

# Abdominal Complications after Lung Transplantation-Systematic Review and Meta-Analysis

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## Abstract

**Background:** Lung transplantation is well accepted therapy for end-stage lung disease. Abdominal complications after lung transplantation are well known, have been described in retrospective, descriptive series, and are important causes of morbidity and mortality.

**Aim:** To assess the incidence of abdominal complications in patients after lung transplantation, to estimate the surgical approach and mortality.

**Methods:** Medical literature database searches were performed through 31.1.2018. Eligible studies were included if they met the following criteria: 1. Published as full articles, 2. Written in English, 3. Being observational studies, 4. Described abdominal complications in patients after lung transplantation. Event rates (ER, 95% confidence intervals (95% CIs)) were calculated by using Der Simonian and Laird method (random effect model). Meta-analysis was performed by utilizing suitable software (Comprehensive Meta-Analysis–Version 2, BIOSTAT INC., Englewood, NJ, USA).

**Results:** There was significant heterogeneity in the included studies ( $Q=393.928$ ,  $df(Q) = 11$ ,  $I^2= 97.208$  %,  $p<0.0001$ ). The pooled ERs (95% CI) for abdominal complications = 0.214, (95%CI 0.124- 0.343, test for overall effect  $Z= -3.013$ ). To assess the mortality, surgery needed to deal with the abdominal complications and the relative contribution of lower and upper gastrointestinal tract, separate meta-analyses were performed and found significant pooled ERs (95%CI): **0.039** (0.024-0.062), **0.096** (0.071-0.128), **0.087** (0.057-0.129) and **0.052** (0.015-0.166), respectively.

**Conclusion:** Abdominal complications, more of the lower gastro-intestinal tract than the upper, are not rare after lung transplantation, and exceed 21%. Up to 10% of the patients may need surgery and about 3.9% will die.

**Keywords:** Lung transplantation; Abdominal complications; Gastrointestinal complications; Immune-suppression

## Introduction

Lung transplantation, uni- or bi-lateral, is well accepted therapy for end-stage lung disease, with 1, 5 and 10-year survival of 78%, 51% and 28%, respectively [1]. Abdominal complications after lung transplantation are well known, have been described in retrospective, descriptive series or in case reports, and are important causes of morbidity and mortality [2-13]. With better technique and experience more patients survive the peri-operative period, and abdominal complication becomes a major cause of mortality. Early surgical intervention may be beneficial [7].

The incidence of abdominal complications varies widely, ranges from 7% to 59%, and differs significantly between the published series [2-13]. Moreover, different complications were described with changing incidence, surgical or non-surgical approach, and early (within 30 days of the transplantation) or late appearance. These differences may be explained by different groups of patients or different clinical definitions. In cases where cystic fibrosis is the cause of transplantation the issue is more complicated, since the gastrointestinal tract is directly involved by the disease, and one can mistake between complication of the transplantation or the disease outcome [14-16]. Study populations are different in etiology, severity of the disease, background diseases and patients selection for lung transplantation. Experience and knowledge of the surgeon and teams is also a very important factor that cannot be measured or compared.

The main causes of abdominal complication are inflammation (colitis, diverticulitis, intestinal obstruction and perforation, pancreatitis, cholecystitis) and upper gastrointestinal diseases (gastroesophageal reflux disease, peptic ulcer and gastroparesis) [17-22]. Other factors such as chronic steroids therapy, diverticulitis in immunocompromized host, CMV infection with colitis or colonic

perforation, and post-transplant lympho-proliferative disorder (PTLD) may be the cause of the complication.

In this meta-analysis and systematic review we tried to assess the incidence of abdominal complications in patients after lung transplantation, to estimate the surgical approach and mortality.

## Methods

### Identification of studies, data extraction

PubMed, MEDLINE and Embase database medical literature searches were performed through 31.1.2018, using key words (“abdomen” [MeSH Terms] OR “abdomen” [All Fields] OR “abdominal” [All Fields]) AND complication [All Fields] AND (“lung transplantation” [MeSH Terms] OR (“lung” [All Fields] AND “transplantation” [All Fields]) OR “lung transplantation” [All Fields]). A manual search of reviews, editorials and the references of original studies was performed. The work was conducted accordance to PRISMA Guidelines [23].

### Selection criteria

Inclusion and exclusion criteria were delineated before the literature search. Eligible studies were included if they met the following criteria:

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- Published as full articles,
- Written in English,
- Observational studies,
- Described abdominal complications in patients after lung transplantation.

Studies that did not met these criteria or without data for retrieval, were excluded.

