



Does morbid obesity influence perioperative outcomes after video-assisted thoracic surgery (VATS) lobectomy for non-small cell lung cancer? Analysis of the Italian VATS group registry

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Abstract

Objectives Obesity in Europe, and worldwide, has been an increasing epidemic during the past decades. Moreover, obesity has important implications regarding technical issues and the risks associated with surgical interventions. Nevertheless, there is a lack of evidence assessing the influence of obesity on video-assisted thoracic surgery (VATS) lobectomy results. Our study aimed to assess the impact of morbid obesity on perioperative clinical and oncological outcomes after VATS lobectomy using a prospectively maintained nationwide registry.

Methods The Italian VATS lobectomy Registry was used to collect all consecutive cases from 55 Institutions. Explored outcome parameters were conversion to thoracotomy rates, complication rates, intra-operative blood loss, surgical time, hospital postoperative length of stay, chest tube duration, number of harvested lymph-node, and surgical margin positivity. **Results** From 2016 to 2019, a total of 4412 patients were collected. 74 patients present morbid obesity (1.7%). Multivariable-adjusted analysis showed that morbid obesity was associated with a higher rate of complications (32.8% vs 20.3%), but it was not associated with a higher rate of conversion, and surgical margin positivity rates. Moreover, morbid obesity patients benefit from an equivalent surgical time, lymph-node retrieval, intraoperative blood loss, hospital postoperative length of stay, and chest tube duration than non-morbid obese patients. The most frequent postoperative complications in morbidly obese patients were pulmonary-related (35%).

Conclusion Our results showed that VATS lobectomy could be safely and satisfactorily conducted even in morbidly obese patients, without an increase in conversion rate, blood loss, surgical time, hospital postoperative length of stay, and chest tube duration. Moreover, short-term oncological outcomes were preserved.

Keywords Obesity · Lobectomy · Video-assisted thoracic surgery · Morbidity · Mortality · Lung Cancer

Obesity in Europe, and worldwide, has been an increasing epidemic during the past decades [1, 2]. In particular, in

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Italy, the obesity rate augments from 6% in 1991 to 10% in 2018 [3].

Increasing obesity incidence represents a noteworthy health problem, particularly considering that it is associated with the risk of developing chronic diseases such as

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cardiovascular disease, musculoskeletal disorders, type 2 diabetes, hypertension, coronary heart disease, sleep apnea, and kidney failure [2, 4, 5] in addition to a generally decreased life expectancy, principally in the young adult population [6-8]. Moreover, all these conditions could increase the risk of postoperative surgical complications, with mutual boost effects [9, 10]. Additionally, obesity itself has important implications regarding technical issues during the surgical procedure [11, 12].

In the literature, there is emerging evidence on relationship between higher BMI and lung cancer [13]. Indeed, the ratio of overweight and obese patients with lung cancer who present for major pulmonary resection for NSCLC incessantly raised during the last decades [14].

In order to increase perioperative outcomes and decrease postoperative complications, minimally invasive thoracic surgical procedures [i.e., video-assisted thoracic surgery (VATS) lobectomy] have been largely adopted worldwide, in alternative to classic open surgery via thoracotomy [14]. Recently, the results of a UK multicentric VIOLET randomized controlled trial showed a relationship between VATS lobectomy and enhanced postoperative clinical outcome [15]. However, there is a lack of evidence assessing the influence of morbid obesity on VATS lobectomy results.

The aim of our study was to assess the impact of morbid obesity (Body Mass Index \geq 40) on perioperative clinical and oncological outcomes after VATS lobectomy using a prospectively maintained nationwide registry, the Italian VATS group registry [16].

Methods

From 2016 to 2019, out of a total of 4972 patients submitted to thoracoscopic major lung resection by 55 centers of the Italian VATS Group database, 4412 patients submitted to VATS lobectomy for lung cancer were included in the present study. Patients submitted to VATS segmentectomy, bilobectomy, or pneumonectomy were excluded. Informed consent was obtained from all individual participants included in the study.

