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Original Article

Unplanned Reoperation After Anatomical Pulmonary Resection for Lung Cancer: Rate, Risk Factors, Early Outcomes and Long-term Prognostic Influence Within a Prospective Multicentre Database

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ABSTRACT

Objectives: The study aimed to identify perioperative variables associated with unplanned reoperation (UR) following anatomical pulmonary resection for lung cancer and investigate its impact on long-term prognostic outcomes.

Methods: The records of patients who underwent anatomical pulmonary resection for lung cancer from December 2016 to March 2018 within a nationwide prospective registry were reviewed. Multivariable logistic regression analyses were performed to find the risk factors for UR. The short-term outcomes were compared, and the adjusted odds ratios for in-hospital and 90-day mortality were calculated. The prognostic value of UR for overall survival (OS) and disease-free survival (DFS) was assessed using the Kaplan–Meier method and log-rank test after propensity score matching for balancing baseline confounders.

Results: Data from 3085 patients were examined, revealing a UR incidence of 4.12%. Multivariable logistic regression analyses revealed that male gender (OR = 3.288, P = 0.004), ppoDLCO% (OR = 0.975, P = 0.003), pneumonectomy (OR = 4.748, P = 0.038), strong pleural adhesions (OR = 3.449, P < 0.001) and hospital volume ≥150 cases (OR = 1.75, P = 0.026) were independently associated with UR. Risk of in-hospital and 90-day mortality was higher in UR cases (adjusted OR = 7.312, P < 0.001, and OR = 5.188, P < 0.001, respectively). Ninety-eight UR and 347 matched non-UR cases were included in the long-term follow-up analysis. The median follow-up time was 50.4 months. No significant differences were found in OS, and DFS between groups (log rank P = 0.953 and P = 0.352, respectively).

Conclusion: Male gender, ppoDLCO%, pneumonectomy, strong pleural adhesions, and surgical unit workload were all independently associated with UR. UR was associated with an increased perioperative mortality, but not with a higher long-term mortality.

Introduction

Anatomical lung resection with lymph node dissection remains the standard of care for functionally operable early-stage non-small cell lung cancer (NSCLC).[1–3] Nevertheless, these procedures are not without risks and are often associated with a wide range of postoperative complications.[4] Although in most cases postoperative complications may be managed conservatively or with minor interventions, some patients may require reoperation given the urgency and severity of the perioperative complications.

Therefore, patients requiring readmission to the operating room have been found to experience significantly prolonged in-hospital stays and increased medical expenses.[5,6] In addition, reintervention may result in higher morbidity and mortality rates, often due to secondary injuries and anaesthesia-related factors.[6]

On the other hand, unplanned reoperation (UR) has been extensively utilized as an indicator of surgical care quality across hospitals, as it signifies the capacity of hospitals to identify and manage surgical complications.[6–9]

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According to the latest studies investigating UR, its incidence following lung surgery ranges from 0.27% to 4.6%.[7–12] Some of these studies have tried to identify underlying risk factors for UR with the aim of implementing measures that can effectively mitigate the occurrence of UR.[8,9,12] However, the studies are retrospective and single-institutional, imposing limitations on their findings.

In addition, to the best of our knowledge, there is a lack of reports on the impact of UR on postoperative outcomes. The question of whether UR is independently associated to worse short-term outcomes and particularly long-term survival has remained unanswered until now.

Hence, this study aims to investigate the incidence and risk factors associated with UR occurring within 30 days after anatomical pulmonary resection for lung cancer using a prospective nationwide database. Additionally, we examine the impact of UR on both short-term perioperative outcomes and long-term prognostic outcomes, including overall survival (OS) and disease-free survival (DFS).

Methods

Ethical Statement

The Spanish Group of Video-Thoracoscopic Surgery (GEVATS) project[13] was approved by the ethics committees of all the participating centres and informed consent was obtained from the recruited patients. This specific study was evaluated and approved by the scientific committee of GEVATS and the need of a specific informed consent was waived (approval by Ethics Committee of Aragon Health Research Institute PI15/0072 on 20 May 2015).