### Statistical analysis

We calculated the pooled event rate (ER, 95 % confidence intervals (CIs)) and compared outcomes of individual studies by using DerSimonian and Laird method (random effect model) [24]. Forest plots were constructed for ERs of individual studies. Heterogeneity was evaluated with the Cochran Q test [25].  $I^2$  statistic was used to measure the proportion of inconsistency in individual studies with  $I^2 > 50\%$  representing substantial heterogeneity [26]. Meta-analysis was performed by utilizing suitable software (Comprehensive Meta-Analysis-Version 2, BIOSTAT INC., Englewood, NJ, USA).

### Sensitivity analyses/publication bias

In the presence of significant heterogeneity sensitivity analysis was performed. To evaluate a possible excessive influence of a single study, we repeated the meta-analyses with exclusion of this study. We also performed subgroup analyses, stratifying by factors that could potentially influence the results. The likelihood of publication bias was assessed by constructing funnel plot.

## Results

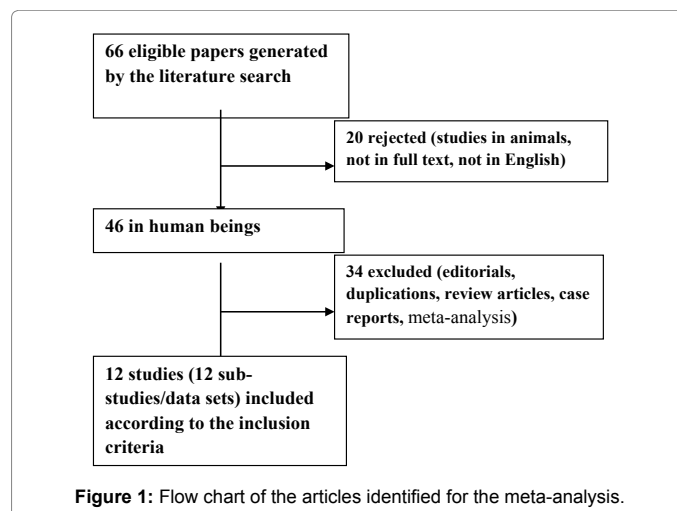
### Descriptive assessment and study characteristics

A flow chart describing the process of study selection is shown in Figure 1. Out of 66 initial titles, 12 studies remained eligible for

the meta-analysis [2-13]. Twenty papers were rejected, performed in animals, not in full text, and not in English. Thirty four papers were excluded being editorials, duplications, review articles, case reports or meta-analysis. The main characteristics of the 12 eligible studies are shown in Table 1. Three papers were added to Table 1, describing abdominal complications in cystic fibrosis patients after lung transplantation. Since the disease attacks also the gastrointestinal tract and the pancreas, we dealt with these patients separately. A total of 2663 subjects who underwent lung transplantation, from 8 countries, were included.

### Abdominal complications in patients after lung transplantation

There was no evidence of publication bias as judged by the construction of funnel plot and estimation of its symmetry (Figure 2). There was significant heterogeneity in the included studies



Series	Year	Country	Data-set	Results
Smith PC [2]	1995	USA	75 (1 bilateral, 74 unilateral)	Abdominal complications in 12 (16%), all underwent operation, 4 (33%) died
Berkowitz N [14]	1995	USA	38 CF patients	Gastroparesis in 9 (24%)
Lubetkin E [3]	1996	USA	45 patients	Abdominal complications in 23 (51%), 5 died, 8 (34.8%) underwent operation
Wekerle T [4]	1997	Austria	124 unilateral	Abdominal complications in 12 (9.6%), 5 died (41.6%), all underwent operation (100%)
Minkes RK [15]	1999	USA	70 bilateral in CF patients	Abdominal complications in 7 (10%), most of them after a previous surgical intervention, none died
Maurer JR [5]	2000	USA	210 (88 bilateral, 122 unilateral)	Abdominal complications in 27 (13%), 10 died (37%), 11 underwent operation (40.7%)
Hoekstra HJ [6]	2001	The Netherlands	127	Abdominal complication in 12 (10%), all needed operation, no mortality
Gilljam M [16]	2003	Sweden	73 CF patients	Abdominal Complications in 25 (34.2%), 15 (20%) with distal intestinal obstruction syndrome
Miller CB [7]	2006	USA	232 (130 bilateral, 102 unilateral)	Abdominal complications in 53 (23.1%), 13 died (24.5%), 23 (36.5%) underwent operation, better survival with early surgery
Bravo C [8]	2007	Spain	58 patients	Abdominal complications in 28 (48.6%)
Paul S [9]	2009	USA	208 (71 bilateral, 137 unilateral)	Abdominal complications in 90 (43%), 11 died (12.2%), 21(23.3%) underwent surgery
Lahon B [10]	2011	France	351 (86 bilateral, 265 unilateral)	Early abdominal complications in 26 (7.4%), 20 (76.9%) underwent operation, 5 (19.2%) died
Timrott K [11]	2011	Germany	754 (664 bilateral, 90 unilateral)	Abdominal complications needed surgery in 55 (7%), 12 (1.5%) died
Grass F [12]	2015	Switzerland	205 (169 bilateral, 36 unilateral)	Abdominal complications in 127 (62%), 4 (2%) died, 43 (21%) underwent operation
Costa HF [13]	2017	Brazil	274 (219 bilateral, 55 unilateral)	Abdominal complications in 49 (17.8%), 28 (10.2%) died, 20 (40.8%) underwent operation

