

Thoracic Cancer 9 (2018) 1741–1753

Abstract

Background: The study was conducted to demonstrate the predictive value of body surface area (BSA) for chylothorax complicating video-assisted thoracoscopic surgery (VATS) lobectomy for non-small cell lung cancer (NSCLC).

Methods: Large-scale retrospective analysis was conducted on the data of 1379 patients who underwent VATS lobectomy between January 2014 and October 2017 at our institution. Receiver operating characteristic analysis was conducted to determine a threshold BSA value for the prediction of chylothorax. This optimal BSA cutoff, other clinicopathological variables, and $P < 0.15$ were included into a multivariable logistic regression model to determine the risk factors for chylothorax.

Results: Twenty-six patients (1.9%) developed postoperative chylothorax. The mean BSA in patients with chylothorax was significantly higher than in patients without (1.84 ± 0.14 vs. 1.73 ± 0.16 m²; $P = 0.001$). A BSA of 1.69 m² was identified as the threshold value with maximum joint sensitivity (96.2%) and specificity (43.8%). Patients with BSA > 1.69 m² had a significantly higher incidence of chylothorax (3.0% vs. 0.3%; $P < 0.001$) and a longer hospital stay (log rank $P < 0.001$) than patients with BSA ≤ 1.69 m². Multivariable logistic regression analysis suggested that BSA > 1.69 m² (odds ratio 7.35, 95% confidence interval 1.54–35.71; $P = 0.013$) was predictive of postoperative chylothorax.

Conclusions: BSA can serve as a novel categorical predictor for chylothorax complicating VATS lobectomy for NSCLC. It may be more helpful to incorporate a BSA cutoff into routine risk stratification tools for lung cancer surgery.

Introduction

Rationale

Lung cancer is the leading cause of malignancy-related death worldwide.^{1–4} Nowadays, radical surgery is regarded not only as the optimal therapeutic option for early-stage non-small-cell lung cancer (NSCLC), but also as the cornerstone of multidisciplinary treatments for more advanced NSCLC.^{4–7} Since the 1990s, single lobectomy via video-assisted thoracoscopic surgery (VATS), a minimally invasive procedure providing access to the chest cavity, has been developed as a modern surgical modality for operable

NSCLC, offering more advantages than conventional thoracotomy in terms of the cosmetic wounds, pain and stress control, preservation of pulmonary function, and enhanced recovery.^{6,8–12} Despite advances in surgical techniques and perioperative care, however, the morbidity rate after VATS lobectomy remains 26.2–36.3%.^{6,11–13}

As a fatal complication following elective pulmonary resection, the postoperative management of chylothorax (which is generally secondary to thoracic duct injury, with its tributaries), poses a great challenge to thoracic surgeons because of the uncontrollable accumulation of fatty lymphatic fluid in the pleural space and subsequently high

mortality, up to 30%. The incidence of chylothorax ranges from 1.4% to 4.0% in the literature.^{14–17} A better understanding of potent predisposing factors is urgently required in order to recognize the risk of chylothorax early, which may help to limit chylothorax-induced adverse effects. Unfortunately, the perioperative risk factors of chylothorax have not been well defined.¹⁴

Body surface area (BSA) is widely utilized as a basic biometric unit to normalize physiological variables and determine the appropriate drug dosages of cancer chemotherapy.¹⁸ Velez-Cubian *et al.* first reported the clinical significance of BSA in lung cancer surgery in a small cohort of 208 robotic-assisted thoracoscopic lobectomy cases, but the association between BSA and risk of chylothorax remained unclear.¹⁹ In our earlier series of 442 patients undergoing VATS anatomical resections, we found that larger BSA was significantly associated with surgical procedure-related complications but we did not investigate the impact of BSA on individual complications.⁶

Objectives

The primary purpose of our study was to show whether BSA could predict the occurrence of chylothorax complicating VATS lobectomy for NSCLC based on a large population. Our secondary goal was to evaluate the effects of BSA on the length of stay (LOS) and length of chest drainage (LOCD).

Methods

Study design and protocol

This single institution retrospective analysis was performed on a prospectively maintained dataset with additional medical records at our unit. It was written in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (Appendix Data 1).²⁰ Our regional ethics committee approved the study protocol and waived the need for informed consent (ID: 2016–255).

Participant selection

Settings

We retrospectively reviewed the clinical data of consecutive patients who underwent VATS lobectomy for operable NSCLCs in our institution between January 2014 and October 2017. Their perioperative outcome data were carefully collected and further analyzed.

Inclusion and exclusion criteria

Patients who met all of the following eligibility criteria were enrolled: (i) the target disease was operable primary

NSCLC; (ii) standardized single lobectomy with systematic mediastinal lymph node dissection (SMLND) via a complete VATS procedure had been performed (any additional surgical procedure, such as prophylactic thoracic duct ligation or conversion to thoracotomy, were not included because of the potential confounding influence induced by their effects on postoperative morbidity); (iii) the entire clinical pathway was completed during hospitalization; and (iv) complete and accurate records were available.

Follow-up

As the endpoints of our study were outcomes during hospitalization, a follow-up period of 30 days after surgery was sufficient.

Outcome data, measures and definitions

We recorded and defined the following characteristics and outcome data.

Preoperative variables

The baseline patient information collected included age, gender, body mass index (BMI, calculated by weight [kg]/height [m]²), BSA, forced expiratory volume in one second (FEV₁), FEV₁ to forced volume capacity ratio (FEV₁/FVC), and smoking history (former/current/never-smoker).

Taking account of potential ethnic differences between Chinese and Western populations, we calculated the baseline BSA according to an updated formula for contemporary Chinese subjects in this study: $BSA (m^2) = (0.0061 \times \text{height [cm]} + 0.0124 \times \text{weight [kg]} - 0.0099)$.⁶

Preoperative underlying comorbidities included: chronic obstructive pulmonary disease, tuberculosis, preoperative respiratory infection (PRI), hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, renal insufficiency, severe liver disease, previous malignancy, and steroid use. We defined the PRI as the existence of one or more of the following preoperative infectious conditions: bacterial/viral/fungal respiratory tract infection, obstructive pneumonia, aspiration pneumonia, bronchiectasis, and lung abscess. Severe liver disease included hepatitis B and C, hepatocirrhosis, severe fatty liver, and hepatic parasitic infections.^{6,12,13,21–23}

Multidisciplinary team meetings were held when necessary to discuss whether combined treatment modalities were required before surgery. Neoadjuvant/adjuvant therapy comprised cisplatin/paclitaxel-based chemotherapy or chemoradiotherapy with sustainable courses and dosages according to National Comprehensive Cancer Network Guidelines: China Edition.

