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Clinical impact of the lower limit of normal of FEV1/FVC on survival in lung cancer patients undergoing thoracic surgery

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ABSTRACT

Background: Previously, it has been shown that using a fixed ratio of FEV1/FVC of 0.7 to classify airway obstruction could not predict survival outcomes in lung cancer patients undergoing thoracic surgery. We demonstrated that use of the lower limit of normal (LLN) of FEV1/FVC may allow better risk stratification for postoperative outcomes in patients with chronic obstructive pulmonary disease (COPD) patients. Nevertheless, it remained unclear whether survival outcomes in this population could be predicted by LLN-defined airway obstruction.

Objective: To evaluate the clinical relevance of LLN-defined airway obstruction to survival outcomes.

Methods: The clinical relevance of LLN-defined airway obstruction was analyzed and compared in 699 subjects, using Kaplan–Meier curves and the log-rank test. A Cox regression model was used to explore prognostic risk factors.

Results: One hundred-and-seventy-eight subjects were assigned to the below-LLN group, in which airflow obstruction determined by the FEV1/FVC ratio was below the LLN. Five hundred-and-twenty-one subjects were assigned to the above-LLN group. The below-LLN group had a worse overall survival (OS) and disease-free survival (DFS) than the above-LLN group. The diffusing capacity of the lung for carbon monoxide and the ratio of the inspiratory capacity divided to the total lung capacity were independent risk factors for OS and DFS.

Conclusions: A standardized assessment of LLN-defined airway obstruction may allow risk stratification for survival likelihood in lung cancer patients who undergo thoracic surgery.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are projected to continue to contribute to an increase in the overall worldwide burden of disease until 2020 [1]. Smoking is closely associated with lung cancer as well as chronic lung diseases, including COPD [2]. We previously showed that lung cancer patients with more severe airflow obstruction may not be considered for thoracic surgery with curative intent [3], indicating the clinical impact of COPD for newly diagnosed lung cancer patients.

Although COPD is generally diagnosed by using the fixed ratio of FEV1/FVC of 0.7 [4], studies of consecutively enrolled lung cancer patients who were classified using this ratio could not show a clinical association of COPD with overall survival in lung cancer patients who underwent resection with curative intent [5–7]. Thus, spirometric assessment of airway obstruction for the purpose of risk stratification for survival outcome in this population requires further study. The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines on lung function testing recommend diagnosing COPD by using as cut-off a FEV1/FVC ratio below the lower fifth percentile of a large healthy reference group (the statistically defined lower limit of normal [LLN]) [8]. Recent studies indicated that airway obstruction defined by the LLN of FEV1/FVC may be an important predictor of mortality [9–11]. Nevertheless, it has not yet been established whether classification by means of the LLN of FEV1/FVC could effectively predict survival outcome in lung cancer patients undergoing thoracic surgery.

In the present study, we evaluated the clinical relevance of LLN-defined airway obstruction to survival outcome in Japanese lung cancer patients who had undergone thoracic surgery.

2. Patients and methods

2.1. Study population

The medical records of patients with newly diagnosed lung cancer who were sequentially registered and who had undergone thoracic surgery at the Nagoya University Hospital from January 2006 to December 2011 were retrospectively reviewed. The study was approved by the Institutional Review Board of Nagoya University Graduate School of Medicine (Approval date: April 21, 2014; Approval #: 2014-0052). The requirement for written informed consent was waived due to the retrospective design of the study.

2.2. Patient characteristics and spirometric pulmonary function variables

Patient data were obtained retrospectively from the hospital records, as previously reported [3,5,12]. Pathological staging of lung cancer was based on the tumor, node, and metastasis (TNM) staging using the standards of the Union International Contre le Cancer (UICC), 7th edition [13]. In the present study, pathological staging was classified as stage I (IA/IB), II (IIA/IIB), and III (IIIA/IIIB)/IV, respectively. Histological type, i.e., adenocarcinoma, squamous cell carcinoma (Sq), large cell carcinoma (Large), and other subtypes, was determined according to the World Health Organization's classification [14]. COPD-related systemic comorbidities were defined as diabetes, hypertension, or ischemic cardiac disease [3].