Study Design and Data Source

A retrospective observational study was conducted on the prospectively recorded data of the multicentre national registry of GEVATS. The database holds information on all anatomical lung resections, approached by VATS or thoracotomy, from December 2016 to March 2018. Overall, 33 thoracic surgery departments took part in gathering the data, while 30 thoracic departments completed the follow-up ending in September 2022. Variables were adapted according to standardized definitions and terminology.[14] Cases with a diagnosis other than lung cancer were excluded.

Primary and Secondary Outcomes

UR was defined as any adverse event occurring within 30 days after the operation that required an intervention under general anaesthesia (grade IIIb in Clavien–Dindo classification[15]).

The primary endpoints were in-hospital and 90-day mortality. Secondary outcomes were OS and DFS. Patients who died within 90 days after surgery and incomplete follow-up records or with missing data were excluded from the long-term analysis.

Statistical Analysis

Potential risk factors for UR were first analysed by univariate logistic regression. Variables with a *P*-value of <0.15 were fed into a multivariable logistic regression model via stepwise backward elimination based on the Wald statistics. Only variables with a *P*-value <0.05 were retained in the final model.

Multivariable logistic regression analyses were then performed to find the independent association between UR and in hospital and 90-day mortality. First, a crude analysis for each cohort was performed followed by an adjusted analysis controlling for potential confounding factors (those included in the Eurolung 2 model[16]) by using a forced entry method in the logistic regression analyses. Adjusted odds ratios (OR) on in-hospital and 90-days mortality were produced with their exact 95% confidence intervals (CIs).

Table 1
Causes of Unplanned Reoperation.

Complication	*N* (%)	In-hospital Mortality With Reoperation (%)
Bleeding	46 (36.2)	3 (6.5)
Prolonged air leak	31 (24.4)	2 (6.5)
Bronchopleural fistula	16 (12.6)	8 (50)
Empyema	12 (9.4)	0 (0)
Lung infarction	4 (3.1)	1 (25)
Lobar torsion	3 (2.4)	0 (0)
Atelectasis	3 (2.4)	0 (0)
Pulmonary artery stenosis/thrombosis	3 (2.4)	0 (0)
Peripheral artery ischemia	2 (1.6)	1 (50)
Other	7 (5.5)	0 (0)

Regarding long-term outcomes, OS was defined as the time between surgery and death by any cause, or date of the last follow-up. The DFS corresponded to the time from surgery to tumour recurrence of the same lung cancer (local, regional or distant) or death from any cause, whichever came first, with censorship at last radiological imaging test. OS and DFS rates were examined for all the included patients with Kaplan–Meier curves and compared between UR and non-UR with the log-rank test. The prognostic value of UR for OS and DFS was finally assessed using a univariate Cox proportional hazard analysis after the propensity score matching.

Missing data were dealt by casewise deletion analysis when <5% of patients had incomplete registries.

Propensity Score Matching

We performed propensity score matching (PSM) to reduce the bias due to confounding variables when comparing long-term outcomes. We applied a 1:4 nearest neighbour matching without replacement method with a caliper of 0.01. The variables used for propensity score matching were selected according to their clinical importance and statistical significance: age, sex, type of resection, pStage, ASA score and histology. Covariate balance was assessed by the standardized mean difference (SMD), before and after matching. SMD <0.1 or 0.05 were considered good or excellent, respectively, to exclude residual imbalance.[17]

RStudio (version 4.3.2, The R Foundation, Vienna, Austria) with the "MatchIt" package version 4.5.5 was used for PSM and SPSS v28.0 (SPSS Inc., Chicago, IL, USA) for further data analysis.

Our manuscript is reported according to the STROBE and TRIPOD recommendations.

Results

The study flowchart is presented in Fig. 1.

We examined data for 3085 patients. The incidence of UR was 4.12% (127 cases). The primary cause was intra-thoracic bleeding (36.2%), followed by prolonged air leak (24.4%). Both causes were associated with a mortality rate of 6.5%. Bronchopleural fistula, which accounted for 12.6% of cases, was the third leading cause of UR, but it was associated with a mortality rate of 50%. Table 1 details UR causes and its associated mortality rates.