Primary outcomes explored were conversion to thoracotomy rates and complication rates (Grade ≥ 2 according to the Clavien–Dindo classification [17]). An additional analysis on primary endpoints was performed stratifying patients according to BMI as follows: $\leq 30, 30-40, \geq 40$.

As secondary outcomes, surgical margin positivity rates, intra-operative blood loss, surgical time, hospital postoperative length of stay, chest tube duration, and the number of harvested lymph-node were assessed.

Statistical analysis

Baseline patient characteristics are summarized by number and percentages, or median and interquartile range (IQR), as appropriate. Between-group differences were evaluated by Wilcoxon–Mann–Whitney test (continuous variables) or χ^2 test or Fisher's exact test (categorical variables), as appropriate.

Univariable and multivariable-adjusted logistic regression models were used to evaluate categorical outcomes, while different continuous outcomes were compared by the Wilcoxon–Mann–Whitney test. The variables in the adjusted models were age, gender, smoking history, CCI, ECOG performance status, FEV1%, DLCO%, surgeon experience, pT stage, pN stage, preoperative diagnosis, and performed adhesiolysis.

All statistical tests were two-sided and P values of 0.05 or less were considered statistically significant. Data analysis was performed using Stata software version 15.1 (Stata-Corp, College Station, Texas).

Results

Median BMI in the present cohort was 25.8 (IQR 23.4–28.7) (Table 1). Most of the patients present a BMI < 40 (4338–98.3%), while out of 74 patients were morbidly obese (BMI \geq 40). Most patients were male (2681–60.7%) and the mean age at the time of surgery was 69 years (IQR 62–75). 425 (9.6%) cases of conversion to thoracotomy were observed in the whole population. Median surgical time was 174 min (IQR 135–210), the median number of harvested lymph-nodes was 11 (IQR 7–16), median intraoperative blood loss 100 ml (IQR 50–200), median chest drain duration 4 days (IQR 3–5), and median postoperative length of stay 5 days (IQR 4–7). In the whole cohort, 906 (20.5%) complications and 100 (2.3%) surgical margin positivity cases were observed (Table 2).

At the univariable analysis, the Morbid obesity group showed a significant higher post-operative morbidity rate (26 vs 880—35.1% vs 20.3%) [Odds Ratio (OR) 2.13, 95% C.I. 1.31–3.45, P = 0.002). The most frequent postoperative complications in morbidly obese patients were pulmonary-related (9–35%): 3 persistent pleural effusion/ empyema, 2 prolonged air leak (>7 days), 2 prolonged mechanical ventilation, 1 pulmonary embolism, 1 atelectasis. Morbid obesity was not associated with a higher rate of conversion (10 vs 415—13.5% vs 9.6%) (OR 1.48, 95% C.I. 0.75–2.90, P = 0.26) and surgical margin positivity rates (1 vs 99—1.4% vs 2.4%) (OR 0.58, 95%

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 Table 1
 Baseline characteristics in the overall population

Table 2 Baseline characteristics: morbid obesity (BMI \geq 40) vs Nonmorbid obesity (BMI < 40) groups

| Factor | All | | | |
|---|------------------|--|--|--|
| | n=4412 | | | |
| BMI, <i>n</i> (%) | | | | |
| Median (IQR ^a) | 25.8 (23.4–28.7) | | | |
| ≥ 40 | 74 (1.7) | | | |
| <40 | 4338 (98.3) | | | |
| Age (years), median (IQR) | 69 (62–75) | | | |
| Gender (male), n (%) | 2681 (60.7) | | | |
| Smoking history (ever), n (%) | 3137 (71.1) | | | |
| CCI, median (IQR) | 3 (3–4) | | | |
| ECOG, median (IQR) | 0 (0–1) | | | |
| FEV1 (%), median (IQR) | 93 (80–106) | | | |
| DLCO (%), median (IQR) | 83 (71–95) | | | |
| Surgeon experience ^b , n (%) | 2676 (60.7) | | | |
| cT stage, <i>n</i> (%) | | | | |
| cT1a-b-c | 2939 (66.6) | | | |
| cT2a–b | 1067 (24.2) | | | |
| cT3 | 322 (7.3) | | | |
| cT4 | 83 (1.8) | | | |
| cN stage, <i>n</i> (%) | | | | |
| cN0 | 3873 (87.9) | | | |
| cN1 | 274 (6.3) | | | |
| cN2 | 256 (5.8) | | | |
| pT stage, <i>n</i> (%) | | | | |
| pT1a–b–c | 2893 (66.1) | | | |
| pT2a–b | 1054 (24.1) | | | |
| pT3 | 336 (7.6) | | | |
| pT4 | 97 (2.2) | | | |
| pN stage, <i>n</i> (%) | | | | |
| pN0 | 3873 (81.8) | | | |
| pN1 | 418 (9.9) | | | |
| pN2 | 351 (8.3) | | | |
| Preoperative diagnosis (yes), n (%) | 1900 (43.1) | | | |
| Adhesiolysis (yes), n (%) | 1218 (27.6) | | | |