Spirometry was performed with a calibrated dry spirometer (FUDAC-77; Fukuda Denshi Co., Ltd., Tokyo, Japan), according to the American Thoracic Society (ATS) standards that are routinely applied in our hospital [9]. Spirometric variables included vital capacity (VC), total lung capacity (TLC), inspiratory capacity (IC), IC/TLC, FEV1, FVC, FEV1/FVC, and functional residual capacity (FRC). TLC was assessed with the helium dilution method. The diffusion capacity of the lung for carbon monoxide (DLCO) was measured by the single breath-holding method [15]. Airflow obstruction was functionally defined by a FEV1/FVC ratio of 0.7 or the LLN of FEV1/FVC [8]. The LLN of FEV1 and FVC were calculated using the reference equations of the National Health and Nutrition Survey III (NHANES III) [16]. The LLN of FEV1/FVC was determined according to the following equations: $78.388 - 0.2066 * \text{age (years)}$ for males and $81.015 - 0.2125 * \text{age (years)}$ for females [15,16].

2.3. Postoperative complications and outcome data collection

In our hospital, all patients received standardized care according to the clinical practices used for inpatients at our institution. Prolonged oxygen therapy (POT), prolonged postoperative stay (PPS), and postoperative complications were evaluated based on the definition previously reported [12,15]. Overall survival (OS) was measured from the date of surgery to the date of death (event), or the last date the patient was known to be alive (censored) [5,17]. Disease-free survival (DFS) was defined as the time from the date of surgery to the first date of recurrence of cancer, or death from any cause [5,17]. Date of recurrence was obtained by reviewing the hospital records of all patients [5,17]. For patients who had been referred to other hospitals for further support, we contacted the relevant primary physicians to obtain follow-up information [5,17].

2.4. Statistical analysis

All data were checked for completeness, and the analyzed variables were tested for normality of distribution using the Shapiro–Wilk test. Normally distributed variables were compared between the below- and above-LLN groups using the t-test and non-normally distributed variables using the Mann–Whitney test. Comparisons between proportions were made using the χ^2 test or Fisher's exact test. Associations between LLN-defined airway obstruction and survival

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outcomes were evaluated using Kaplan–Meier curves and the log-rank test. Factors that were found to be predictive for survival in the above-mentioned univariate analyses were entered into a Cox regression model to identify independent factors for survival. Statistical analyses were performed with PASW Statistics version 18.0 (SPSS Inc, Chicago, IL), and a P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. *Survival analysis*

The medical records of 712 patients with newly diagnosed lung cancer who underwent spirometry and thoracic surgery were

