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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Preoperative risk factors of airway complications in adult lung transplant recipients: A systematic review and meta-analysis

Erişkin akciğer nakli alıcılarında hava yolu komplikasyonlarının ameliyat öncesi risk faktörleri: Sistematik derleme ve meta-analiz

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ABSTRACT

Background: In this systematic review and meta-analysis, we aimed to identify recipient-related preoperative risk factors for airway complications following lung transplantation in adults.

Methods: Articles published between November 1995 and February 2023 were searched by a thorough exploration of databases. Studies that addressed recipient-related risk factors for airway complications following adult lung transplantation, such as cohorts, case-control, or cross-sectional studies, were included. Fixed-effects or random-effects models were used to calculate the odds ratios (ORs) or mean differences (MDs) with 95% confidence interval (CI).

Results: Twenty-one studies including a total of 38,321 recipients fulfilled the inclusion criteria. Based on the pooled analyses, taller height (MD=5.98, 95% CI: 5.69-6.27, I^2=57.32%), intraoperative mechanical ventilation (OR=1.83, 95% CI: 1.41-2.38, I^2=0%), male sex (OR=1.52, 95% CI: 1.33-1.74, I^2=15.91%), preoperative extracorporeal membrane oxygenation (OR=1.58, 95% CI: 1.1-2.26, I^2=41.47%), and preoperative steroid use (OR=1.21, 95% CI: 1.04-1.41, I^2=0%) elevated the risk of airway complications following lung transplantation.

Conclusion: Taller height, intraoperative mechanical ventilation, male sex, preoperative extracorporeal membrane oxygenation, and preoperative steroid use can increase the risk of airway complications after lung transplantation. Identifying high-risk recipients or riskless situations can support the advancement of selective treatments or prevent the unnecessary avoidance of certain interventions.

Keywords: Airway complications, lung transplantation, risk factors.

ÖZ

Amaç: Bu sistematik derleme ve meta-analizde, erişkinlerde akciğer nakli sonrasında hava yolu komplikasyonlarının alıcı ile ilişkili ameliyat öncesi risk faktörleri belirlendi.

Çalışma planı: Kasım 1995 - Şubat 2023 tarihleri arasında yayımlanan makaleler kapsamlı bir veri tabanı araştırması ile tarandı. Kohortlar, vaka kontrol veya kesitsel çalışmalar gibi erişkin akciğer naklini takiben hava yolu komplikasyonları için alıcı ile ilişkili risk faktörlerini değerlendiren çalışmalar dahil edildi. %95 güven aralığı (CI) ile birlikte olasılık oranlarını (OR) veya ortalama farklarını (MD) hesaplamak için sabit etki veya rastgele etki modelleri kullanıldı.

Bulgular: Toplam 38.321 alıcının yer aldığı 21 çalışma dahil edilme kriterlerini karşıladı. Birleştirilmiş analizlere göre uzun boy (MD=5.98, %95 CI: 5.69-6.27, I^2=%57.32), ameliyat sırası mekanik ventilasyon (OR=1.83, %95 CI: 1.41-2.38, I^2=%0), erkek cinsiyeti (OR=1.52, %95 CI: 1.33-1.74, I^2=%15.91), ameliyat öncesi ekstrakorporal membran oksijenizasyonu (OR=1.58, %95 CI: 1.1-2.26, I^2=%41.47) ve ameliyat öncesi steroid kullanımı (OR=1.21, %95 CI: 1.04-1.41, I^2=%0) akciğer nakli sonrası hava yolu komplikasyon riskini artırdı.

Sonuç: Uzun boy, ameliyat sırası mekanik ventilasyon, erkek cinsiyeti, ameliyat öncesi ekstrakorporal membran oksijenizasyonu ve ameliyat öncesi steroid kullanımı akciğer nakli sonrası hava yolu komplikasyon riskini artırabilir. Yüksek riskli alıcıları veya hava yolu komplikasyon riskini artırmayan durumları belirlemek, selektif tedavilerin seçimini destekleyebilir veya belirli girişimlerden gereksiz yere kaçınmayı önleyebilir.

Anahtar sözcükler: Hava yolu komplikasyonları, akciğer nakli, risk faktörleri.

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Lung transplantation (LTx) is the most effective form of treatment for end-stage lung disease. It also increases survival and quality of life. Despite the extensive surgical and postoperative management advances in this field, airway complications (ACs) remain a common cause of morbidity and mortality.[1] There are many different types of AC such as granulation, stenosis, tracheobronchomalacia, bronchial fistula, anastomotic infection, and dehiscence. A significant contributing factor to AC has been found as postoperative decreased blood flow in the donor bronchus, despite the fact that the exact mechanism is yet unknown.[2]

Lung transplantation is the only solid organ transplantation in which systemic arterial blood supply is not routinely anastomosed.[3] Traditionally, bronchial arteries have been severed during transplantation. This results in ischemia until pulmonary artery collaterals develop in the submucosal plexus; this frequently takes weeks or months to establish. By boosting arterial resistance and interfering with collateral development, postoperative interstitial edema and reperfusion injury may be more responsible for anastomotic ischemia consequences.[1] As a result, the bronchial anastomosis is allowed to repair while being ischemic.[4]

A variety of potential risk factors for the development of AC have been found. These risk factors can be associated with the donor or recipient, surgical techniques, infections, medications, or immunosuppression.[5] Numerous research have been conducted to identify these risk variables.[2,6-25] In this systematic review and meta-analysis, we identify the most significant preoperative risk factors for ACs among adult LTx recipients.