BMI Body Mass Index, CCI Charlson comorbidity index, ECOG Eastern Cooperative Oncology Group performance status

^aInterquartile range

^b > 50 VATS lobectomy procedures performed

C.I. 0.080–4.23, P = 0.59). Morbid obesity patients presented an equivalent surgical time (180 min vs 173 min, P = 0.116), lymph-node retrieval (9 vs 11, P = 0.835), intraoperative blood loss (100 ml vs 100 ml, P = 0.554), chest tube duration (4 days vs 4 days, P = 0.969), and hospital post-operative length of stay (5 days vs 5 days, P = 0.729) than non-morbid obese patients (Figs. 1 and 2).

At the multivariable analyses (Table 3), Morbid obesity resulted to be an independent prognostic factor for postoperative morbidity rate (OR 2.74, 95% C.I. 1.63-4.61,

| Factor | $BMI \ge 40$ | BMI < 40 | Р |
|---|--------------|-------------|-------|
| | n=74 | n=4338 | |
| Age (years), median (IQR ^a) | 68 (59–63) | 69 (63–75) | 0.089 |
| Gender (male), n (%) | 40 (54.1) | 2641 (60.9) | 0.233 |
| Smoking history (ever), n (%) | 50 (67.6) | 3087 (71.2) | 0.499 |
| CCI, median (IQR) | 3 (2–4) | 3 (3–4) | 0.041 |
| ECOG, median (IQR) | 0 (0–1) | 0 (0–1) | 0.835 |
| FEV1 (%), median (IQR) | 93 (82–109) | 93 (80–106) | 0.884 |
| DLCO (%), median (IQR) | 89 (78–100) | 83 (71–95) | 0.008 |
| Surgeon experience ^b , n (%) | 39 (52) | 2637 (60.8) | 0.099 |
| cT stage, <i>n</i> (%) | | | 0.103 |
| cT1a–b–c | 58 (78.3) | 2881 (66.4) | |
| cT2a–b | 14 (18.9) | 1053 (24.3) | |
| cT3 | 1 (1.4) | 321 (7.4) | |
| cT4 | 1 (1.4) | 82 (1.9) | |
| cN stage, <i>n</i> (%) | | | 0.683 |
| cN0 | 63 (85.1) | 3810 (87.9) | |
| cN1 | 7 (9.5) | 267 (6.2) | |
| cN2 | 4 (5.4) | 343 (5.9) | |
| pT stage, <i>n</i> (%) | | | 0.063 |
| pT1a-b-c | 57 (77.0) | 2836 (65.9) | |
| pT2a–b | 14 (18.9) | 1040 (24.1) | |
| pT3 | 1 (1.4) | 335 (7.8) | |
| pT4 | 2 (2.7) | 95 (2.2) | |
| pN stage, <i>n</i> (%) | | | 0.584 |
| pN0 | 55 (77.4) | 3406 (81.9) | |
| pN1 | 8 (11.3) | 410 | |
| pN2 | 8 (11.3) | 343 (8.2) | |
| Preoperative diagnosis (yes), n (%) | 2469 (56.9) | 43 (58.1) | 0.837 |
| Adhesiolysis (yes), n (%) | 3139 (72.4) | 55 (74.3) | 0.708 |

BMI Body Mass Index, CCI Charlson comorbidity index, ECOG Eastern Cooperative Oncology Group performance status

^aInterquartile range

^b > 50 VATS lobectomy procedures performed

P < 0.001). Morbid obesity was not associated with a higher rate of conversion (OR 1.63, 95% C.I. 0.79, 3.39, P=0.19).