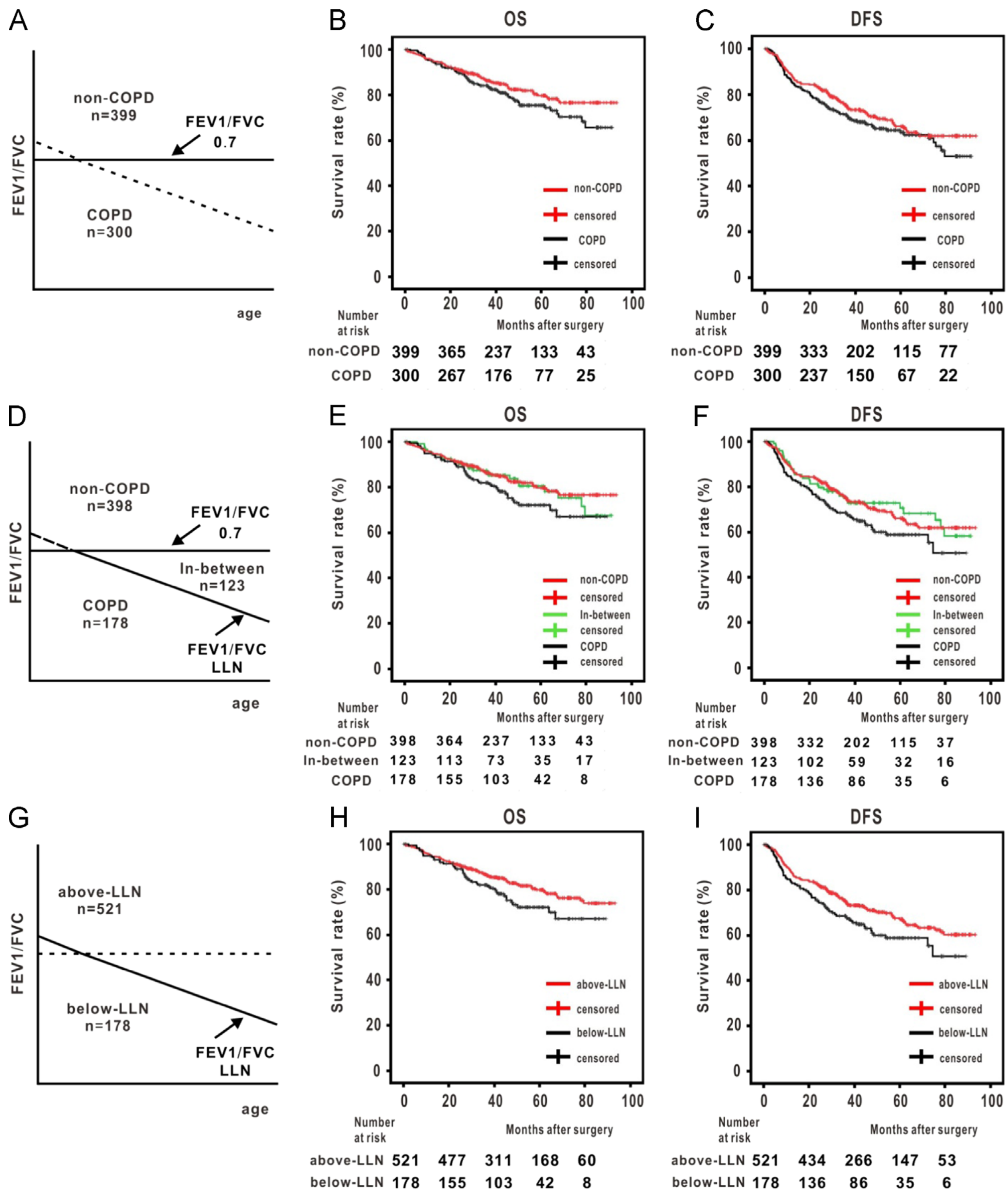

Fig. 1 – Kaplan–Meier estimates of disease-free and overall survival in resected lung cancer patients with curative intent. (A) Diagram depicting the fixed 0.7 ratio of FEV1/FVC and the decline of the LLN of FEV1/FVC with aging. *Solid line*: **the fixed 0.7 ratio.** *Dotted line*: **the LLN of FEV1/FVC with aging. (B) Overall survival (OS) in 699 patients assigned to the non-COPD and COPD groups. (C) Disease-free survival (DFS) in 699 patients assigned to the non-COPD and COPD groups. (D) Diagram depicting the fixed 0.7 ratio of the FEV1/FVC and the decline of the LLN of FEV1/FVC with aging. (E) OS in the non-COPD, in-between, and COPD groups. (F) DFS in the non-COPD, in-between, and COPD groups. (G) Diagram depicting the fixed 0.7 ratio of FEV1/FVC and the decline of the LLN of FEV1/FVC with aging.** *Solid line*: **the LLN of FEV1/FVC with aging.** *Dotted line*: **the fixed 0.7 ratio. (H) OS in the study population classified as the above-LLN and below-LLN groups. (I) DFS in the study population classified as the above-LLN and below-LLN groups.**

Table 1 – Patient characteristics among the above-LLN and below-LLN groups.