MATERIALS AND METHODS

Search strategy

The PubMed and ISI Web of Science were systematically searched for articles published between November 1995 and February 2023. The following keywords were used in searching: "Airway Complications" and "Lung Transplantation". There were no limits on languages. The literature search was independently assessed based on the title, abstract, or descriptors to locate possibly pertinent papers for in-depth assessment. References from primary or review papers were also manually checked to look for any more applicable studies.

The meta-analysis included original studies comparing groups with and without ACs in terms of risk factors. Studies without a control group, those concentrating on pediatric LTx or re-LTx, or those managing ACs were not included. The rat or animal experiments were also excluded. Case reports, case series studies, image interests, comments, and full texts that could not be accessed were not considered. Studies from the same author, study group, or institution that were the longest or most recent series were included, while others were excluded.

Selection criteria

Cohort, case-control, and cross-sectional studies were included, if they investigated which recipient's factors directly influencing the development of ACs after LTx. Variables included age, male sex, body mass index (BMI), height, ischemic cardiac disease, diabetes mellitus (DM), preoperative diagnoses (i.e., chronic obstructive pulmonary disease [COPD], cystic fibrosis, pulmonary fibrosis, pulmonary hypertension), prior thoracic surgery, cytomegalovirus (CMV) positivity, microbiological colonization, preoperative steroid use, intraoperative mechanical ventilation, and preoperative extracorporeal membrane oxygenation (ECMO). After obtaining the complete text of the papers, the authors separately assessed eligibility. After the differences between the two reviewers were resolved, they were able to agree on the final set of data by reviewing relevant papers.

Data extraction

Two researchers independently compiled summaries of the papers that met the inclusion criteria and extracted data using a common data sheet. The following data were extracted from each study: first author's name, study design, publication year, study date (initial and end), country, comparison groups, sample size, number of postoperative ACs, AC delineations, the Newcastle-Ottawa Scale (NOS) (Table 1).

Study quality evaluation

Based on the following nine questions, the NOS was used to rate the excellence of observational studies: The following criteria must be met: *(i)* representativeness of the exposed cohort; *(ii)* choice of the non-exposed cohort; *(iii)* determination of exposure; *(iv)* proof that the outcome was not present at the start of the study; *(v)* comparability; *(vi)* assessment of outcome; *(vii)* adequate length of follow-up; *(viii)* adequate participant follow-up; and *(ix)* total stars. There is a maximum score of 9 on this scale. A total score of 7 to 9 was considered "good," a score of 4-6 was considered "fair," and a score of 4 was considered "poor."

Table 1. Baseline characteristics of the included studies

Study number	Authors	Study design	Publication year	Study dates	Country	Comparison groups	Sample size	Number of airway complications	Airway complication delineations	Newcastle-Ottawa Scale
1	Kim et al.[2]	Single centre retrospective analysis	2023	2008-21	Republic of Korea	Groups with and without airways complications	137	30	Bronchial stenosis, bronchial ischemia, bronchial necrosis, bronchomalacia	Good
2	Atchade et al.[6]	Prospective active controlled non-randomized trial	2022	2016-19	France	Groups with and without bronchial anastomotic dehiscence	156	42	Dehiscence	Good
3	Delbove et al.[7]	Single-center retrospective analysis	2022	2010-16	France	Groups with and without symptomatic anastomotic complication	121	32	Bronchial stenosis, dehiscence	Good
4	Furukawa et al.[8]	Single-center retrospective analysis	2022	2011-20	USA	Groups with and without bronchial dehiscence	811	38	Bronchial dehiscence	Good
5	Mendogni et al.[9]	Prospective, observational, single-center cohort study	2019	2011-17	Italy	Groups with and without airways complications	147	10	Bronchial stenosis, bronchomalacia	Good
6	Nęcki et al.[10]	Single-center retrospective study	2020	2013-19	Poland	Groups with and without airways complications	165	63	Bjronchial stenosis	Good
7	Malas et al.[11]	A multi-institutional retrospective observational study	2019	2007-17	USA	Groups with and without airways complications	18122	275	Dehiscence	Good
8	Kim et al.[12]	Single-center retrospective analysis	2018	2014-15	Korea	Lung transplantation patients with/without prescription steroids preoperatively	66	13	Bronchial stenosis, bronchopulmonary fistula	Good
9	Awori Hayanga et al.[13]	Multiple-center retrospective analysis	2016	2000-12	USA	Groups with and without airways complications	16156	233	General statement	Good
10	Yserbyt et al.[14]	Single-center retrospective analysis	2015	2005-13	Belgium	Groups with and without airways complications	490	93	Scar tissue, bronchial stenosis, bronchial ischemia/necrosis, inflammation/granulomas, bronchomalacia	Good
11	Cho et al.[15]	Single-center retrospective analysis	2015	2006-14	Korea	Groups with and without airways complications	75	33	General statement	Good
12	FitzSullivan et al.[16]	Single-center retrospective analysis	2011	2000-07	USA	Groups with and without anastomotic complications	230	34	General statement	Good