Intraoperative variables

The intraoperative variables within our analysis are presented as follows: tumor location, severity of pleural adhesion (none/light/moderate/severe/atresia), degree of pulmonary fissure completeness, number of mediastinal lymph node dissections, estimated intraoperative blood loss (EIBL), and operation duration.^{12,21–23}

Pathological variables

The following major pathological parameters were evaluated: histological subtype, differentiation degree (low/moderate/high), tumor invasion (T stage), lymph node metastasis (LNM, N stage), and TNM stage, all of which were defined according to the seventh edition Union for International Cancer Control TNM Classification.

Primary and secondary outcomes

The primary outcome of interest was postoperative chylothorax. A diagnosis of chylothorax was initially identified by the copious chest tube output (> 500 mL/day) or the appearance of milky drainage. It was finally confirmed by biochemical analysis of the pleural fluid if the triglyceride level was > 110 mg/dL.^{14,24}

The secondary outcomes were the LOS and LOCD. The LOS was calculated from the date of surgery to discharge. The LOCD was defined as the number of postoperative days (PODs) that chest tube drainage was required.

Grouping criteria

The patients were divided into groups of with and without chylothorax. We then compared all patient characteristics between these groups to identify the clinicopathological variables that might predispose postoperative chylothorax.

Receiver operating characteristic (ROC) analysis was conducted to determine a threshold value of BSA with the discriminatory ability to predict the risk of chylothorax. We then investigated the demographic differences in baseline characteristics and surgical outcomes between the groups classified by this optimal BSA cutoff value.

Surgical procedure and perioperative care

Our single lobectomy was operated by a three-portal VATS procedure using the single-direction modified fissureless technique, as previously described by Liu *et al.*²⁵ Mechanical staplers were used in all included patients to divide the incomplete interlobar fissures and to close the bronchial stumps. SMLND was then routinely performed at the paratracheal nodes (Stations 2, 4) on the right side, subaortic and para-aortic nodes (Stations 5, 6) on the left side, subcarinal nodes (Station 7), para-esophageal nodes (Station 8), and pulmonary ligamentous nodes (Station

9).¹⁷ Small lymph ducts were usually observed during the SMLND, especially when performing lymph node dissection in Stations 4R or 7. We treated these small ducts using energy devices, and sometimes further enforced the injured area with surrounding tissue. After surgery, patients were managed in compliance with a standardized clinical pathway. The institutional policies for intensive pulmonary rehabilitation, residual lung recruitment assessment, chest tube management, and discharge criteria, have been reported in our previous studies.^{6,12,13,21–23,26–29}

An algorithm of chylothorax management is shown in Figure 1. Once diagnosed with chylothorax, patients were initially managed with oral intake cessation (OIC) and total parenteral nutrition (TPN). The attending surgeon sometimes administered a no-to-low adipose diet. After a diagnosis of chylothorax, conservative treatment should be strictly followed for three days. If the chest tube output remains > 400 mL or milky on the fourth day, pleurodesis with an intrapleural injection of interleukin-2 should be performed within the next 24 hours. If the pleurodesis controls the chest tube drainage, conservative treatment should be continued. If abundant chylous drainage persists after pleurodesis, surgical intervention via thoracic duct ligation with clipping of the leakage site should be determined based on the patients' general condition. Chylothorax was considered resolved when the chest tube output became serous and was < 200 mL/day, and patients started a normal diet, with

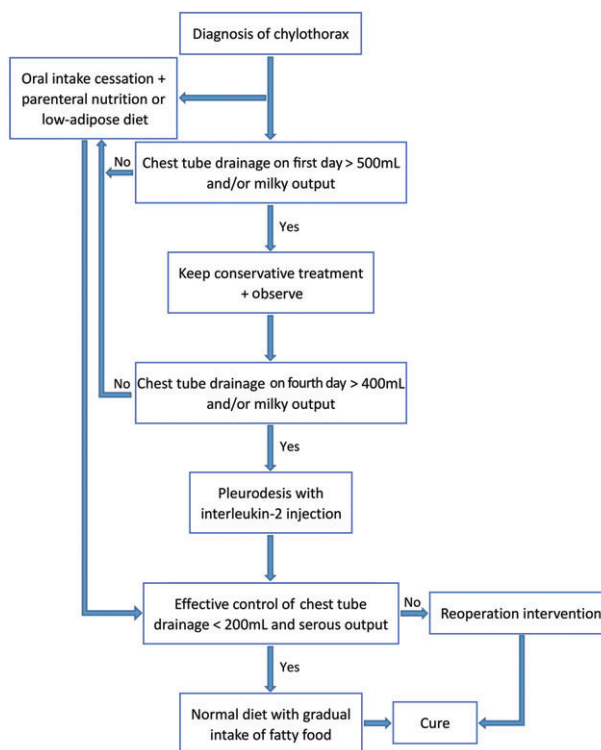


Figure 1 Management of chylothorax.

gradual resumption of fatty food. The chest tube can be removed if chylous drainage and air leak are no longer detected from the thoracic drainage system.

Statistical analysis

The dichotomous data are presented as patient numbers with percentages, and the continuous data as means with standard deviations and medians with interquartile ranges (IQRs). We employed Pearson's chi-squared or Fisher's exact tests to compare categorical variables and the Mann-Whitney *U* test to compare continuous variables. The effects of BSA on the LOS and LOCD were assessed by Kaplan–Meier analysis using a log-rank test.

Receiver operating characteristic analysis was performed to estimate the discriminative power of BSA to predict chylothorax. The area under curve (AUC) with its 95% confidence interval (CI) was also obtained.