	All cases ($n=699$)	Above LLN ($n=521$)	Below LLN ($n=178$)	p Value
Cases	100 (699)	74.5 (521)	25.5 (178)	
Age, years[a]	67.3 (26–87)	67.1 (26–87)	67.9 (42–85)	0.566
Sex, male	67.4 (471)	61.6 (321)	84.3 (150)	0.0001[#]
History of smoking	72.1 (504)	64.9 (338)	93.3 (166)	0.0001[#]
COPD-related systemic comorbidities	52.9 (370)	52.6 (274)	53.9 (96)	0.794
Diabetes	17.8 (124)	19.4 (101)	12.9 (23)	0.054
Ischemic cardiac disease	8.9 (62)	7.3 (38)	13.5 (24)	0.015[#]
Hypertension	421.2 (288)	42.4 (221)	37.6 (67)	0.29
Spirometric variables				
FEV1/FVC [a]	70.6 (10.7)	75.2 (7.0)	57.0 (7.8)	0.0001[#]
%FEV1 predicted [a]	103.7 (21.7)	110.2 (18.7)	84.9 (18.8)	0.0001[#]
FEV1 (ml) [a]	2235 (588)	2326 (581)	1966 (525)	0.0001[#]
VC (%) [a]	110.0 (17.9)	109.4 (17.6)	112.0 (18.8)	0.287
DLCO (%)[a]	111.0 (29.2)	114.4 (28.4)	101.2 (29.4)	0.0001[#]
DLCO/VA (%)[a]	96.1 (28.0)	101.3 (26.6)	81.2 (26.5)	0.0001[#]
IC (%)[a]	89.3 (17.6)	89.2 (18.0)	89.6 (16.4)	0.986
IC/TLC (%)[a]	41.1 (7.3)	41.6 (7.6)	39.7 (6.2)	0.005[#]
BMI (kg/m2)[a]	22.3 (3.4)	22.4 (3.4)	22.6 (3.1)	0.289

n indicates number.
All other data are shown as % (numbers).
BMI: body mass index.
[a] Data are shown as mean (range).
[#] $p<0.05$.

reviewed. Thirteen patients were excluded from the analysis for the following reasons: preoperative pulmonary assessment by spirometry, including FEV1/FVC, was not performed ($n=8$); combined surgery for lung cancer and other diseases ($n=4$); and emergency thoracic surgery ($n=1$). Thus, the study population eventually comprised 699 patients (98.2%), in which 224 recurrences and 137 deaths were observed. The median follow-up time among subjects who remained alive was 48.5 months (range: 0.2–93.4 months). Median OS and DFS were 44.4 months (range: 0.2–93.4 months) and 40.2 months (range: 0.2–93.4 months), respectively. The 5-year OS and 5-year DFS rates for this cohort were 77.8% and 64.9%, respectively.

3.2. *Impact of airflow obstruction on survival in lung cancer patients who had undergone resection with curative intent*

To evaluate the clinical impact of COPD in lung cancer patients who had undergone resection with curative intent, airflow obstruction in the population was firstly classified by the fixed ratio of FEV1/FVC of 0.7. Subjects were assigned to the COPD group if airflow obstruction determined by the FEV1/FVC ratio was below 0.7 ($n=399$; Fig. 1A). The remaining subjects were assigned to the non-COPD group ($n=300$). Kaplan–Meier curves and log-rank testing did not suggest that COPD defined by a fixed ratio of FEV1/FVC of 0.7 was associated with worse OS and DFS in this study population ($p=0.093$ for OS and $p=0.169$ for DFS; Fig. 1B and C).

We hypothesized that misclassification of the study population by use of this fixed ratio may underlie the absence of a significant association between COPD and survival of patients with lung cancer who underwent thoracic surgery. Therefore, we evaluated the impact of airflow obstruction determined by the fixed ratio of 0.7 and the LLN of FEV1/FVC. Subjects were assigned to the COPD group if airflow obstruction determined by the FEV1/FVC ratio was below 0.7 and below the LLN ($n=178$) (Fig. 1D). If airflow obstruction according to FEV1/FVC was below 0.70, but above the LLN, or if FEV1/FVC was above 0.7, but below the LLN, subjects were assigned to the in-between group ($n=123$); the remaining subjects were again assigned to the non-COPD group ($n=398$). The Kaplan–Meier curve for the in-between group appeared to overlie that of the non-COPD group (Fig. 1E and F).

3.3. *Clinical relevance of LLN-determined airflow obstruction on survival in lung cancer patients who had undergone resection with curative intent*

We evaluated whether classification of airflow obstruction as defined by the LLN of FEV1/FVC may be associated with worse survival in the study population. Subjects were assigned to the below-LLN group if airflow obstruction determined by the FEV1/FVC ratio was below the LLN ($n=178$; Fig. 1G). The remaining subjects were assigned to the above-LLN group ($n=521$). Table 1 shows a comparison of the patient characteristics between the two populations. The proportion of males with a smoking history in the below-LLN group was significantly higher than in the above-LLN group.