Table 1. Continued

Study number	Authors	Study design	Publication year	Study dates	Country	Comparison groups	Sample size	Number of airway complications	Airway complication delineations	Newcastle-Ottawa Scale
13	Fernández-Bussy et al.[17]	Single-center retrospective analysis	2011	1999-2007	USA	Groups with and without airways complications	223	52	Bronchial stenosis, bronchomalacia, dehiscence, granulation tissue	Good
14	Weder et al.[18]	Single-center retrospective analysis	2009	1992-2007	Switzerland	Groups with and without luminal narrowing during the first surveillance bronchoscopy.	206	10	Fistulisation, bronchial stenosis	Good
15	Moreno et al.[19]	Single-center retrospective analysis	2008	1993-2006	Spain	Groups with and without airways complications	214	27	Bronchial stenosis, bronchomalacia, dehiscence	Fair
16	Van De Wauwer et al.[20]	Single-center retrospective analysis	2007	1991-2004	Belgium	Groups with and without airways complications	321	55	Bronchial stenosis, bronchomalacia, fistulisation, dehiscence	Fair
17	Alvarez et al.[21]	Single-center retrospective analysis	2001	1993-2000	Spain	Groups with and without airways complications	90	6	Stenosis, granulation, dehiscence	Good
18	Herrera et al.[22]	Single-center retrospective analysis	2001	1988-1997	United Kingdom	Groups with and without airways complications	138	28	Stenosis, dehiscence	Good
19	Date et al.[23]	Single-center retrospective analysis	1995	1988-1994	USA	Groups with and without airways complications	348	29	Stenosis, dehiscence	Good
20	Golovinskiy et al.[24]	Single-center retrospective analysis	2017	2014-17	Russian Federation	Groups with and without distal bronchial stenosis	31	6	Stenosis	Good
21	Ruttmann et al.[25]	Single-center retrospective analysis	2004	1993-2002	Austria	Anastomoses required surgical treatment/ interventional therapy with anastomoses free from severe bronchial complications	71	11	Stenosis, dehiscence	Good

Statistical analysis

Statistical analysis was performed using the Medical Research Support (MedicReS E-PICOS Version 21.3, NY, United States) program. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between binary factors (age, male sex, BMI, height, ischemic cardiac disease, DM, COPD, cystic fibrosis, pulmonary fibrosis, pulmonary hypertension, prior thoracic surgery, CMV positivity, microbiological colonization, preoperative steroid use, intraoperative mechanical ventilation, and preoperative ECMO) and development of AC. We assessed the mean differences (MDs) for LTx subjects with and without AC, when the mean values and SDs for a specific risk factor were given. Fixed-effects models or random-effects models were used to produce the statistical estimates of effect based on I^2. The I^2 statistic was used to quantify heterogeneity. Using accepted guidelines, an I^2 between 0 and 40% was considered to exclude heterogeneity, 30 and 60% moderate heterogeneity, 50 and 90% substantial heterogeneity, and 75 and 100% considerable heterogeneity. Publication bias was assessed with funnel plots.

RESULTS

Initially, a total of 216 articles on Web of Science and 218 on PubMed were found to be potentially qualified (Figure 1). Of potentially relevant publications, 99 were chosen for careful consideration after articles that were irrelevant to the current meta-analysis were eliminated. Finally, 21 trials with 38,321 patients were incorporated into the meta-analysis. Table 1 displays the primary details of the studies that were used. Twenty-one included studies consisted of a prospective active controlled non-randomized trial,[6] a prospective, observational, single-center cohort study,[9] a multi-institutional retrospective observational study[11] and 18 retrospective cohort studies.[2,7,8,10,12-25]

According to the NOS, all studies had excellent methodological quality (good or fair) (Table 1).

Age: Seventeen studies (sample size=37,588) examined the impact of recipient age on the happening of AC following LTx.[2,6-11,13,15-21,24,25] The outcomes of this analysis displayed no significant difference in the mean age between patients who had AC (n=987) and those who did not (n=36,601) (MD=0.56, 95% CI: -0.72-1.84, p=0.69). Heterogeneity was considerable (I^2=95.81%, p<0.001) and random model and meta regression were used.

Male sex: Nineteen studies (sample size=38,216) examined the impact of male sex on the happening of AC following LTx.[2,6-11,13-20,22-25] The outcomes of this analysis presented a significant difference in in the proportion of male sex between patients who had AC (n=1,112) and those who did not (n=37,104) (OR=1.52, 95% CI: 1.33-1.74, p<0.001). Populations were homogeneous (I^2=15.91%, p=0.26) and fixed effect model was used (Figure 2).