Risk Factors

Table 2 shows the univariate analysis of patient characteristics and surgical features for the outcome UR. Multivariable logistic regression analyses revealed that male gender, ppoDLCO%, pneu-

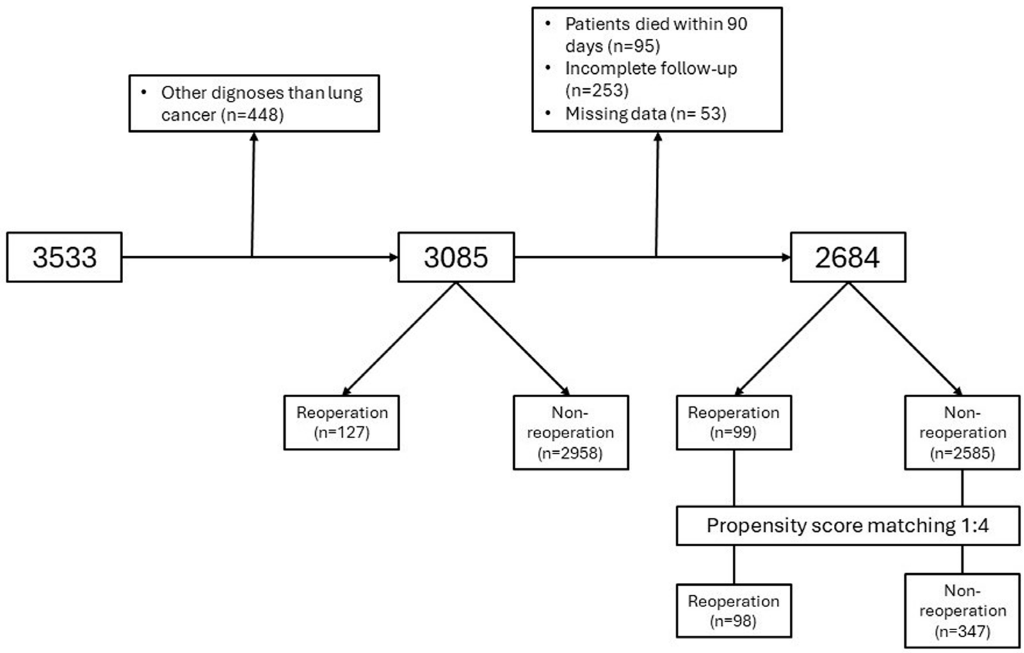

Fig. 1. Study flowchart.

monectomy, strong pleural adhesions, and hospital volume ≥150 cases were independently correlated with UR (Table 3).

Primary Endpoints

Compared to non-UR cases, UR was associated with a higher rate of in-hospital mortality (1.2% vs 11.8%, $P<0.001$), 90-day mortality (2.5% vs 16.7%, $P<0.001$), readmission (6.8% vs 24.5%, $P<0.001$) and a longer length of hospital stay (non-UR median: 5, interquartile range (IQR): 4–7 vs UR median: 13, IQR: 8–22, $P<0.001$).

After adjusting for confounding factors, UR was found to significantly increase the risk of in-hospital mortality by 7-fold and 90-day mortality by 5-fold (Table 4).

Secondary Endpoints

Finally, 2684 patients completed the long-term follow-up. After PSM, 445 patients were compared (98 UR and 347 non-UR cases). Table 5 shows the baseline characteristics of patients before and after matching. No significant differences were found in OS, and DFS between groups (log rank $P=0.953$ and $P=0.352$, respectively) (Fig. 2). According to the univariate survival analyses, UR was not associated with OS and DFS ($P=0.954$ and $P=0.421$, respectively).

Discussion

In general thoracic operations, most postoperative complications are mainly managed through conservative measures or minor interventions, while reoperations are typically reserved for addressing severe or life-threatening complications. In the present study, the UR rate following pulmonary resection was 4.12%, which is consistent with the rate reported by Foroulis et al.,[9] but slightly higher than that described by other authors.[7,8,10–12] This discrepancy could be explained by the fact that in our series all analysed cases involved surgical procedures for lung cancer consisting of anatomical lung resection and lymphadenectomy.