Variables of spirometry and operative procedures were also evaluated (Table 1). IC/TLC and DLCO values were significantly worse in the below-LLN group than in the above-LLN group. To evaluate the association of airflow obstruction defined by the LLN of FEV1/FVC with lung cancer characteristics, the pathological findings and clinical staging data were compared between the below- and above-LLN groups (Table 2). The prevalence of adenocarcinoma was significantly lower in the below-LLN group

Table 2 – Characteristics of lung cancer status among the above-LLN and below-LLN groups.

	All cases (n=699)	Above LLN (n=521)	Below LLN (n=178)	p Value
Pathology				0.0001[#]
Adenocarcinoma	70.5 (493)	75.8 (395)[##]	55.1 (98)	
Sq	23.5 (164)	19.2 (100)	36.0 (64)[##]	
Large	4.1 (29)	2.9 (15)	7.9 (14)[##]	
Other subtype[a]	1.9 (13)	2.1 (11)	1.1 (2)	
Pathological stage				0.015[#]
I	67.7 (473)	70.4 (367)[##]	59.6 (106)	
II	18.6 (130)	16.3 (85)	25.3 (45)[##]	
III and IV	13.7 (96)	13.2 (69)	15.2 (27)	

n indicates number.
All data are shown as % (numbers).
[#] $p<0.05$.
[##] Significant difference.
[a] Other subtype includes non-small cell carcinoma, carcinoid.

Table 3 – Characteristics of interventions among the above-LLN and the below-LLN groups.

	All cases (n=699)	Above LLN (n=521)	Below LLN (n=178)	p Value
Surgical procedure				0.002[#]
Bilobectomy/pneumonectomy	4.5 (31)	2.9 (15)	9.0 (16)[##]	
Lobectomy	90.1 (630)	91.2 (475)	87.1 (155)	
Others[a]	5.4 (38)	6.0 (31)	3.9 (7)	
Neoadjuvant therapies	1.7 (12)	1.7 (9)	1.7 (3)	1.000
Adjuvant therapies	19.7 (138)	19.6 (102)	19.7 (35)	1.000
Postoperative outcomes				
POT**	27.6 (193)	19.4 (101)	51.7 (92)	0.0001[#]
PPS***	28.9 (202)	24.4 (127)	42.1 (75)	0.0001[#]
Postoperative complications****	22.2 (155)	18.8 (98)	23.0 (57)	0.0001[#]

n indicates number.
All data are shown as % (numbers).
POT, prolonged oxygen therapy; PPS, prolonged postoperative stay.
POT** was defined by the need of oxygen therapy for more than 2 days or the restart of oxygen therapy.
PPS*** was defined as a stay of more than 11 days.
Postoperative complications**** included pneumonia, prolonged ventilation, the need of minitracheostomy, prolonged air leakage, and supraventricular arrhythmias.
[#] $p<0.05$.
[##] Significant difference compared with the above-LLN group.
[a] Others include segmentectomy and wedge resection.

than in the above-LLN group. The incidence rates of postoperative outcomes including POT, PPS, and postoperative complications were significantly higher in the below-LLN group than in the above-LLN group (Table 3). In pulmonary resections, the total number of cases of bilobectomy and pneumonectomy was significantly higher in the below-LLN group, whereas that of lobectomy and other procedures was not different between the study populations (Table 3). The proportion of the patients receiving neoadjuvant or adjuvant therapies was not significantly different between the two groups (Table 3). Median OS and DFS were 45.7 months (range: 0.8–93.4 months) and 40.5 months (range: 0.8–93.4 months) in the above-LLN group, respectively, whereas median OS and DFS were 42.7 months (range: 0.2–89.2 months) and 38.7 months (range: 0.2–89.2 months) in the below-LLN group, respectively (Fig. 1H and I). Although the 5-year OS and 5-year DFS rates for the above-LLN group were 79.8% and 67.1%, respectively, the 5-year OS and 5-year DFS rates for the below-LLN group were 72.1% and 58.8%, respectively (Fig. 1H and I). Kaplan–Meier curves and log-rank testing suggested that the below-LLN group was associated with worse OS and DFS in the study population (p=0.043 in OS and p=0.030 in DFS, respectively; Fig. 1H and I).