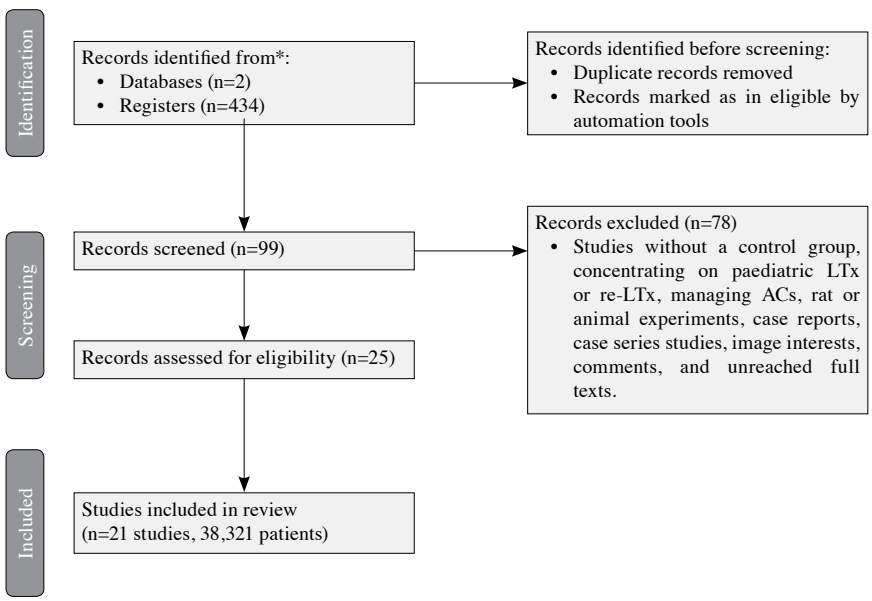
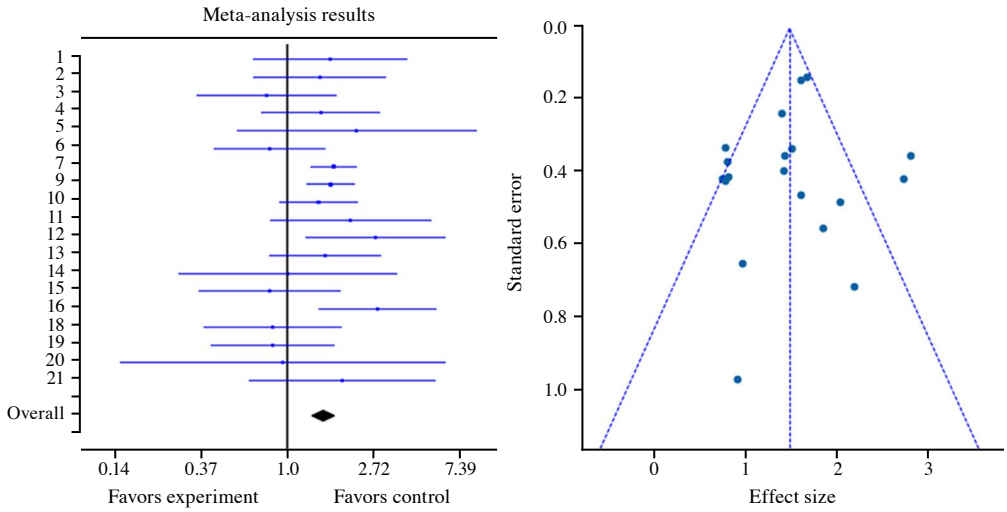


Figure 1. Flowchart of the meta-analysis.
* 216 papers on Web of Science and 218 on PubMed.

BMI: Seven studies (sample size=17,681) examined the impact of recipient BMI on the happening of AC following LTx.[2,7-10,13,25] The outcomes of this analysis exhibited no significant difference in the mean BMI between patients who had AC (n=434) or and those who did not (n=17,247) (MD=0.72, 95% CI: -0.73-2.18, p=0.33). Heterogeneity was considerable (I^2=95.1%, p<0.001) and random model and meta regression were used.

Height: Three studies (sample size=674) examined the impact of recipient height on the happening of AC following LTx.[9,18,20] The outcomes of this analysis



Study results (Fixed)			
Study name	Sample size	OR fixed effect (95% CI)	Fixed weight (%)
1	137	1.64 [0.67-4.03]	2.12
2	156	1.46 [0.68-3.15]	3.01
3	121	0.78 [0.35-1.75]	3.59
4	811	1.47 [0.74-2.92]	3.81
5	147	2.23 [0.55-9]	0.78
6	165	0.81 [0.43-1.54]	5.56
7	18,122	1.72 [1.32-2.23]	24.84
9	16,156	1.65 [1.25-2.18]	22.51
10	490	1.43 [0.91-2.26]	8.43
11	75	2.08 [0.82-5.32]	1.65
12	230	2.78 [1.23-6.26]	2.08
13	223	1.55 [0.81-2.95]	4.12
14	206	1 [0.28-3.56]	1.29
15	214	0.81 [0.36-1.85]	3.35
16	321	2.86 [1.44-5.66]	3
18	138	0.84 [0.38-1.88]	3.53
19	348	0.84 [0.41-1.72]	4.41
20	31	0.94 [0.14-6.26]	0.6
21	125	1.9 [0.64-5.58]	1.33
Total	38,216	1.52 [1.33-1.74]	100

Figure 2. The effect of recipient male sex on airway complications.
OR: Odds ratio; CI: Confidence interval.

revealed a significant difference in the mean height between patients who had AC (n=75) or those who did not (n=599) (MD=5.98, 95% CI: 5.69-6.27, p<0.001). Heterogeneity was moderate (I^2=57.32%, p=0.1) and fixed model was used (Figure 3).