Although the necessity for perioperative reoperation is uncommon, it imposes an additional burden on patients. In our cohort, we saw an in-hospital mortality rate among UR cases of 11.8%, while the adjusted risk of mortality was 7.3. Previous studies reported similar rates ranging from 5.13% to 12.2%.[7–9,11,12] In line with these findings, reintervention was found as the most significant predictor factor for mortality in patients experiencing major complications following anatomical lung resection, with an OR of 12.26.[18]

Within our cohort, haemothorax was revealed as the primary cause necessitating reoperation as previously described.[7–12] Notably, 24.4% of patients required UR due to prolonged air leak, constituting the second most prevalent cause of UR in our series, contrary to that shown in the above mentioned studies[7,8,10–12] where air leak was an uncommon cause of UR. This fact underscores that the management of air leak stays a subject of debate. While some authors advocate for conservative treatment, others prefer reoperation, arguing that a more aggressive approach could lead to a faster recovery and reduced hospital stay.[9] Additionally, bronchopleural fistula emerged as the UR indication with the highest postoperative mortality rate, reaffirming the gravity of this complication even when addressed promptly.[19,20]

Understanding UR risk factors will help early detection and the implementation of appropriate preventive measures to minimize the risk of reoperation. Several authors have investigated predictive factors for UR[8,9,11,12,21] concluding that reoperation typically occurs in patients belonging to high-risk groups or those undergoing complex surgeries. In our series, the multivariable logistic regression analysis revealed that male gender, ppoDLCO%, pneumonectomy, strong pleural adhesions and hospital volume ≥150 cases were independently correlated with UR.

Pneumonectomy increases UR risk by 4.7 times compared to lobectomy. This observation is consistent with the fact that pneumonectomy is the procedure most frequently associated with bronchopleural fistula, with reported rates ranging from 4.5% to 20%,[22] mainly attributed to the lack of protective mechanisms in the bronchial stump and the higher airway pressure within the main bronchus.

The presence of pleural adhesions poses another potential risk factor for UR, owing not only to bleeding but also air leaks and empyema.[23]

Remarkably, our research reveals that high hospital volume correlated with a higher risk of UR. A previous study on the

Table 2
Univariate Analysis of Patient Characteristics and Surgical Features for the Outcome UR.