Finally, according to the latest European Association of Cardio-Thoracic Surgery statistical and data reporting guidelines, we entered the threshold value of BSA and other dichotomous variables with a univariable *P* value of < 0.15 into a multivariable binary logistic-regression model using the Hosmer–Lemeshow test for precision and the C-statistic for calibration to identify the independent risk factors for chylothorax.³⁰

In order to provide concise and informative factors for the prediction of chylothorax, the continuous variables in the multivariable logistic regression model were dichotomized according to the clinically meaningful cutoffs widely accepted for risk stratification in routine clinical practice, including: the geriatric state, categorized by age > 65 years; overweight/obese state defined by BMI > 25 kg/m²; impaired lung function categorized by FEV1% < 80 and FEV1/FVC% < 70; and excessive VATS blood loss categorized by EIBL > 100 mL²² and prolonged VATS operation duration of > 150 minutes.³¹ We also included a BMI > 25 kg/m² into this multivariable logistic regression model to eliminate the potential confounding influence from an inextricable connection between BMI and BSA, although it had no statistical significance in univariable analysis. Odds ratios (ORs) with 95% CIs were extrapolated.

We used SPSS version 22.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. Statistical significance was revealed in both univariable and multivariable analyses at *P* < 0.05.

Results

Patient characteristics and outcomes

Patient characteristics

During the study period, a total of 1379 patients who underwent VATS lobectomy for operable NSCLC met the

eligibility criteria and were included in the study. Their baseline characteristics are presented in Table 1.

Our cohort consisted of 736 male and 643 female patients (53.4% vs. 46.6%), with a mean age of 61.41 ± 8.84 years (median 62 years, IQR 55–68 years). A frequency distribution histogram of BSA is presented in Figure 2. The mean BMI and BSA of the entire cohort were 23.34 ± 3.06 kg/m² (median 23.24 kg/m², IQR 21.11–25.30 kg/m²) and 1.73 ± 0.16 m² (median 1.71 m², IQR 1.62–1.83 m²), respectively. There were 562 active smokers (40.8%), and 960 patients (69.6%) were preoperatively diagnosed with one or more comorbidities. Neoadjuvant therapy was administered to 69 patients (5.0%), while 234 patients (17.0%) received adjuvant chemotherapy followed by VATS lobectomy.

The mean operation duration of the entire cohort was 113.34 ± 40.54 minutes (median 110, IQR 80–130 minutes). Lung adenocarcinoma was diagnosed in 1094 patients (79.3%), followed by squamous cell carcinoma in 255 (18.5%), and other NSCLC subtypes in 30 (2.2%) patients. Mediastinal LNM was confirmed by pathological criteria in 83 patients (6.0%). The mean number of mediastinal lymph nodes harvested per patient was 9.33 ± 2.19 (median 9, IQR 8–10) during VATS lobectomy.

Outcomes

Postoperative chylothorax developed in 26 patients (1.9%). A diagnosis of chylothorax was determined on 1–13 PODs (mean 3.11, median 3 PODs).

The major characteristics of 26 chylothorax cases are summarized in Table 2. Twenty of these patients were initially managed with oral intake cessation plus total parenteral nutrition, and another six patients received a low-adipose diet. Pleurodesis was further applied in 16 patients according to the algorithm (Fig 1), and none of the patients ultimately required reoperation. Chylothorax was resolved in all 26 cases, with the time to resolution ranging from 2 to 15 PODs (mean 5.04, median 4 PODs).

The mean LOCD and LOS of the entire cohort were 4.28 ± 3.04 days (median 3, IQR = 2–5 days) and 6.32 ± 4.82 days (median 5, IQR = 4–7 days), respectively. The mean LOCD and LOS in patients with chylothorax were 8.31 ± 4.46 days (median 9, IQR = 7–11 days) and 10.50 ± 4.42 days (median 11.5, IQR = 7–13 days), respectively.

Receiver operating characteristic analysis of body surface area (BSA) for the prediction of chylothorax

The ROC analysis of BSA showed an AUC of 0.70 (95% CI 0.62–0.79; *P* < 0.001) for predicting the risk of