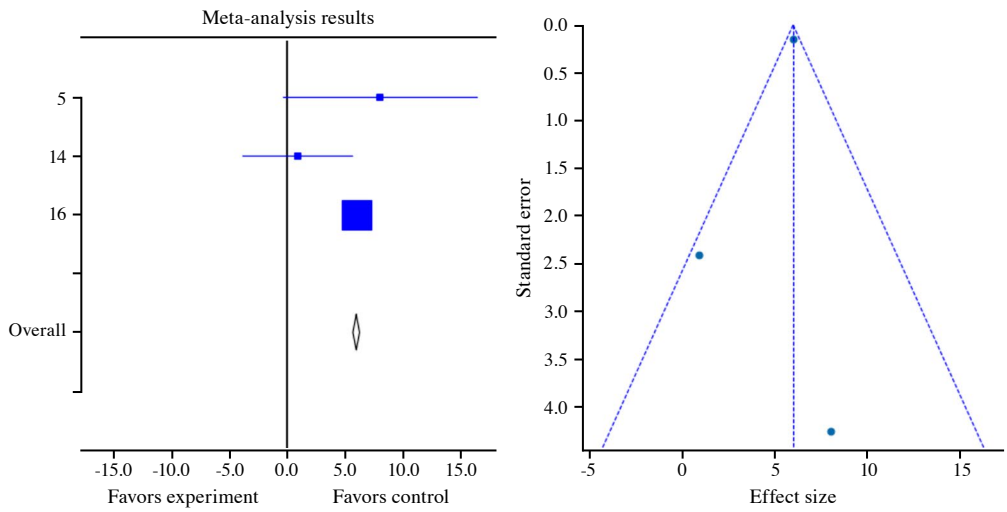
Ischemic cardiac disease: Four studies (sample size=854) examined the impact of ischemic cardiac disease on the happening of AC following LTx.[6,9,16,20] The outcomes of this analysis indicated no significant difference in the proportion of ischemic cardiac disease between patients who had AC (n=141) and those who did not (n=713) (OR=0.74, 95% CI: 0.46-1.16, p=0.19). Heterogeneity was moderate (I^2=30.27%, p=0.24) and fixed effect model was used.

DM: Five studies (sample size=34,591) examined the impact of DM on the happening of AC following LTx.[2,6,9,11,13] The outcomes of this analysis showed no significant difference in the proportion of DM between patients who had AC (n=588) and those who did not (n=34,003) (OR=1.06, 95% CI: 0.86-1.31, p=0.6). Populations were homogeneous (I^2=0%, p=0.52). Fixed effect model was used.

COPD: Fourteen studies (sample size=19,138) examined the impact of COPD on the happening of AC following LTx.[6,8-10,13,16-23,25] The outcomes of this analysis displayed no significant difference in the proportion of COPD between patients who had AC (n=645) or and those who did not (n=18,493) (OR=0.91, 95% CI: 0.76-1.1, p=0.33). Heterogeneity was moderate (I^2=37.18%, p=0.08) and fixed effect model was used.

Cystic fibrosis: Ten studies (sample size=18,242) examined the impact of cystic fibrosis on the happening of AC following LTx.[9,10,13,14,16-21] The outcomes of this analysis presented no significant difference in the proportion of cystic fibrosis between patients who had AC (n=583) and those who did not (n=17,659) (OR=0.99, 95% CI: 0.78-1.25, p=0.92). Study populations were homogeneous (I^2=9.08%, p=0.36) and fixed effect model was used.

Pulmonary fibrosis: Sixteen studies (sample size=19,863) examined the impact of pulmonary fibrosis on the happening of AC following LTx.[2,6-9,13-23] The outcomes of this analysis displayed no significant difference in the proportion



Study results (Fixed)			
Study name	Sample size	OR fixed effect (95% CI)	Fixed weight (%)
5	147	8 [-0.34-16.34]	0.12
14	206	0.9 [-3.82-5.62]	0.38
16	321	6 [5.71-6.29]	99.5
Total	674	5.98 [5.69-6.27]	100

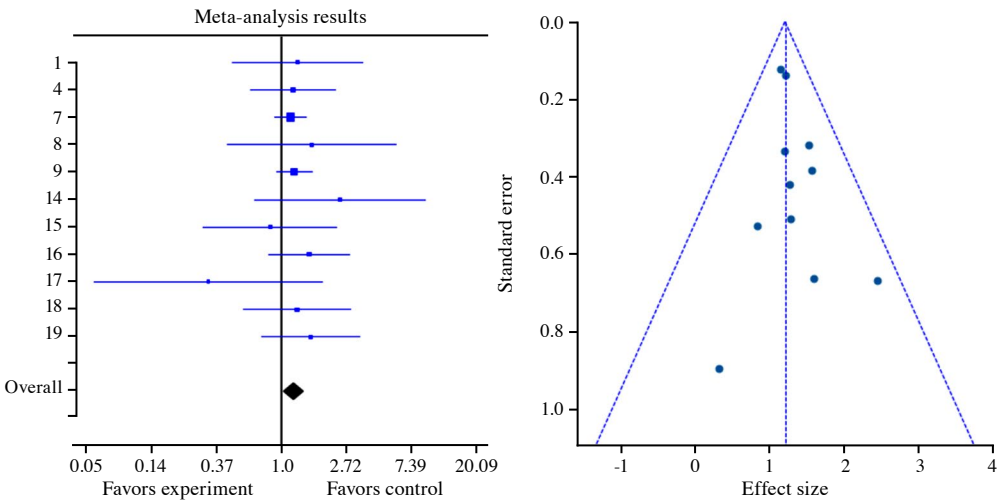
Figure 3. The effect of recipient height on airway complications.
OR: Odds ratio; CI: Confidence interval.

of pulmonary fibrosis between patients who had AC (n=758) or and those who did not (n=19,105) (OR=1.06, 95% CI: 0.9-1.26, p=0.49). Heterogeneity was moderate (I^2=47.11%, p=0.02) and fixed effect model was used.