3.4. *Impact of airflow obstruction on survival in resected lung cancer patients with stage I disease and lobectomy*

To minimize the influence of pathological stage, the impact of airflow obstruction was evaluated in lung cancer patients with stage I disease who had undergone lobectomy (Fig. 2A–F). The study population comprised 432 patients. The COPD group, classified by the fixed ratio of FEV1/FVC of 0/7, was associated with worse OS and DFS (p=0.008 in OS and p=0.044 in DFS,

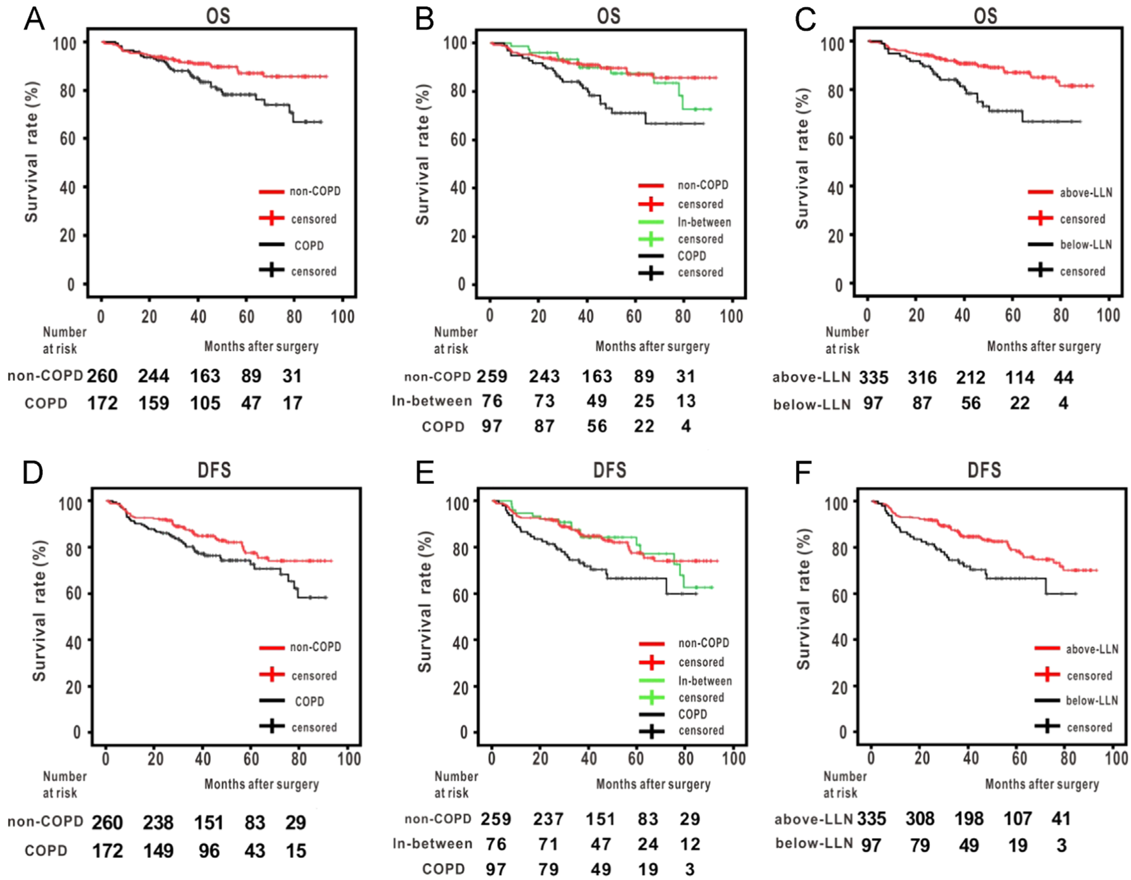

Fig. 2 – Kaplan–Meier estimates of disease-free and overall survival (OS) in resected lung cancer patients with stage I disease and lobectomy. (A–C) OS in 432 patients classified by the 0.7 fixed ratio (A), the 0.7 fixed ratio and the LLN of FEV1/FVC (B), and the LLN of FEV1/FVC (C). (D–F) Disease-free survival (DFS) in 432 patients classified by the 0.7 fixed ratio (D), the 0.7 fixed ratio and the LLN of FEV1/FVC (E), and the LLN of FEV1/FVC (F).

Table 4 – Multivariate analysis of risk factors for DFS.