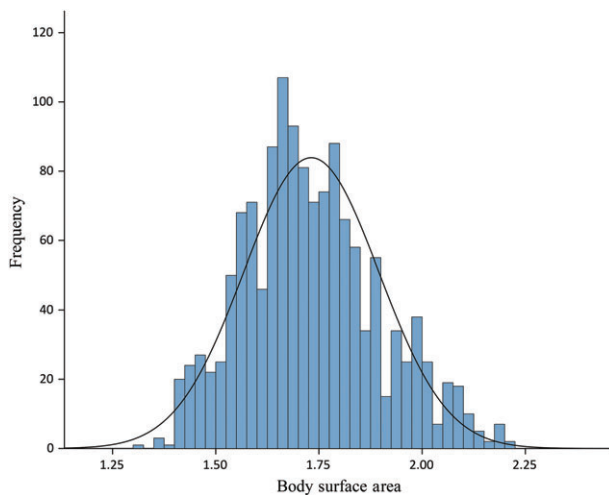
Table 1 Patient characteristics

Characteristics	Total (n = 1379)	Postoperative chylothorax		P
		Yes (n = 26)	No (n = 1353)	
Basic information				
Age (years)				
Mean ± SD	61.41 ± 8.84	63.38 ± 6.29	61.38 ± 8.87	0.33
Median (IQR)	62 (55–68)	63 (58–70)	62 (55–68)	
Gender (male, %)	736 (53.4%)	21 (80.8%)	715 (52.8%)	0.005
Body mass index (kg/m ²)				
Mean ± SD	23.34 ± 3.06	23.68 ± 2.82	23.33 ± 3.07	0.47
Median (IQR)	23.24 (21.11–25.30)	23.78 (20.82–25.61)	23.23 (21.11–25.27)	
Body surface area (m ²)				
Mean ± SD	1.73 ± 0.16	1.84 ± 0.14	1.73 ± 0.16	0.001
Median (IQR)	1.71 (1.62–1.83)	1.87 (1.70–1.94)	1.71 (1.62–1.83)	
FEV ₁ %				
Mean ± SD	83.75 ± 17.51	77.16 ± 17.61	83.88 ± 17.49	0.071
Median (IQR)	84.23 (75.44–92.86)	80.73 (56.58–86.09)	84.23 (75.61–92.86)	
FEV ₁ /FVC (%)				
Mean ± SD	77.22 ± 10.36	75.18 ± 8.69	77.26 ± 10.39	0.11
Median (IQR)	78.39 (73.26–82.86)	76.11 (71.74–78.85)	78.44 (73.51–82.86)	
Smoking history	562 (40.8%)	17 (65.4%)	545 (40.3%)	0.010
Preoperative underlying comorbidities				
Chronic obstructive pulmonary disease	274 (19.9%)	7 (26.9%)	267 (19.7%)	0.36
Tuberculosis	93 (6.7%)	0 (0.0%)	93 (6.9%)	0.32
Preoperative respiratory infection	169 (12.3%)	2 (7.7%)	167 (12.3%)	0.76
Hypertension	428 (31.0%)	10 (38.5%)	418 (30.9%)	0.41
Diabetes mellitus	170 (12.3%)	7 (26.9%)	163 (12.0%)	0.033
Coronary heart disease	153 (11.1%)	3 (11.5%)	150 (11.1%)	0.76
Hyperlipidemia	58 (4.2%)	2 (7.7%)	56 (4.1%)	0.30
Renal insufficiency	123 (8.9%)	2 (7.7%)	121 (8.9%)	0.83
Severe liver diseases	209 (15.2%)	3 (11.5%)	206 (15.2%)	0.16
Previous malignancy	154 (11.2%)	2 (7.7%)	152 (11.2%)	0.76
Steroid use	36 (2.6%)	1 (3.8%)	35 (2.6%)	0.40
Combined treatment modalities				
Neoadjuvant therapy	69 (5.0%)	2 (7.7%)	67 (4.9%)	0.79
Adjuvant chemotherapy	234 (17.0%)	7 (26.9%)	227 (16.8%)	0.19
Intraoperative parameters				
Tumor location				
Right upper lobe	421 (30.5%)	8 (30.8%)	413 (30.5%)	0.36
Left upper lobe	357 (25.9%)	4 (15.4%)	353 (26.1%)	
Right lower lobe	247 (17.9%)	5 (19.2%)	242 (17.9%)	
Left lower lobe	205 (14.9%)	3 (11.5%)	202 (14.9%)	
Right middle lobe	149 (10.8%)	6 (23.1%)	143 (10.6%)	
Severity of pleural adhesion				
None	578 (41.9%)	7 (26.9%)	571 (42.2%)	0.19
Light	465 (33.7%)	13 (50.0%)	452 (33.4%)	
Moderate	208 (15.1%)	3 (11.5%)	205 (15.2%)	
Severe/pleural atresia	128 (9.3%)	3 (11.5%)	125 (9.2%)	
Pulmonary fissure completeness				
Complete fissures	839 (60.8%)	12 (46.2%)	827 (61.1%)	0.12
Incomplete fissures	540 (39.2%)	14 (53.8%)	526 (38.9%)	
Number of mediastinal lymph nodes				
Mean ± SD	9.33 ± 2.19	9.26 ± 1.47	9.33 ± 2.21	0.16
Median (IQR)	9 (8–10)	9 (8–10)	9 (8–9.5)	
Estimated intraoperative blood loss (mL)				
Mean ± SD	78.10 ± 110.50	85.38 ± 36.36	77.95 ± 111.44	0.34
Median (IQR)	50 (20–100)	60 (50–100)	50 (20–60)	

Table 1 Continued

Characteristics	Total (n = 1379)	Postoperative chylothorax		P
		Yes (n = 26)	No (n = 1353)	
Operation duration (min)				
Mean ± SD	113.34 ± 40.54	137.62 ± 43.72	112.63 ± 42.54	0.002
Median (IQR)	110 (80–130)	120 (120–155)	105 (80–130)	
Pathological parameters				
Histology				
Adenocarcinoma	1094 (79.3%)	22 (84.6%)	1072 (79.2%)	0.72
Squamous cell carcinoma	255 (18.5%)	4 (15.3%)	251 (18.6%)	
Other subtypes of NSCLC	30 (2.2%)	0 (0.0%)	30 (2.2%)	
Differentiation degree				
Low	241 (17.5%)	6 (23.1%)	235 (17.4%)	0.63
Moderate	782 (56.7%)	15 (57.7%)	767 (56.7%)	
High	356 (25.8%)	5 (19.2%)	351 (25.9%)	
Tumor invasion (T-status)				
T ₁	766 (55.5%)	11 (42.3%)	755 (55.8%)	0.027
T ₂	568 (41.2%)	11 (42.3%)	557 (41.2%)	
T ₃	45 (3.3%)	4 (15.4%)	41 (3.0%)	
Lymph node metastasis (N-status)				
N ₀	1201 (87.1%)	22 (84.6%)	1179 (87.1%)	0.59
N ₁	95 (6.9%)	3 (11.5%)	92 (6.8%)	
N ₂	83 (6.0%)	1 (3.8%)	82 (6.1%)	
TNM stage				
I	1101 (79.8%)	18 (69.2%)	1083 (80.0%)	0.14
II	186 (13.5%)	7 (26.9%)	179 (13.2%)	
IIla	92 (6.7%)	1 (3.8%)	91 (6.7%)	

FEV₁, forced expiratory volume in one second; FEV₁/FVC, forced expiratory volume in one second to forced volume capacity ratio; IQR, interquartile range; NSCLC, non-small-cell lung cancer; SD, standard deviation; TNM, tumor node metastasis.

**Figure 2** Frequency distribution histogram of body surface area.

chylothorax (Fig 3). According to the ROC curve, a BSA of 1.69 m² was identified as the optimal cutoff value at which the sensitivity (96.2%) plus specificity (43.8%) was maximal. This threshold value of BSA was determined as the further grouping criterion.

Association between BSA and development of chylothorax

The mean BSA in patients with chylothorax was significantly higher than in patients without (1.84 ± 0.14 vs. 1.73 ± 0.16 m²; $P = 0.001$) (Table 1, Fig 4a). On the basis of the BSA cutoff, 798 patients had a BSA > 1.69 m² and 581 had a BSA ≤ 1.69 m². Of the 26 chylothorax cases, only two patients had a BSA ≤ 1.69 m², and the remaining 24 had BSA > 1.69 m². Thus, the incidence of chylothorax in patients with BSA > 1.69 m² was significantly higher than in patients with BSA ≤ 1.69 m² (3.0% vs. 0.3%; $P < 0.001$).