**Table 1:** Abdominal complications in patients after lung transplantation.

[ $Q=393.928$ ,  $df(Q)=11$ ,  $I^2=97.208\%$ ,  $p<0.0001$ ]. Therefore data were meta-analyzed by the random effects model [pooled ER (95% CI)=0.214, [95%CI 0.124-0.343, test for overall effect  $Z=-3.013$ ] (Figure 3A).

### Subgroup analyses/sensitivity analyses

To assess the mortality, surgery needed to deal with the abdominal complications and the relative contribution of lower and upper gastrointestinal tract to the complications, separate meta-analyses were performed and found significant pooled ERs (95%CI): 0.039 (0.024-0.062), 0.096 (0.071-0.128), 0.087 (0.057-0.129) and 0.052 (0.015-0.166), respectively, (Figure 3B-E). Three papers about abdominal complications after lung transplantation in cystic fibrosis patients revealed ER of 0.212 (0.101-0.391). Exclusion of any study did not alter the magnitude of the summary estimate. In addition, the results of the cumulative meta-analysis of studies, ordered by the year of publication, were consistent over the years (Figure 4).

### Discussion

Abdominal complications are frequent after lung transplantation, and cause significant morbidity and mortality in up to 21% of the patients. Up to 9.6% of the patients may undergo surgery due to abdominal complications, and the mortality rate is around 3.9%. The colon and rectum are more prone to complications than the upper gastrointestinal tract, 8.7% versus 5.2%. The main causes for abdominal complications after lung transplantation are colitis, diverticulitis, CMV infection, steroid therapy, PTLD, distal bowel obstruction, pseudo-obstruction, gastro-esophageal reflux, peptic ulcer, gastroparesis, cholecystitis, and pancreatitis. Interestingly, the incidence of abdominal complications in cystic fibrosis patients after lung transplantation is not different from other patients with other indications, and is also about 21%.

It was speculated that damage or irritation of the vagus nerve in the process of lung transplantation may explain some of the abdominal

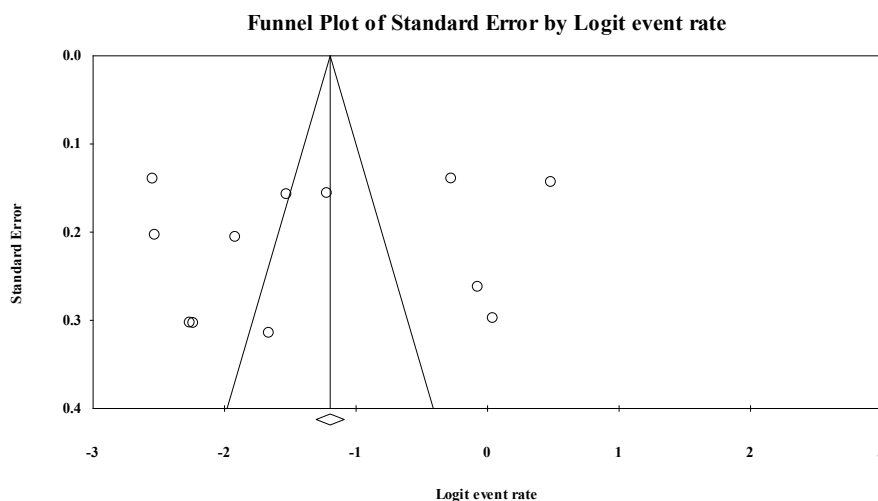


Figure 2: Funnel plot of standard error by log event rate.