	Non-UR (*n* = 2958)	UR (*n* = 127)	OR (95% CI)	*P*-value
Age, mean (SD), years	65.47 (SD: 9.6)	65.8 (SD: 9.26)	1.004 (0.985–1.023)	0.705
Male sex, n (%)	2072 (70.1)	113 (89)	3.447 (1.968–6.041)	<0.001
BMI, mean (SD)	26.9 (SD: 4.58)	25.96 (SD: 4.33)	0.953 (0.914–0.994)	0.024
FEV1/FVC, mean (SD)	0.92 (SD: 0.15)	0.86 (SD: 0.21)	0.068 (0.02–0.232)	<0.001
ppoFEV1%, mean (SD)	69.34 (SD: 17.96)	61.66 (SD: 16.43)	0.97 (0.959–0.985)	<0.001
ppoDLCO%, mean (SD)	65.09 (SD: 18.32)	56.11 (SD: 15.59)	0.99 (0.983–0.982)	<0.001
Smoking history, n (%)				0.153
Never smoker	373 (12.6)	8 (6.3)	1	
Former smoker	1676 (56.7)	74 (58.3)	2.059 (0.984–4.306)	
Current smoker	868 (29.4)	42 (33.1)	2.256 (1.049–4.852)	
Unknown	39 (1.3)	3 (2.4)	3.587 (0.914–14.076)	
Creatinine >2 mg/dl, n (%)	86 (2.9)	1 (0.8)	0.265 (0.037–1.917)	0.188
Previous ipsilateral thoracic surgery, n (%)	79 (2.7)	6 (4.7)	1.807 (0.773–4.227)	0.172
ASA score, n (%)				0.511
I–II	1282 (43.4)	51 (40.5)	1	
III–IV	1669 (56.6)	75 (59.5)	1.13 (0.786–1.624)	
Tumor size, mean (SD)	29.85 (SD: 20.7)	36.15 (SD: 23.56)	1.012 (1.005–1.020)	<0.001
Tumor location, n (%)				0.23
Peripheral	1809 (61.2)	71 (55.9)	1.245 (0.87–1.781)	
Central	1146 (38.8)	56 (44.1)		
Tumor site, n (%)				0.109
Upper lobe	1711 (57.9)	61 (48)	1	
Middle lobe	160 (5.4)	6 (4.7)	1.052 (0.448–2.471)	
Lower lobe	924 (31.3)	48 (37.8)	1.457 (0.99–2.145)	
Multiple lobes	92 (3.1)	6 (4.7)	1.829 (0.771–4.342)	
Main bronchus	68 (2.3)	6 (4.7)	2.475 (1.034–5.025)	
Induction therapy, n (%)	251 (8.5)	12 (9.4)	1.125 (0.612–2.068)	0.704
Surgical approach, n (%)				<0.001
VATS	1604 (54.2)	49 (38.6)	1	
Open	1354 (45.8)	78 (61.4)	1.886 (1.31–2.715)	
Type of resection, n (%)				<0.001
Bi/lobectomy	2595 (87.7)	101 (79.5)	1	
Segmentectomy	163 (5.5)	4 (3.1)	0.631 (0.229–1.734)	
Pneumonectomy	200 (6.8)	22 (17.3)	2.826 (1.744–4.581)	
Extended resection, n (%)	159 (5.4)	8 (6.3)	1.183 (0.568–2.464)	0.653
Lymphadenectomy, n (%)	2920 (98.7)	126 (99.2)	1.64 (0.223–12.038)	0.627
Pleural adhesions, n (%)				<0.001
None or non-significant	1744 (59)	46 (36.2)	1	
Weak adhesions	856 (28.9)	45 (35.4)	1.993 (1.311–3.03)	
Strong adhesions	358 (12.1)	36 (28.3)	3.812 (2.429–5.983)	
Conversion, n (%)	298 (15.7)	19 (27.9)	2.087 (1.211–3.596)	0.008
Operative time (min), mean (SD)	183.12 (69.44)	214.4 (82.606)	1.005 (1.003–1.007)	<0.001
Pathological tumor stage, n (%)				0.049
I	1610 (57)	56 (46.3)	1	
II	662 (23.4)	33 (27.3)	1.433 (0.923–2.224)	
III	500 (17.7)	31 (25.6)	1.782 (1.136–2.796)	
IV	54 (1.9)	1 (0.8)	0.532 (0.072–3.918)	
Surgeon seniority, n (%)				0.726
Faculty >20 years	696 (23.5)	32 (25.2)	1	
Faculty 10–20 years	918 (31)	43 (33.9)	1.019 (0.638–1.627)	
Faculty <10 years	1149 (38.8)	46 (36.2)	0.871 (0.549–1.381)	
Resident	195 (6.6)	6 (4.7)	0.669 (0.276–1.624)	
Hospital volume, n (%)				0.002
<150 cases	1850 (62.5)	62 (48.8)	1	
≥150 cases	1108 (37.5)	65 (51.2)	1.75 (1.226–2.499)	

UR: unplanned reoperation; BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; ppoFEV1%: predicted postoperative forced expiratory volume in the first second; ppoDLCO%: predicted postoperative diffusing capacity of the lung for carbon monoxide; VATS: video-assisted thoracic surgery; IQR: interquartile range; SD: standard deviation; OR: odds ratio; CI: confidence interval.

same database[24] demonstrated that patients undergoing lung surgery in high-volume centres exhibited a lower risk of failure to rescue defined as mortality among patients experiencing major complications.[25] This finding could be attributed to several factors. Firstly, high-volume hospitals typically undertake more complex procedures on higher-risk patients, thereby increasing the likelihood of UR. Secondly, failure to rescue outcomes are significantly influenced by enhanced intensive care services, rapid response teams, and readily available personnel.[26] The combination of these elements in high-volume centres may ease prompt detection and aggressive treatment of complications, thereby averting mortalities.

Table 3
Multivariable Analysis of Risk Factors of UR.