Univariable analysis of risk factors for chylothorax

Table 1 shows the associations between patient characteristics and the risk of chylothorax. Compared to patients without chylothorax, patients who developed chylothorax had were more likely male ($P = 0.005$), with a smoking history ($P = 0.010$), a higher dichotomized BSA ($P < 0.001$), diabetes mellitus ($P = 0.033$), and T₂₋₃-stage tumors ($P = 0.027$). No significant correction

Table 2 Clinicopathological characteristics of patients who experienced postoperative chylothorax (n = 26)

No.	Gender/ age	Location	Histology	Stage	Diagnosis on POD	Chylothorax		Total chest tube drainage (mL)	Treatment	Outcome
						stopped on POD	Daily mean chest tube drainage (mL)			
1	Male/74	Right upper lobe	Adeno-squamous carcinoma	T ₃ N ₀	4	19	284	5945	OIC + TPN + pleurodesis	Cured
2	Female/66	Right middle lobe	Adenocarcinoma	T ₁ N ₀	2	15	378	5300	OIC + TPN + pleurodesis	Cured
3	Female/67	Right upper lobe	Adenocarcinoma	T ₁ N ₀	4	14	305	4580	OIC + TPN + pleurodesis	Cured
4	Male/71	Right upper lobe	Squamous cell carcinoma	T ₁ N ₀	3	5	432	4750	OIC + TPN + pleurodesis	Cured
5	Male/70	Right lower lobe	Squamous cell carcinoma	T ₂ N ₀	4	6	426	4690	Low-adipose diet + pleurodesis	Cured
6	Male/76	Right middle lobe	Adenocarcinoma	T ₂ N ₀	2	11	345	4140	OIC + TPN	Cured
7	Male/56	Right lower lobe	Adenocarcinoma	T ₂ N ₀	6	10	338	4050	Low-adipose diet	Cured
8	Female/63	Left lower lobe	Adenocarcinoma	T ₃ N ₀	1	7	259	1810	OIC + TPN + pleurodesis	Cured
9	Male/61	Right upper lobe	Adenocarcinoma	T ₃ N ₂	3	8	367	3300	OIC + TPN + pleurodesis	Cured
10	Male/61	Left upper lobe	Adenocarcinoma	T ₁ N ₁	3	8	270	3245	OIC + TPN + pleurodesis	Cured
11	Male/59	Left upper lobe	Adenocarcinoma	T ₁ N ₀	3	7	293	2340	OIC + TPN + pleurodesis	Cured
12	Female/63	Right upper lobe	Adenocarcinoma	T ₂ N ₀	2	6	437	2810	OIC + TPN	Cured
13	Male/59	Right middle lobe	Adenocarcinoma	T ₂ N ₁	2	5	264	1320	OIC + TPN	Cured
14	Male/57	Right upper lobe	Adenocarcinoma	T ₂ N ₀	2	4	224	1120	Low-adipose diet	Cured
15	Male/70	Left lower lobe	Adenocarcinoma	T ₂ N ₀	3	6	312	1870	OIC + TPN	Cured
16	Male/70	Left upper lobe	Adenocarcinoma	T ₁ N ₀	2	5	346	1730	OIC + TPN	Cured
17	Male/56	Right middle lobe	Adenocarcinoma	T ₁ N ₀	3	8	383	3066	OIC + TPN + pleurodesis	Cured
18	Male/56	Right lower lobe	Adenocarcinoma	T ₁ N ₀	3	7	377	3015	OIC + TPN + pleurodesis	Cured
19	Male/62	Right lower lobe	Squamous cell carcinoma	T ₃ N ₀	2	7	274	1920	Low-adipose diet + pleurodesis	Cured
20	Male/58	Right middle lobe	Adenocarcinoma	T ₂ N ₀	3	5	277	1385	Low-adipose diet	Cured
21	Male/58	Right upper lobe	Adenocarcinoma	T ₂ N ₁	2	5	374	1870	OIC + TPN	Cured
22	Male/69	Left lower lobe	Adenocarcinoma	T ₁ N ₀	3	6	282	1690	OIC + TPN	Cured
23	Male/71	Left upper lobe	Adenocarcinoma	T ₂ N ₀	2	6	275	1924	Low-adipose diet + pleurodesis	Cured
24	Male/58	Right lower lobe	Adenocarcinoma	T ₁ N ₀	1	8	398	3186	OIC + TPN + pleurodesis	Cured
25	Male/57	Right middle lobe	Adenocarcinoma	T ₁ N ₀	3	7	372	2976	OIC + TPN + pleurodesis	Cured
26	Female/62	Right upper lobe	Adenocarcinoma	T ₂ N ₀	13	17	330	5940	OIC + TPN + pleurodesis	Cured

OIC, oral intake cessation; POD, postoperative day; TPN, total parenteral nutrition.

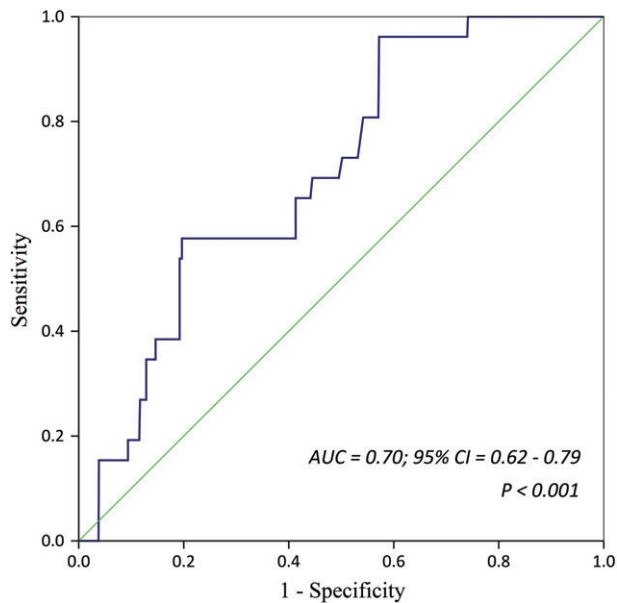


Figure 3 Receiver operating characteristic analysis revealing the discriminative power of body surface area for predicting the risk of chylothorax. AUC, area under the curve; CI, confidence interval.

was found between the risk of chylothorax and other clinicopathological parameters (Table 1).