## Abdominal complications in patients after lung transplantation

Study name	Subgroup within study	Comparison	Time point	Statistics for each study					Event rate and 95% CI
				Event rate	Lower limit	Upper limit	Z-Value	p-Value	
Smith PC	Bilateral 1, unilateral 74	USA	1995	0.160	0.093	0.261	-5.265	0.000	
Lubetkin E	Not specified	USA	1996	0.511	0.368	0.652	0.149	0.882	
Wekerle T	Unilateral 124	Austria	1997	0.097	0.056	0.163	-7.353	0.000	
Maurer JR	Bilateral 88, unilateral 122	USA	2000	0.129	0.090	0.181	-9.282	0.000	
Hoekstra HJ	Not specified	The Netherland	2001	0.094	0.054	0.159	-7.450	0.000	
Miller CB	Bilateral 130, unilateral 102	USA	2006	0.228	0.179	0.287	-7.783	0.000	
Bravo C	Not specified	Spain	2007	0.483	0.358	0.610	-0.263	0.793	
Paul S	Bilateral 71, unilateral 137	USA	2009	0.433	0.367	0.501	-1.936	0.053	
Lahon B	Bilateral 86, unilateral 265	France	2011	0.074	0.051	0.107	-12.393	0.000	
Timrott K	Bilateral 664, unilateral 90	Germany	2011	0.073	0.056	0.094	-18.154	0.000	
Grass F	Bilateral 169, unilateral 36	Switzerland	2015	0.620	0.551	0.683	3.389	0.001	
Costa HF	Bilateral 219, unilateral 55	Brazil	2017	0.179	0.138	0.229	-9.669	0.000	
				0.214	0.124	0.343	-3.913	0.000	

Figure 3A: Abdominal complications in patients after lung transplantation.

## Mortality due to abdominal complication after lung transplantation

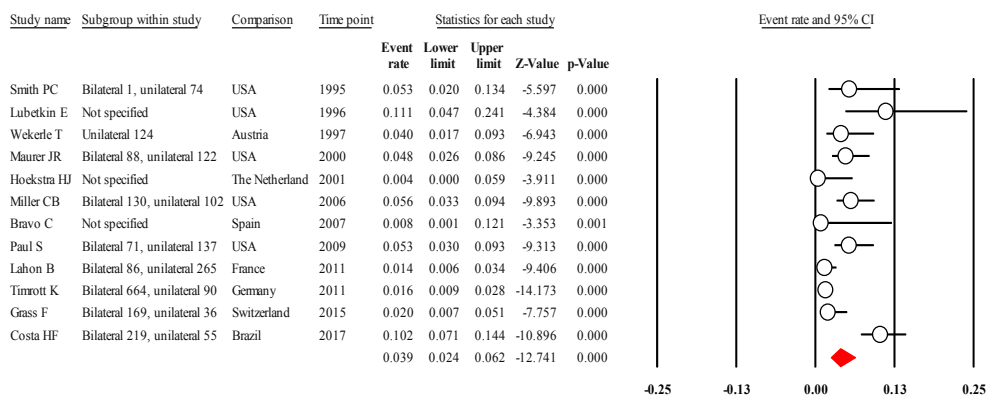


Figure 3B: Mortality due to abdominal complication.

## Abdominal complication needed surgery after lung transplantation

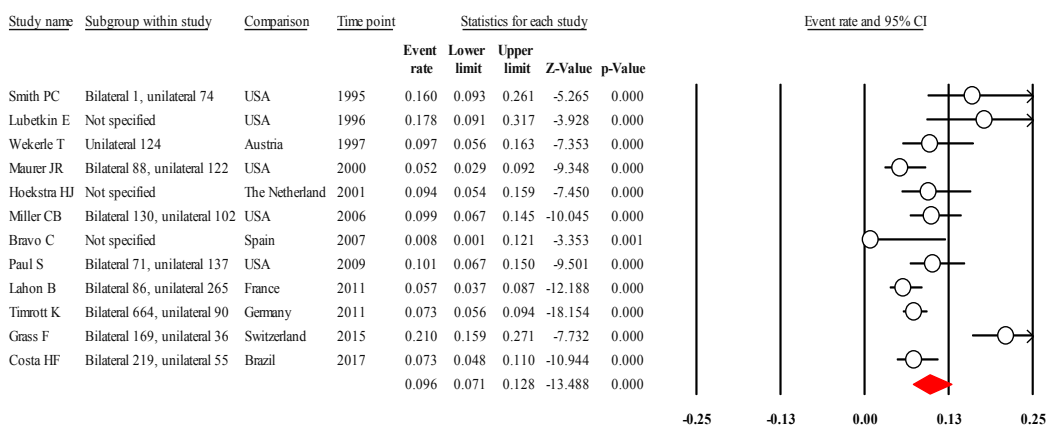


Figure 3C: Abdominal complications needed surgery.