Variables	Odds ratio	95% CI	*p* Value
Pathological stage			$<0.0001^{\#}$
Stage 1	Reference		
Stage 2	2.239	1.617–3.100	$<0.0001^{\#}$
Stage 3	3.728	2.673–5.199	$<0.0001^{\#}$
Postoperative complications			
No	Reference		
Yes	1.426	1.068–1.904	$0.016^{\#}$
%DLCO (per one percentage)	0.992	0.987–0.997	$0.001^{\#}$
%IC/TLC (per one percentage)	0.978	0.960–0.996	$0.015^{\#}$

$^{\#}$ $p<0.05$.

respectively; Fig. 2A and D). When airflow obstruction was classified using the fixed ratio and the LLN of FEV1/FVC, the Kaplan–Meier curve for the in-between group overlaid that of the non-COPD group (Fig. 2B and E).

Next, to clarify the relevance of LLN-defined airflow obstruction, the LLN of FEV1/FVC alone was utilized to classify the population. The below-LLN group comprised 97 patients, and the above-LLN group 335 patients. The below-LLN group had significantly worse OS and DFS than the above-LLN groups ($p=0.001$ in OS and $p=0.004$ in DFS, respectively; Fig. 2C and F).

3.5. *Critical impact of the severity of impaired gas exchange and persistent lung hyperinflation on DFS and OS in patients undergoing thoracic surgery*

We explored whether the severity of airflow obstruction might be a prognostic risk factor for DFS in patients undergoing thoracic surgery. The results of the univariate analysis of the Cox regression model are shown in Table S1. The univariate analysis identified the following risk factors: gender, history of smoking, diabetes, LLN of FEV1/FVC, pathological staging, pathology, postoperative outcomes, and some spirometric variables, including DLCO and IC/TLC. These factors were applied to the multivariate Cox proportional hazard model to identify the prognostic variables independently associated with DFS. This multivariate analysis identified pathological staging, postoperative complications, DLCO, and IC/TLC as independent risk factors for DFS (Table 4).

Finally, we explored whether the severity of airflow obstruction might be a prognostic risk factor for OS in patients undergoing thoracic surgery. The results of the

Table 5 – Multivariate analysis of risk factors for OS.

OS variables	Odds ratio	95% CI	p Value
Pathological stage			
Stage 1	Reference		<0.0001#
Stage 2	1.920	1.276–2.889	0.002#
Stage 3	2.893	1.839–4.552	<0.0001#
%DLCO (per one percentage)	0.989	0.983–0.995	<0.0001#
%IC/TLC (per one percentage)	0.964	0.941–0.988	0.003#
Adjuvant therapies			
No	Reference		
Yes	0.587	0.356–0.967	0.037#
Gender			
Female	Reference		
Male	1.752	1.113–2.756	0.001#
Age (per one year)	1.041	1.017–1.065	0.001#
Diabetes			
No	Reference		
Yes	1.469	1.003–2.151	0.048#

# $p<0.05$.

univariate analysis of the Cox regression models are shown in Table S2. The univariate analysis identified the following risk factors: age, gender, history of smoking, diabetes, LLN of FEV1/FVC, body mass index (BMI), pathological staging, pathology, adjuvant therapies, postoperative outcomes, and some spirometric variables, including DLCO and IC/TLC. These factors were also applied to the multivariate Cox proportional hazard model to identify the prognostic variables independently associated with OS. The multivariate analysis identified pathological staging, adjuvant therapies, gender, age, diabetes, DLCO, and IC/TLC as independent risk factors for OS (Table 5).

4. Discussion

To our knowledge, this is the first study of the clinical relevance of the LLN of FEV1/FVC to OS and DFS using a large cohort of Japanese lung cancer patients who had undergone thoracic surgery.

We have previously demonstrated precise risk stratification for postoperative outcomes in thoracic surgery by using the 0.70 fixed ratio and the LLN of FEV1/FVC [15]. A preoperative assessment of the age-corrected LLN of FEV1/FVC, by which COPD patients could be classified into two groups with different severity of airflow obstruction (the in-between group versus the below group), suggested the involvement of two populations with different levels of postoperative risk among COPD patients who underwent thoracic surgery [15]. Although airflow obstruction as classified by the 0.7 fixed ratio of FEV1/FVC could not show a clinical association of airway obstruction with OS in lung cancer patients who had undergone resection with curative intent [5–7,18], it remained unclear whether LLN-defined airway obstruction could be used to predict OS and DFS in this population. Although we found that airway obstruction as defined by the fixed ratio of FEV1/FVC of 0.7 had no clinical relevance to OS and DFS, a significant association of LLN-defined airway obstruction with survival outcomes was shown in this population.