Pulmonary hypertension: Ten studies (sample size=19,013) examined the impact of pulmonary hypertension on the happening of AC following LTx.[2,6,8,10,13,14,17,18,20,23] The outcomes of this analysis showed no significant difference in the proportion of pulmonary hypertension between patients who had AC (n=649) and those who did not (n=18,364) (OR=1.04, 95% CI: 0.74-1.47, p=0.82). Heterogeneity was moderate (I^2=34.2%, p=0.14) and fixed effect model was used.

Prior thoracic surgery: Three studies (sample size=18,378) examined the impact of prior thoracic surgery on the happening of AC following LTx.[2,8,11] The outcomes of this analysis indicated no significant difference in the proportion of prior thoracic surgery between patients who had AC (n=315) and those who did not (n=18,063) (OR=1.13, 95% CI: 0.77-1.65, p=0.54). Study populations were homogeneous (I^2=0%, p=0.65) and fixed effect model was used.

Cytomegalovirus positivity: Three studies (sample size=757) examined the impact of CMV positivity on the happening of AC following LTx.[16,18,20] The outcomes of this analysis exhibited no significant difference in the proportion of CMV positivity between patients who had AC (n=99)



Study results (Fixed)			
Study name	Sample size	OR fixed effect (95% CI)	Fixed weight (%)
1	137	1.28 [0.47-3.48]	2.35
4	811	1.2 [0.62-2.3]	5.43
7	18,122	1.15 [0.9-1.45]	41.9
8	66	1.6 [0.44-5.85]	1.25
9	15,585	1.22 [0.93-1.59]	31.83
14	206	2.44 [0.66-9.06]	0.81
15	214	0.84 [0.3-2.34]	2.73
16	321	1.53 [0.82-2.85]	5.55
17	90	0.32 [0.06-1.87]	1.5
18	138	1.27 [0.56-2.9]	3.27
19	348	1.57 [0.74-3.33]	3.36
Total	36,038	1.21 [1.04-1.41]	100

Figure 4. The effect of recipient's preoperative steroid use on airway complications.
OR: Odds ratio; CI: Confidence interval.

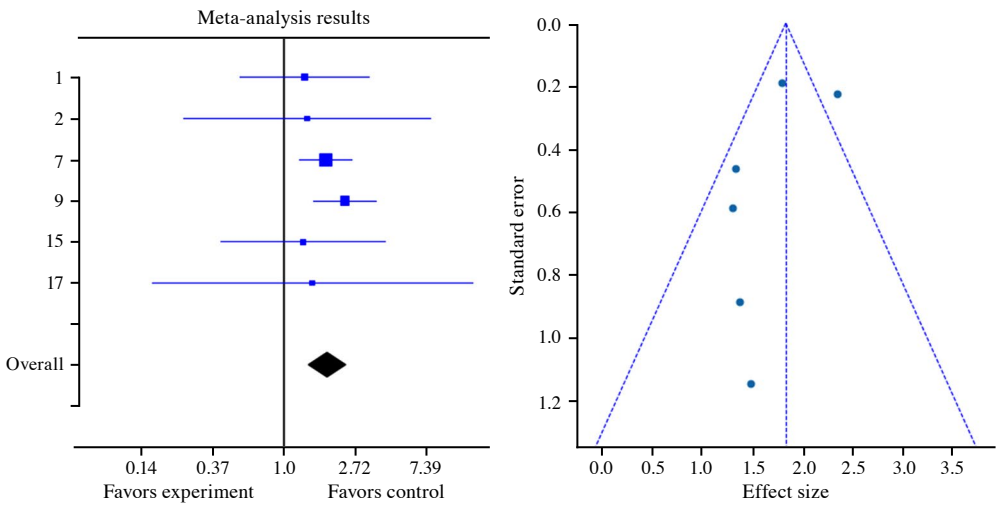
and those who did not (n=658) (OR=0.95, 95% CI: 0.62-1.47, p=0.83). Study populations were homogeneous (I^2=0%, p=0.98) and fixed effect model was used.

Microbiological colonization: Six studies examined (sample size=1,247) the impact of microbiological colonization on the happening of AC following LTx.[2,7,9,14,19,22] The outcomes of this analysis displayed no significant difference in the proportion of microbiological colonization between patients who had AC (n=224) and those who did not (n=1,023) (OR=0.87, 95% CI: 0.4-1.89, p=0.72). Heterogeneity was considerable (I^2=82.47%, p<0.001) and random effect model was used.

Preoperative steroid use: Eleven studies (sample size=36,038) examined the impact of preoperative steroid use on the happening of AC following LTx.[2,8,11-13,18-23] The outcomes of this analysis revealed a significant difference in the proportion of preoperative steroid use between patients who had AC (n=734) and those who did not (n=35,304) (OR=1.21, 95% CI: 1.04-1.41, p=0.02). Study populations were homogeneous (I^2=0%, p=0.88) and fixed effect model was used (Figure 4).