With regard to the continuous variables, the duration of surgery was significantly prolonged in patients with chylothorax ($P = 0.002$). However, there was no difference in the mean age ($P = 0.33$), BMI ($P = 0.47$), FEV₁% ($P = 0.071$), FEV₁/FVC ($P = 0.11$), EIBL ($P = 0.34$), or number of mediastinal lymph nodes ($P = 0.16$) between patients with and without chylothorax (Table 1, Fig 4b).

Multivariable analysis of risk factors for chylothorax

A multivariable logistic regression model involving the BSA cutoff, overweight/obese state defined by BMI > 25 kg/m², and the other nine clinicopathological parameters with univariable $P < 0.15$ is shown in Table 3. The multivariable logistic regression model showed a C-statistic of 0.80 (95% CI 0.71–0.88; $P < 0.001$) and a Hosmer–Lemeshow P of 0.26 for goodness-of-fit (Fig 5). Finally, after adjusting for the confounding influence of other clinicopathological factors by multivariable logistic regression analysis, we found that BSA > 1.69 m² (OR 7.35, 95% CI 1.54–35.71; $P = 0.013$), diabetes mellitus (OR 2.53, 95% CI 1.01–6.34; $P = 0.048$), and operation duration > 150 min (OR 3.01, 95% CI 1.24–7.29; $P = 0.015$) could independently predict the risk of chylothorax.

Effects of dichotomized BSA on the length of hospital stay

Length of chest drainage

A Kaplan–Meier curve of the LOCD between patients with BSA > 1.69 m² and BSA ≤ 1.69 m² is presented in Figure 6a. The Kaplan–Meier analysis showed that the LOCD in patients with BSA > 1.69 m² (mean 4.60, 95% CI 4.30–4.91 days) was significantly longer than in patients with BSA ≤ 1.69 m² (mean 3.84, 95% CI 3.56–4.12 days; log-rank $P < 0.001$).

Length of stay

The LOS between patients with BSA > 1.69 m² and BSA ≤ 1.69 m² is shown in Figure 6b. The Kaplan–Meier analysis indicated that patients with BSA > 1.69 m² (mean 6.64,

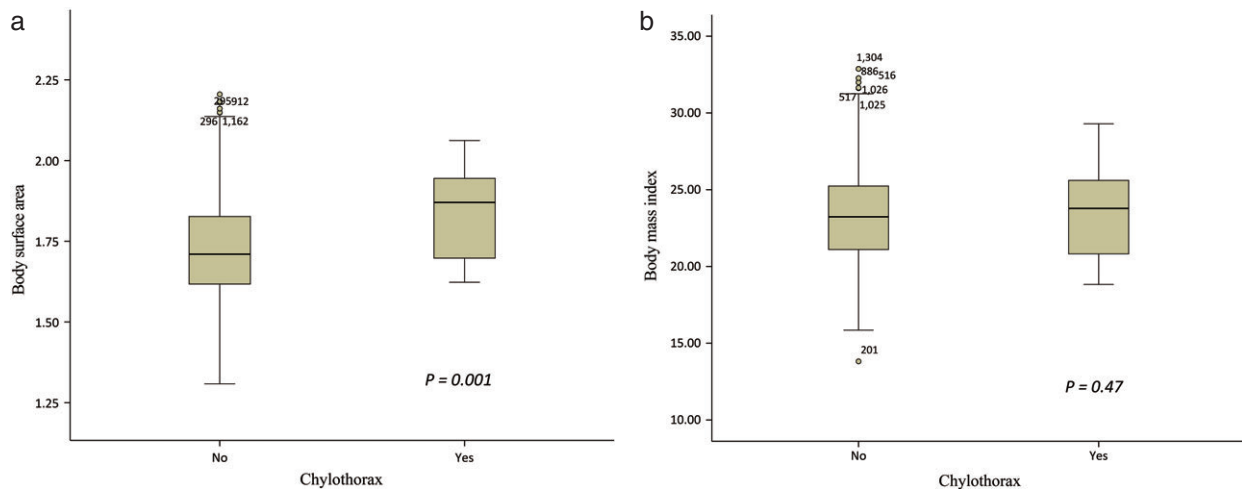


Figure 4 Box-plots revealing the mean (a) body surface area and (b) body mass index between patients with and without chylothorax.

Table 3 Multivariable analysis of risk factors for chylothorax

Estimated factors	Odds ratio	95% Confidence interval	P
Male gender	1.31	0.39–4.41	0.67
Smoking history	1.02	0.36–2.92	0.97
Overweight/obesity (BMI > 25 kg/m ²)	1.62	0.68–3.89	0.28
Body surface area (> 1.69 vs. ≤ 1.69 m ²)	7.35	1.54–35.71	0.013
FEV ₁ % (< 80 vs. ≥ 80)	1.22	0.48–3.07	0.67
FEV ₁ /FVC% (< 70 vs. ≥ 70)	1.62	0.54–4.83	0.38
Diabetes mellitus	2.53	1.01–6.34	0.048
Operation duration (> 150 vs. ≤ 150 min)	3.01	1.24–7.29	0.015
Poorly-developed pulmonary fissure	1.40	0.61–3.24	0.43
T stage (T ₂₋₃ vs. T ₁)	1.15	0.46–2.84	0.77
TNM stage (II–IIIa vs. I)	1.13	0.43–2.99	0.81

BMI, body mass index; FEV₁, forced expiratory volume in one second; FEV₁/FVC, forced expiratory volume in one second to forced volume capacity ratio; TNM, tumor node metastasis.