The additional multivariable analysis showed morbid obesity as independent prognostic factor for morbidity rate (BMI ≤ 30 as reference; BMI 30–40 OR 1.34, 95% C.I. 0.87, $2.07, P = 0.16; \ge 40 \text{ OR } 2.74, 95\% \text{ C.I. } 1.63-4.59, P < 0.001),$ but not for conversion rates (BMI \leq 30 as reference; BMI

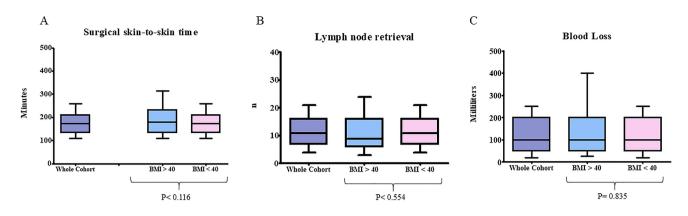


Fig. 1 Morbid obesity (BMI \geq 40) Versus Non-morbid obesity (BMI < 40): Box-and-whisker plots illustrate the distribution of surgical time (A), lymph-node retrieval (B), and blood loss (C)

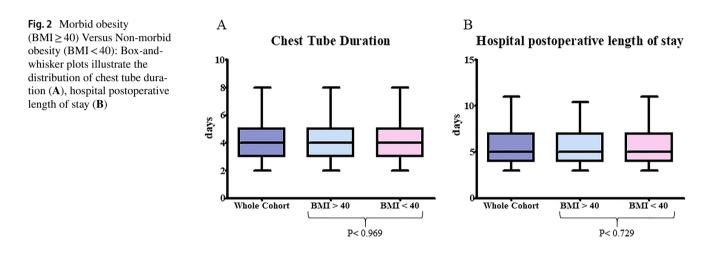


Table 3 Logistic regression models from primary endpoint: Morbid obesity (BMI ≥ 40) vs Non-morbid obesity (BMI < 40) groups

| Factor | _ | BMI<40 <i>n</i> =4338 | Univariable model | Р | Multivariable-adjusted model ^a | Р |
|---|-----------|--------------------------|------------------------------|-------|---|---------|
| Post-operative complications (yes), n (%) | 26 (35.1) | 880 (20.3) | OR 2.13, 95% C.I. 1.31–3.45 | 0.002 | OR 2.74, 95% C.I. 1.63-4.61 | < 0.001 |
| Conversion to thoracotomy (yes), n (%) | 10 (13.5) | 415 (9.6) | OR 1.48, 95% C.I. 0.75-2.90 | 0.26 | OR 1.63, 95% C.I. 0.79, 3.39 | 0.19 |
| Surgical margin positivity (yes), n (%) | 1 (1.4) | 99 (2.4) | OR 0.58, 95% C.I. 0.080–4.23 | 0.59 | OR 0.67, 95% C.I. 0.089, 5.07 | 0.70 |

BMI Body Mass Index

^aAdjusted for age, gender, smoking history, CCI, ECOG performance status, FEV1%, DLCO%, surgeon experience, pT stage, pN stage, preoperative diagnosis, and performed adhesiolysis

30–40 OR 1.48, 95% C.I. 0.86, 2.56, P=0.16; ≥40 OR 1.59, 95% C.I. 0.77, 3.27, P=0.21).

Discussion

The minimally invasive surgical approaches have been established in order to increase perioperative outcomes and decrease postoperative complications, with respect to the standard open approaches.