	Adjusted OR (95% CI)	*P*-value
Male sex	3.288 (1.466–7.375)	0.004
ppoDLCO%	0.975 (0.959–0.991)	0.003
Type of resection		0.038
Bi/lobectomy	1	
Segmentectomy	0.729 (0.217–2.45)	
Pneumonectomy	4.748 (1.385–16.277)	
Pleural adhesions		<0.001
None or non-significant	1	
Weak adhesions	1.163 (0.607–2.229)	
Strong adhesions	3.449 (1.821–6.533)	
Hospital volume		0.026
<150 cases	1	
≥150 cases	1.829 (1.073–3.117)	

OR: odds ratio; CI: confidence interval; ppoDLCO%: predicted postoperative diffusing capacity of the lung for carbon monoxide.

Table 4
Association of UR and In-hospital and 90-day Mortality.

	Odd Ratio (95% CI) (Non-adjusted)	*P*-value (Non-adjusted)	Odd ratio (95% CI) (Adjusted)	*P*-value (Adjusted)
In-hospital mortality	11.185 (5.936–21.077)	<0.001	7.312 (3.705–14.43)	<0.001
90-Day mortality	7.768 (4.608–13.095)	<0.001	5.188 (2.951–9.124)	<0.001

UR: unplanned reoperation; CI: confidence interval.
Adjusted analysis for in-hospital and 90-day mortality. Co-variables: age, sex, BMI, ppoVEF1%, pneumonectomy and thoracotomy (according to parsimonious Eurolung 2).

Table 5
Baseline Characteristics of Patients Completing the Follow-up Before and After Matching.

Variable	Original Cohort (*N* = 2684)			Matched Cohort (*N* = 445)		
	UR (*n* = 99)	Non-UR (*n* = 2585)	SMD	UR (*n* = 98)	Non-UR (*n* = 347)	SMD
Age, mean (SD), years	64.78 (SD: 0.93)	65.48 (SD: 0.19)	0.08	64.92 (SD: 9.23)	66.57 (SD: 8.15)	0.09
Male sex, n (%)	88 (88.9)	1800 (69.6)	0.61	87 (88.8)	310 (89.3)	0.03
Type of resection, n (%)			0.22			0.06
Bi/lobectomy	81 (81.8)	2287 (88.5)		80 (81.6)	307 (88.5)	
Segmentectomy	2 (2)	137 (5.3)		2 (2)	17 (4.9)	
Pneumonectomy	16 (16.2)	161 (6.2)		16 (16.3)	23 (6.6)	
pStage, n (%)			0.23			0.02
I	45 (45.5)	1447 (56)		45 (45.9)	176 (50.7)	
II	25 (25.3)	586 (22.7)		25 (25.5)	77 (22.2)	
III	26 (26.3)	449 (17.4)		25 (25.5)	82 (23.6)	
IV	1 (1)	48 (1.9)		1 (1)	7 (2)	
ASA score, n (%)			0.12			0.1
I	0 (0)	63 (2.4)		0 (0)	1 (0.3)	
II	42 (42.4)	1119 (43.3)		41 (41.8)	119 (34.3)	
III	54 (54.5)	1348 (52.1)		54 (55.1)	220 (63.4)	
IV	3 (3)	55 (2.1)		3 (3.1)	7 (2)	
Histology			0.17			0.04
ADC	48 (48.5)	1418 (54.9)		48 (49)	185 (53.3)	
SCC	33 (33.3)	811 (31.4)		33 (33.7)	107 (30.8)	
Carcinoid tumour	3 (3)	168 (6.5)		3 (3.1)	15 (4.3)	
Large cell carcinoma	12 (12.1)	115 (4.4)		11 (11.2)	24 (6.9)	
SCLC	1 (1)	17 (0.7)		1 (1)	5 (1.4)	
Other	2 (2)	56 (2.2)		2 (2)	11 (3.2)	

UR: unplanned reoperation; SMD: standardized mean difference; SD: standard deviation; ASA: American Association Anesthesiology; ADC: adenocarcinoma; SCC: squamous cell carcinoma; SCLC: small cell lung cancer.

Previous studies concluded that postoperative complications were associated with unfavourable OS and DFS.[27,28] However, our results show that UR is not associated with worse prognostic outcomes. These findings are supported by Gabryel et al.[29] who identified predictors for long-term survival after VATS lobectomy for stage IA NSCLC and found that reoperation was not associated with OS in the univariate analysis. Therefore, although UR significantly impairs early surgical outcomes, this study indicates that it does not influence the long-term cancer-specific survival of patients undergoing anatomical pulmonary resection for lung cancer. This underscores the need to optimize perioperative care to reduce the incidence of UR and its associated early morbidity, while ensuring that long-term oncological outcomes remain unaffected.