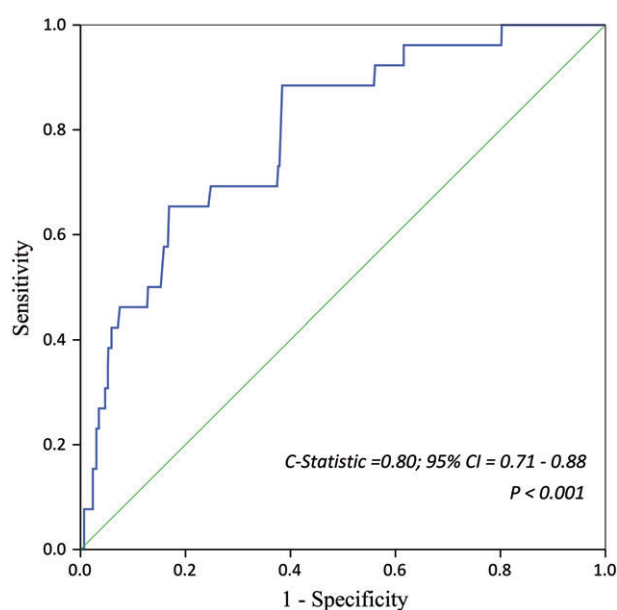


Figure 5 C-statistic revealing discriminative power of the multivariable logistic regression model for the prediction of postoperative chylothorax. CI, confidence interval.

95% CI 6.28–7.01 days) had significantly prolonged LOS compared to patients with BSA ≤ 1.69 m² (mean 5.89, 95% CI 5.53–6.24 days; log-rank *P* = 0.001).

Discussion

Key results

The main finding of the present study was that patients with a larger BSA suffered from a significantly higher risk

of chylothorax complicating VATS lobectomy for NSCLC. ROC analysis showed an optimal cutoff value of BSA of 1.69 m², with maximum joint sensitivity (96.2%) and specificity (43.8%) for the prediction of chylothorax. Finally, we found that BSA > 1.69 m² could serve as an independent risk factor for postoperative chylothorax after eliminating the bias risks from other confounding factors by multivariable logistic regression analysis. In addition, Kaplan–Meier analysis showed both prolonged LOCD and LOS in patients with BSA > 1.69 m².

Interpretations

As a rare but challenging complication, postoperative chylothorax can cause increased mortality if proper intervention is not applied in time, because thoracic duct rupture causes a significant loss of protective adipose, protein, and T-lymphocytes, which predisposes malnutrition and immunosuppression and disorders induced by the accumulation of pleural chyle.¹⁴ The most common cause of chylothorax complicating thoracic surgery is iatrogenic injury when performing en bloc resections with radical SMLND, resulting in some levels of lymphatic drainage disruption and chyle leakage into the pleural space.^{14,15} Chylothorax is a particularly severe complication after esophagectomy because a leakage usually occurs within the main thoracic duct.^{14,32} However, for elective pulmonary resections, lymphatic disruption generally originates from an injury to the small collaterals of the thoracic duct within the mediastinum at the base of N₂-stage lymph nodes, increasing the probability of cure by conservative treatment.¹⁵

In our cohort of 1379 VATS lobectomy cases, we found a lower incidence of postoperative chylothorax (1.9%) than the range of 1.4% to 4.0% reported in the most recent large registry studies.^{15–17} This variation may relate to the fact that the patients underwent VATS lobectomy with SMLND at a later period in our study, as a result of our learning curve. The morbidity rate will drop with an increase in experience of VATS. Prior studies have shown various results addressing the risk of chylothorax. Neoadjuvant therapy, right anatomical side, and pneumonectomy with aggressive lymphadenectomy seem to have the potential to predict the occurrence of chylothorax, however conclusive evidence is currently lacking.^{15–17} These clinicopathological factors were found to be predictive of chylothorax in our study population.

The highlight of the present study was to demonstrate for the first time the specific impact of BSA on the risk of chylothorax complicating VATS lobectomy in a large cohort of patients. As an easy way to measure the body size, BSA has a much closer connection to height than BMI because of some essential differences between their formulas. With BMI calculation, the height is positioned

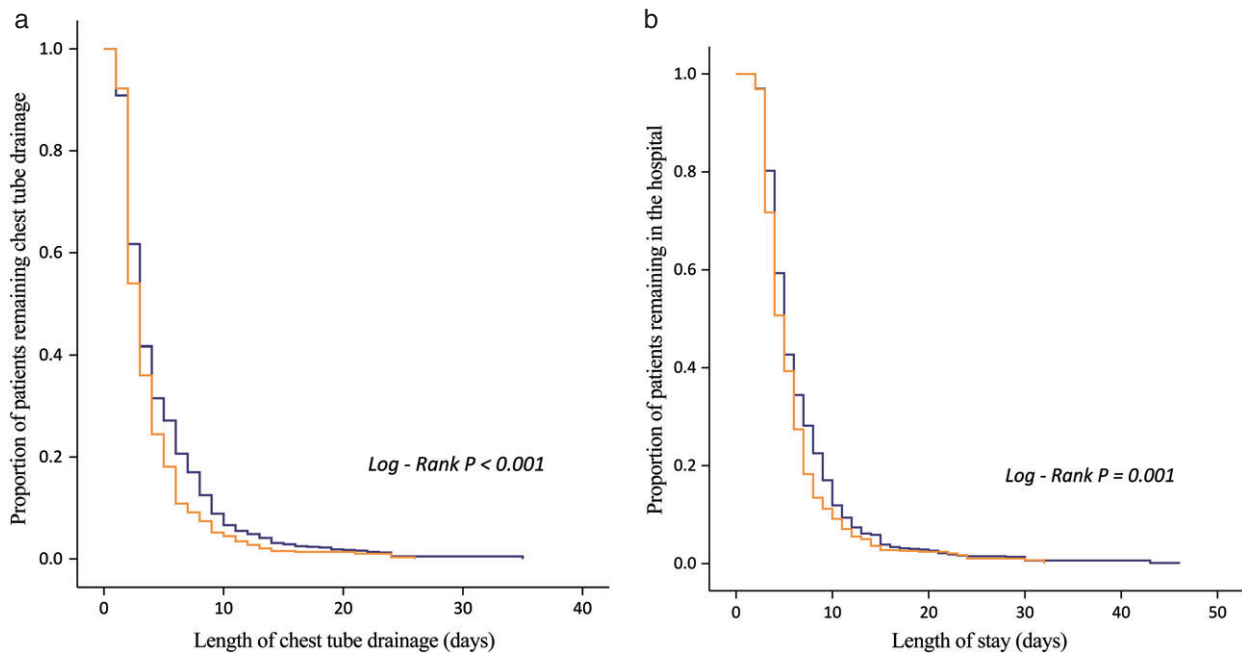


Figure 6 Kaplan–Meier analysis curves for (a) length of chest drainage and (b) length of stay between patients with body surface area (BSA) > 1.69 m² and BSA ≤ 1.69 m². (—) BSA > 1.69 and (---) BSA ≤ 1.69.