Also, in thoracic surgery, these approaches [i.e., VATS and robotic-assisted thoracic surgery (RATS)] should be

advisable especially in the high-risk surgical populations, like the elderly and obese ones [18]. Presumably, the ratio of patients with elevated BMI referred to thoracic surgical procedures will constantly increase in the next future [11, 14]. Consequently, it is mandatory to obtain a comprehensive insight into the effect of morbid obesity on perioperative outcomes in such patients [11, 14].

The results of the present study suggest that, in the cohort from the Italian VATS Group database,

- (1) Morbid obesity was not associated with a higher rate of conversion and surgical margin positivity rates.
- (2) Morbid obesity was associated with a higher rate of complications, in particular with the pulmonary-related one.
- (3) Morbid obesity patients benefit from an equivalent surgical time, lymph-node retrieval, intraoperative blood loss, hospital postoperative length of stay, and chest tube duration than non-morbid obese patients.

Normally, patients with increased BMI are characterized by the presence of cardiovascular comorbidities, which could jeopardize hemodynamic stability. Similarly, obese patients present a decrease of residual capacity, augmented airway resistance, and a reduction of chest wall compliance, which may increase the risk of pulmonary complications [4, 19–22]. Furthermore, more than 40% of obese patients had Obstructive Sleep Apnea Syndrome [23]. OSAS patients present the incapacity to maintain airway patency, with intermittent respiratory obstruction and intensification of respiratory efforts. Finally, drug metabolism could strongly differ between patients with normal and increased BMI; consequently, titration and careful dosing should be mandatory. For all these reasons, it could be intuitive that patients with elevated BMI developed more frequently post-operative complications. Nevertheless, the current literature presents contradictory results on this topic, and the "obesity paradox," namely the protective effect of obesity on complication incidence, has been observed also in the thoracic surgery cohort analysis [24–28]. On the other hand, several studies presented a higher incidence of complications (notably pulmonary ones) in obese patients submitted to thoracic surgery [12, 21, 29].

The foundation of the obesity paradox has not been clearly elucidated, but protective effect peripheral body fat and reduced inflammatory response are common assumptions reported in the literature [10]. Nevertheless, Childers and Allison [30] proposed a mathematical model (U-shaped curve) in order to explain this occurrence: the highest mortality was presented by severe BMI values (both morbid obesity and severe underweight), while overweight, light, or moderate obesity shown lower mortality rate. Indeed, Tulinskýc et al. suppose that if the ratio of morbidly obese patients in their cohort was higher, the occurrence of complications would have been higher [28]. Coherently, in the present study, we focalize on morbidly obese patients. Our results showed that morbid obesity was associated with a higher rate of complications after VATS lobectomy, with a high rate of pulmonary-related complications. In particular, only 30% of the pulmonary complications observed in Morbid could be considered major one. Nevertheless, greater care and attention must be paid in the early recognition and treatment of this kind of morbidity, that this particularly related to obesity pathophysiology [5].

Interestingly, we did not find an association between morbid obesity and other perioperative clinical or technical outcomes, as the rate of conversion, surgical time, and surgical margin positivity rates, lymph-node retrieval, intraoperative blood loss, hospital postoperative length of stay, and chest tube duration. In particular, our findings are in contrast with St Julien et al. that investigated the database of the society of thoracic surgeons and observed an increased operating time by 7.2 min for every 10-unit increase in BMI [29]. On the other hand, our results were in line with a recent study on RATS lobectomy that demonstrated equivalence in surgical time between obese and non-obese patients [24].

The present study could be affected by several limitations, principally associated with a large multi-institutional dataset setting, and the retrospective nature of the research. Nevertheless, the major strength of our analysis is the use of a large, homogeneous, and prospectively maintained national scale patient cohort, as the one proved by the Italian VATS Group database. This fact permits the data reliability and, consequently, reinforces our conclusions.

To conclude, our findings showed that VATS lobectomy could be safely and satisfactorily conducted even in morbidly obese patients, without an increase in conversion rate, blood loss, surgical time, hospital postoperative length of stay, and chest tube duration. Moreover, short-term technical and oncological outcomes were preserved. Nevertheless, greater care and attention must be paid to the possible development of morbidity, and in particular pulmonary ones, in the postoperative period.

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