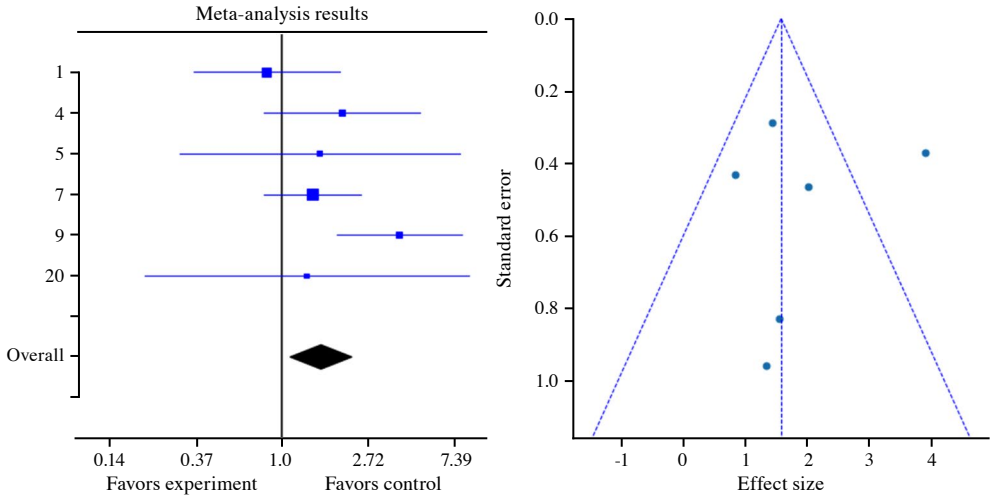
Intraoperative mechanical ventilation: Six studies (sample size=34,875) examined the impact of intraoperative mechanical ventilation on the happening of AC following LTx.[2,6,11,13,19,21] The outcomes of this analysis revealed a significant difference in the proportion of intraoperative mechanical ventilation between patients who had AC (n=613) and those who did not (n=34,262) (OR=1.83, 95% CI: 1.41-2.38, p<0.001). Study populations were homogeneous (I^2=0%, p=0.82) and fixed effect model was used (Figure 5).

Preoperative ECMO: Six studies (sample size=35,404) examined the impact of preoperative ECMO on the happening of AC following



Study results (Fixed)			
Study name	Sample size	OR fixed effect (95% CI)	Fixed weight (%)
1	137	1.34 [0.54-3.3]	12.44
2	156	1.38 [0.24-7.8]	3.03
7	18,122	1.79 [1.23-2.6]	48.55
9	16,156	2.34 [1.51-3.63]	27.34
15	214	1.3 [0.41-4.12]	6.99
17	90	1.48 [0.16-13.99]	1.64
Total	34,875	1.83 [1.41-2.38]	100

Figure 5. The effect of recipient's intraoperative mechanical ventilation on airway complications.
OR: Odds ratio; CI: Confidence interval.



Study results (Fixed)			
Study name	Sample size	OR fixed effect (95% CI)	Fixed weight (%)
1	137	0.84 [0.36-1.96]	27.5
4	811	2.01 [0.81-4.98]	12.39
5	147	1.55 [0.31-7.87]	4.92
7	18,122	1.43 [0.82-2.52]	41.05
9	16,156	3.9 [1.89-8.04]	9.54
20	31	1.33 [0.2-8.71]	4.6
Total	35,404	1.58 [1.1-2.26]	100

Figure 6. The effect of preoperative ECMO support for recipient on airway complications.
OR: Odds ratio; CI: Confidence interval; ECMO: Extracorporeal membrane oxygenation.

LTx.[2,8,9,11,13,24] The outcomes of this analysis revealed a significant difference in the proportion of preoperative ECMO between patients who had AC (n=592) and those who did not (n=34,812) (OR=1.58, 95% CI: 1.1-2.26, p=0.01). Heterogeneity was moderate (I^2=41.47%, p=0.14) and fixed effect model was used (Figure 6). The forest plot of the all parameters can be seen in Figure 7.

DISCUSSION

This systematic review and meta-analysis examined 21 studies published between November 1995 and February 2023, including 38,321 recipients, for risk factors for AC. According to pooled analyses, male sex, taller stature, intraoperative mechanical ventilation, preoperative ECMO, and preoperative steroid use were significant preoperative risk factors and there was sufficient evidence to support these findings.

Airway complications have been a major factor limiting the development of LTx throughout history and associated with considerable morbidity and mortality.[2] Among the risk factors of AC, male sex was a significant risk factor in our analysis. The bronchial arteries' origins, number, dimensions, and courses can differ greatly among individuals and between sexes. [27] Men have much more bronchial arteries than women, both in terms of size and number. Men may, therefore, have lower ischemia tolerance.

A similar argument could be possible for the height of the patients. The bronchus is greater in diameter in tall patients, and emphysema patients typically have less peribronchial fatty tissue, which can be used to cover the anastomosis.[20] This is probably due to a recipient-donor size discrepancy, as seen by the recipient's wider bronchial circumference and the donor bronchus' requirement for intussusception.[28] There will, therefore, be a requirement for telescopic anastomosis, which has the potential to result in more AC than end-to-end anastomosis. Similarly, our study supports that the strongest recipient's risk factor is the height.