at the denominator, whereas the height is directly used as one of the variables in a binary linear formula to extrapolate the BSA.^{6,13} Accordingly, BSA may be more closely related to anthropometric measurements and potentially affect some perioperative outcomes. In the present study, BSA > 1.69 m² was identified as the optimal cutoff value by ROC analysis and thus used for further grouping. We initially found a significantly higher incidence of chylothorax in patients with BSA > 1.69 m² than in patients with BSA ≤ 1.69 m², and show the significant predictive value of BSA > 1.69 m² to predict the risk of chylothorax. Both the LOCD and LOS were also significantly prolonged in patients with a higher dichotomized BSA.

In an earlier cohort of 208 consecutive robotic-assisted lobectomies, Velez-Cubian *et al.* suggested that small body habitus has the potential to increase the surgical difficulty and risk of perioperative complications because patients with a smaller BSA generally have smaller pleural cavities, which results in limited access to the operative field and poor thoroscopic visualization.¹⁹ Our present results, as well as those in our earlier study, seem contrary to this explanation;⁶ however there is no evidence to explain these varying results. We suggest that the following two hypotheses may be considered for possible interpretations.

First, current evidence shows that a larger body size, which is usually indicated by a higher BSA or BMI, may predispose to LNM and further require extensive lymph node dissection in a variety of oncological specialties,

resulting in a poor prognosis.^{33–37} In our cohort, both N1 and N2 stage LNM were more frequently observed in patients with BSA > 1.69 m² than in patients with BSA ≤ 1.69 m², although LNM is not associated with a risk of chylothorax (Table 1). Mediastinal lymph nodes are generally located around important blood vessels and airways. Once they are affected by oncological progression, enlarged lymph nodes can directly obscure the local anatomical structures and increase the surgical difficulty of thoroscopic SMLND. In addition, several adjuvant therapeutic options applied in patients with LNM, such as neoadjuvant therapy, may further aggravate the severity of calcification and adhesion over the mediastinal structures. Thus, when performing SMLND in patients with mediastinal LNM, forcible and sharp adhesiolysis may easily cause injury to the thoracic duct with its branches, resulting in the development of chylothorax.

Another possible explanation may be the potential connection between BSA and vasculature size. Patients with a higher BSA are considered to have larger diameters of vessels and ducts.³⁸ Therefore, thoroscopic SMLND adjacent to the enlarged thoracic duct collateral may increase the probability of rupture of lymphatic drainage. Moreover, once a chyle leakage occurs, patients with a larger vasculature size can rapidly accumulate more chylous fluid in the pleural space. Our results showing an obviously higher daily pleural drainage in chylothorax cases with BSA > 1.69 m² verify this hypothesis to some extent.

Generalizability

Comprehensive perioperative risk assessment can affect surgeons' decisions on surgical procedure. Our multivariable results suggest that incorporating a BSA categorization into a risk stratification tool to stratify the morbidity risk and assist to design the best therapeutic strategy may be a more adequate method, even though BSA cannot be significantly modified by preoperative interventions. In addition, our results may help to select the participants for a teaching program of VATS techniques or during a surgeon's early learning, in order to avoid adverse events and train young surgeons more effectively.

Limitations

The following major limitations in this study must be sufficiently acknowledged. First, the study was subject to the inherent limitations of any single institutional retrospective analysis. On the one hand, potential selection bias might complicate our findings, although we made a significant effort, including the establishment of strict eligibility criteria, expansion of sample size, and adjustment of the multivariable logistic regression model, to minimize the bias risks from potential confounding factors. On the other hand, although there were over 1300 patients included in our series, only 26 cases developed chylothorax cases, which may not be sufficient to establish an effective logistic regression model with 11 perioperative parameters, because the validity of multivariable logistic regression analysis would obviously be attenuated if there were few target events for each included variable. We speculate that the limited sample may have led to slightly larger 95% CIs of OR statistics in this study, which have the potential to produce some unstable outcomes.

Second, the AUC derived from ROC analysis was slightly low but with a *P* value of < 0.001. This may be insufficient evidence of the clinical significance of BSA. The threshold value of BSA has high sensitivity (96.2%) but relatively low specificity (43.8%) to predict chylothorax. The optimal BSA cutoff value determined by ROC analysis might carry selection bias because this criterion of cut-point establishment has the potential to introduce an increased rate of misclassification under the intuitive visualization, as Perkins *et al.* described in their epidemiological report by exemplifying a dataset of preeclampsia.³⁹ This might attenuate the practical purpose of our findings in routine clinical practice.

Third, the rate of chylothorax can also depend on the experience of the surgeon. However, it may be difficult to conduct appropriate quantitative analysis on this artificial factor.

Fourth, both conservative and surgical treatments of chylothorax were not discussed because of limitations in the primary study objectives, although surgeons perceive chylothorax management as more clinically meaningful.

Finally, some discrepancies between currently available BSA formulas should be taken into account. We used a formula developed among contemporary Chinese subjects for this study. Thus, our findings should be judiciously evaluated in other ethnic populations.

In conclusion, our study demonstrates that BSA has the ability to act as a novel categorical risk factor for chylothorax complicating VATS lobectomy for NSCLC. Meanwhile, a higher level of BSA is also significantly associated with the prolonged LOS and LOCD. It may be more helpful to incorporate a BSA cutoff into the perioperative risk assessment models. More large-scale multi-center analyses with accurate evaluation methods are highly advocated to further confirm and modify our findings in the future.

Acknowledgments

We thank Miss. Jing Liu, from the Institution of Medical Statistics, West China School of Public Health, Sichuan University, Chengdu, China, for her help proofreading the statistical analyses in this manuscript.

Disclosure

No authors report any conflict of interest.

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