The present study has several limitations. First, data are based on a multicentre voluntary registry, so that, bias related to patient selection and quality of data could have influenced our findings. Secondly, this study lacked specific details regarding potential factors influencing UR, including preoperative anticoagulant ther-

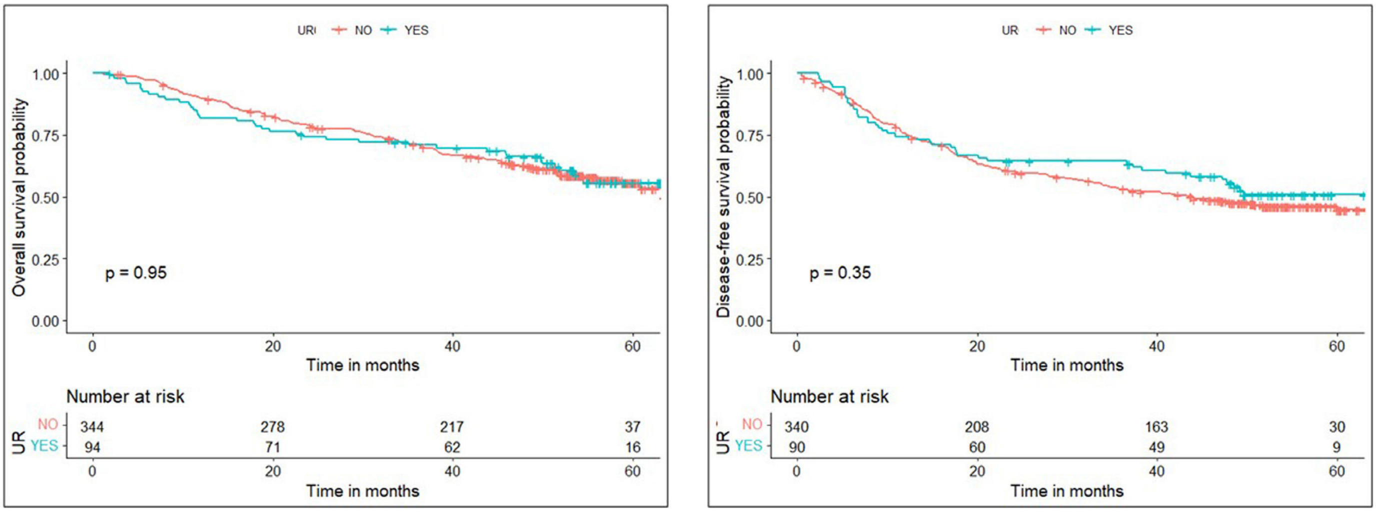

Fig. 2. Kaplan–Meier curves for overall survival and disease-free survival.

apy, surgical challenges or timing of the UR. Consequently, further prospective studies with comprehensive data on UR-related factors, conducted using large multi-institutional databases, are necessary to validate and expand upon our findings.

Conclusion

In our cohort, UR rate after anatomical lung resection for lung cancer is 4.12% and is associated with male gender, ppoDLCO%, pneumonectomy, strong adhesions and hospital volume. UR was found to be linked with prolonged hospital stay, readmission and higher perioperative mortality, yet it may not be directly correlated with long-term survival. These findings could help identify patients at high risk for UR who might benefit from preoperative counselling, optimization, and tailored postoperative management strategies to reduce the need for reoperation.

CRediT Authorship Contribution Statement

Declaration of substantial contributions to:

1. Study conception and design: MTGH, MFJ
2. Acquisition of data: All authors.
3. Analysis and interpretation of data: MTGH, GV
4. Drafting of the manuscript or critical revision for relevant intellectual content: MTGH, GV, MFJ
5. Final approval of the version to be submitted: All authors.

All authors have read and agreed to the published version of the manuscript.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

The authors declare that any of the material has been produced with the help of any artificial intelligence software or tool.

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Conflicts of Interest

The authors declare no conflicts of interest.

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