Because pathological stage was an independent factor associated with the decision-making process and survival outcomes in thoracic surgery with curative intent [3,13], we next evaluated the relevance of the LLN-defined airway obstruction to survival outcomes in patients with stage I lung cancer who underwent lobectomy. Our findings further supported the notion that the LLN of FEC1/FVC may allow better risk stratification for survival outcomes than the fixed ratio of FEV1/FVC of 0.7. Kaplan–Meier curves and log-rank test suggested that there was no difference in OS and DFS between the non-COPD and the in-between groups in resected lung cancer patients with stage I disease and lobectomy. Thus, although an in-between status, with mild airflow obstruction, could independently identify patients at risk in terms of postoperative outcomes [15], the mild airflow obstruction did not affect survival outcomes in lung cancer patients who underwent resection with curative intent. Our data clearly indicated the critical association of airway obstruction with survival outcomes in this population.

Consistent with previous studies [17,19], our data suggested that the prevalence of adenocarcinoma was significantly lower in the below-LLN group than in the above-LLN group, while that of Sq was significantly higher.

We also determined the candidate variables that may independently predict survival outcomes in this population. Multivariate analysis indicated that the criterion of the LLN of FEV1/FVC may not be an independent factor for DFS and OS in this population, whereas DLCO and IC/TLC remained independently associated with these prognostic outcomes. As recent studies have suggested that DLCO may be closely associated with the existence and extent of chest computed tomography (CT)-detected emphysema [20,21], DLCO may be a spirometric variable that predicts destructive change and loss of lung parenchyma in COPD [20]. The IC/TLC ratio, as an important predictor of mortality in COPD, may also be a functional index of hyperinflation and CT-detected emphysema [22]. DLCO and TLC are somewhat more complicated to assess than FEV1/FVC; nevertheless, because worsening DLCO and IC/TLC may predict worse survival outcomes in patients with LLN-defined airflow obstruction, our finding provides an impetus for evaluating DLCO and IC/TLC as further assessment tools [23]. It should also be noted that pathological staging according to TNM staging UICC 7th edition was one of the independent prognostic factors in DFS and OS [13].

Our study was based on the retrospective analysis of data from 699 out of a total of 712 cases from a single institution. Nonetheless, using data from 98.2% of all patients at a single institution who had been consecutively registered and who underwent a pulmonary resection from 2006 to 2011 could minimize confounding by treatment-related prognostic factors and selection bias. The NHANES III reference equation [16] was used to calculate the LLN of FEV1/FVC in this study, because of a lack of an appropriate reference equation for Japanese individuals. However, many studies suggest that a race/ethnic adjustment factor should not be applied to the FEV1/FVC ratio, a finding supported by a recent study comparing Caucasian and

Asian-American participants [8–10]. Although the LLN of FEV1/FVC and percentage of predicted FEV1 (%FEV1 predicted) are functions of time, the fixed ratio of FEV1/FVC of 0.7 is not. Recent studies have shown that when severity of airflow obstruction is used for evaluating the impact on survival outcomes in COPD patients, all-cause mortality was associated with age-corrected severity of airflow obstruction at base line, defined by spirometric cut-off points of the LLN, but not by the 0.7 fixed ratio or %FEV1 predicted [24–26]. Therefore, we based our study on spirometric assessment performed preoperatively.

5. Conclusion

Airway obstruction defined by the LLN of FEV1/FVC at preoperative assessment is closely associated with poor prognosis in resected lung cancer patients. A standardized assessment of the age-corrected LLN of FEV1/FVC for the population may enable us to classify COPD patients with different risk levels in terms of survival outcomes more precisely.

Authors' contributions

AM, NH, and YH had full access to all of the data in the study and are responsible for the integrity of the data and the accuracy of the data analysis.

SO, TT, KK, and TF: contributed to collection of the data.

KW: contributed to the development of the analytic concept, data analyses.

KY: contributed to critical revision of the manuscript.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2015.11.006.

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