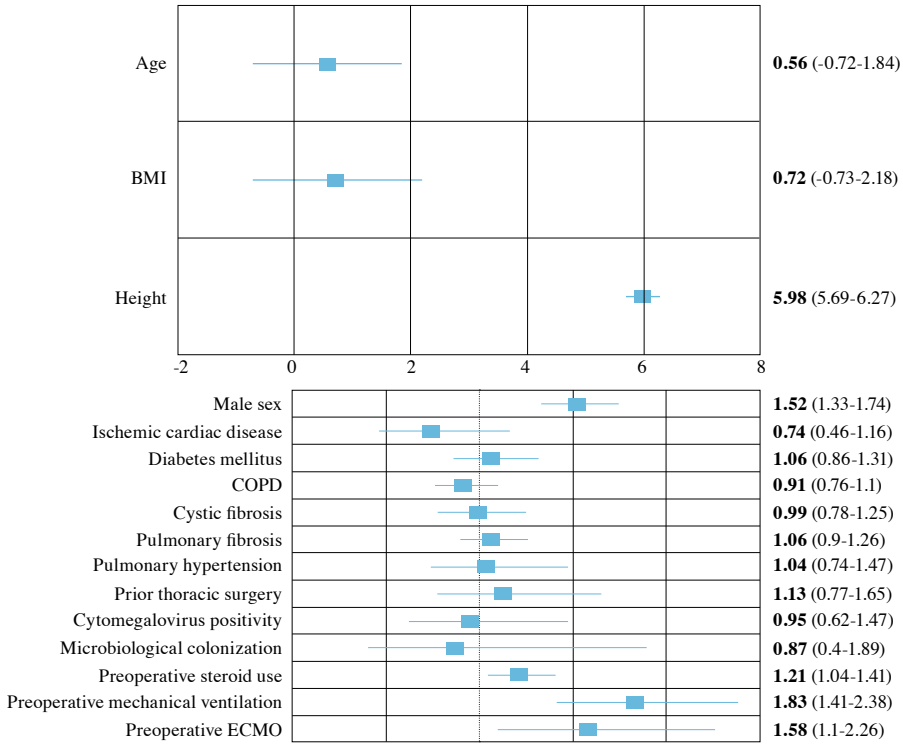


Figure 7. Forest Plot of the 21 studies on the effect of recipient's risk factors on airway complications.

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; ECMO: Extracorporeal membrane oxygenation

Mechanical ventilation is an important component in the perioperative management of LTx. Mechanical ventilation poses a risk of bronchial ischemia, as it damages the bronchial mucosa and increases arterial resistance.[29] Ischemia makes the bronchial anastomoses sites more vulnerable to poor healing, infection, and complications with the anastomotic airway. Additionally, perfusion of transplanted airways may be compromised by positive pressure mechanical ventilation, particularly when large inflation pressures are necessary. The pulmonary flow to the main bronchi would be decreased by any allograft parenchymal pathology, such as primary graft disfunction, infection, or rejection, which would impair anastomotic recovery. Anastomotic stress and bronchial wall deterioration can be also caused by positive pressure ventilation. Some studies have found a connection between the likelihood of anastomotic ACs and high airway pressures and longer ventilation periods.[30] Our study showed that intraoperative mechanical ventilation increases the risk of AC after LTx.

Due to the interruption of microcirculation, inflammatory responses that cause endothelial damage, or issues specifically associated with ECMO, it is possible that ECMO would impair the healing of the airways. Due to the fact that ECMO is used to treat AC-related high-risk disorders such as primary graft disfunction, it can also seem to increase the risk.[2] In our study, there was also a slightly higher risk of ECMO.

It is well known that perioperative steroid medication has a negative impact on the repair of bronchial anastomoses; however, recent findings have indicated that this is debatable. High doses of steroids within the first year following surgery increase the chance of AC. Patients receiving high doses of corticosteroids run the risk of having worse early postoperative outcomes, which cannot be ruled out. To optimize the early preoperative course, it is crucial to customize and limit the preoperative steroid dose.[12] In our study, preoperative steroid use moderately increased AC.

Nonetheless, there are some limitations to this analysis. Although the evaluation or diagnosis of AC was made according to global standards, there was heterogeneity between studies. The follow-up period

was also variable between studies, although it was long enough to yield results. Additionally, numerous problems were identified in detail in some research, while others only provided a single definition for them. The primary diseases leading to LTx, for instance, were noticed to be classified differently in each study. Our analysis covered the most frequently studied ones, and we concluded that the primary diagnosis indicative of LTx did not increase the risk of airway problems. Some of the studies also focus on a single variable, treatments or survival. The other limitations could be potential publication bias, heterogeneity, not all variables are comparable, cannot overcome subjectivity, and only deals with main effects.

In conclusion, our analysis show that recipient's preoperative risk factors such as taller height, preoperative mechanical ventilation, male sex, preoperative extracorporeal membrane oxygenation, and preoperative steroid use can increase the risk of airway complications after lung transplantation based on pooled analyses. Identifying the high-risk recipients or riskless situations can support the personalized approaches such as advancement of selective treatments or prevent the unnecessary avoidances.

Ethics Committee Approval: The study protocol was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (date: 28.07.2023, no: E-10840098-772.02-4639). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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