## Lower gastrointestinal complications after lung transplantation

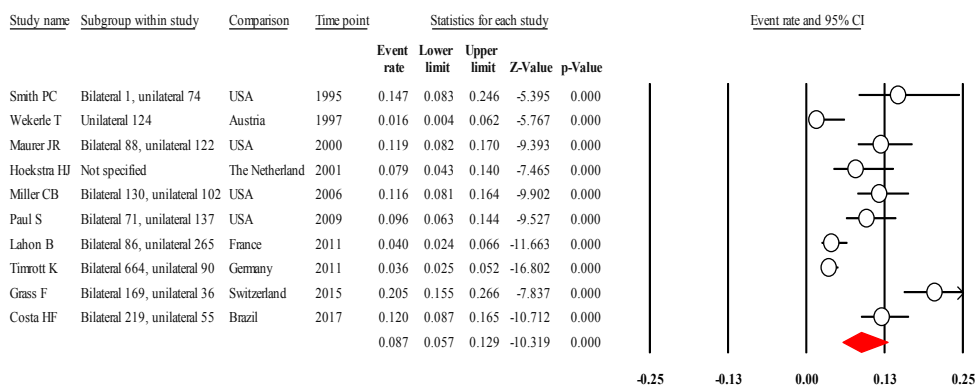


Figure 3D: Lower gastrointestinal tract complications.

## Upper gastrointestinal complications after lung transplantation

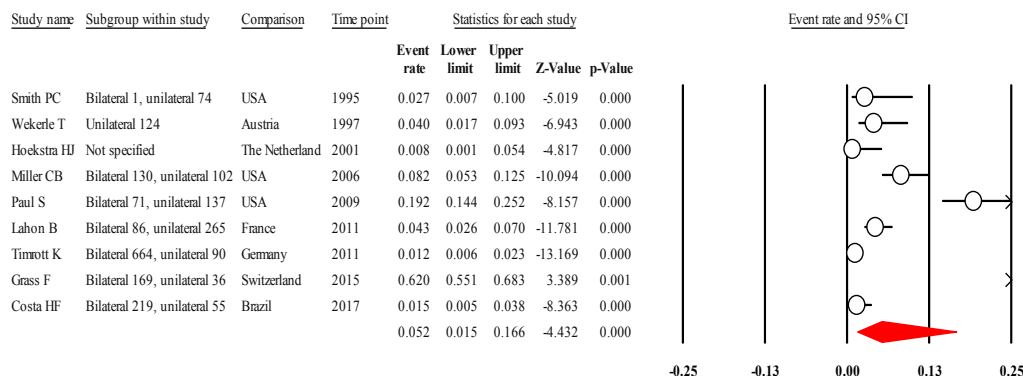


Figure 3E: Upper gastrointestinal complications.

## Abdominal complications in CF patients after lung transplantation

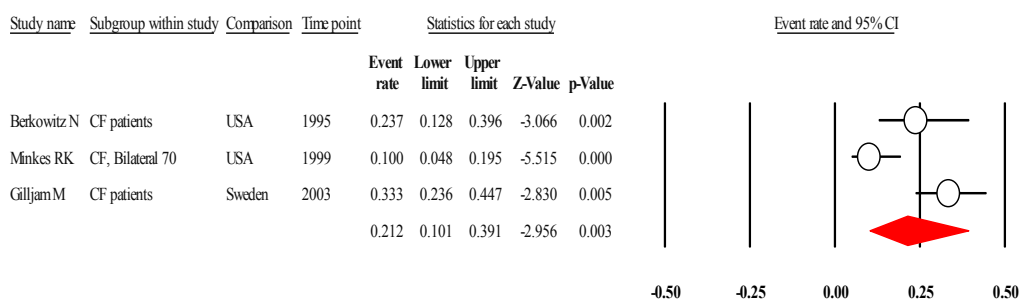


Figure 4: Abdominal complications in cystic fibrosis patients.

complications. The proximity of the vagus nerve to the dorsal aspect of the bronchus on both sides, close to where the recipient bronchus is resected, makes it vulnerable. In the process of anastomosis, hemostasis or dissection, the nerve may be damaged, and its functions compromised. Delayed emptying of the stomach, gastroparesis, impaired intestinal motility, paralytic ileus, and bowel perforation were described [27-29].

The limitation of the study is in the retrospective, descriptive nature of the individual series, which have been performed in different populations, and its inability to deal separately with unilateral or bilateral lung transplantation. To overcome some of these limitations the random effects model for meta-analysis was chosen.

In conclusion, abdominal complications, more of the lower gastrointestinal tract than the upper, are not rare after lung transplantation, and should be taken into consideration in the early period after the operation. Early surgical intervention may decrease mortality of these devastating complications.

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