

# Incidence and Risk Factors of Abdominal Complications After Lung Transplantation

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Published online: 27 May 2015  
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## Abstract

**Background** Due to the underlying diseases and the need for immunosuppression, patients after lung transplantation are particularly at risk for gastrointestinal (GI) complications that may negatively influence long-term outcome. The present study assessed the incidences and impact of GI complications after lung transplantation and aimed to identify risk factors.

**Methods** Retrospective analysis of all 227 consecutively performed single- and double-lung transplantations at the University hospitals of Lausanne and Geneva was performed between January 1993 and December 2010. Logistic regressions were used to test the effect of potentially influencing variables on the binary outcomes overall, severe, and surgery-requiring complications, followed by a multiple logistic regression model.

**Results** Final analysis included 205 patients for the purpose of the present study, and 22 patients were excluded due to re-transplantation, multiorgan transplantation, or incomplete datasets. GI complications were observed in 127 patients (62 %). Gastro-esophageal reflux disease was the most commonly observed complication (22.9 %), followed by inflammatory or infectious colitis (20.5 %) and gastroparesis (10.7 %). Major GI complications (Dindo/Clavien III–V) were observed in 83 (40.5 %) patients and were fatal in 4 patients (2.0 %). Multivariate analysis identified double-lung transplantation ( $p = 0.012$ ) and early (1993–1998) transplantation period ( $p = 0.008$ ) as independent risk factors for developing major GI complications. Forty-three (21 %) patients required surgery such as colectomy, cholecystectomy, and fundoplication in 6.8, 6.3, and 3.9 % of the patients, respectively. Multivariate analysis identified Charlson comorbidity index of  $\geq 3$  as an independent risk factor for developing GI complications requiring surgery ( $p = 0.015$ ).

**Conclusion** GI complications after lung transplantation are common. Outcome was rather encouraging in the setting of our transplant center.

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## Introduction

Lung transplantation offers an established treatment option for different end-stage lung diseases [1] with a steadily increasing number of annually performed transplantations over time [2]. Recent advances of the perioperative management and new immunosuppressive drugs have dramatically improved the short-term and long-term outcomes of lung-transplanted patients related to improved cardio-pulmonary management, a decrease of early graft rejection and advances in the management of chronic lung allograft dysfunction (CLAD) [3–6].

While strict surveillance of the cardio-pulmonary function in the post-transplant phase is a self-evident requirement, gastrointestinal complications are often an underestimated, but very important, matter for the post-operative outcome. The need for a strong immunosuppression, preexisting diseases, and sequelae of transplantation put these patients at particular risk, and acute cholecystitis, intestinal perforation, and distal intestinal obstruction syndromes are well-known complications [7–10]. Early identification and efficient management are of utmost importance to limit the negative impact on long-term pulmonary function and patient survival.

This present study aimed to assess the incidence, type, and management of GI complications after lung transplantation and to identify possible predictors in a consecutive series of 227 patients.

## Methods

The current study included all single- and double-lung transplantations performed between January 1993 and December 2010 at the University hospitals of Lausanne and Geneva, both tertiary referral transplantation centers in Switzerland. Since 2004, lung transplantation is regrouped at the Centre Universitaire Romand de Transplantation (CURT) which reunifies the University Hospitals of Lausanne and Geneva in a joint network. Both centers dispose of transplant-specific units comprising intensive care, transplant surgeons, and specialized transplant pneumologists.

All patients were prospectively followed and documented in an electronic database. For this study, data regarding the specific aspects of GI complications related to lung transplantation were extracted and >100 single items for each patient were recorded. Patients with incomplete datasets were excluded from further analysis. At the time of transplantation, patients gave informed consent to the scientific analysis of data throughout the analyzed period, in accordance with our institutional Ethics Committees.

Demographic data included age at the time of transplantation, gender, indication for transplantation, body mass index (BMI), ASA score, Charlson comorbidity index [11], and the potential presence of previous abdominal disease or surgery. Further, any preoperative prednisone therapy was recorded. Operative data included time of transplantation, type of transplantation (single lung, double lung, or multiorgan), blood loss, and the need of extracorporeal circulation. Postoperative data included length of stay, type of immunosuppressive therapy (tacrolimus, mycophenolate mofetil, azathioprine, or ciclosporine), and length of follow-up or time of death. For the purpose of comparing early and late experience, the observed time frame was divided into three different periods: 1993–1998 (early experience), 1998–2004, and 2004–2010 (CURT experience).

The primary endpoint for the present analysis was the overall GI complication rate. The incidence and type of GI complications were identified in each patient. In particular, symptomatic gastro-esophageal reflux disease (GERD), gastroparesis, peptic ulcer disease, cholecystitis, pancreatitis, diverticulitis, infectious colitis, hepatitis (defined as significant transaminase alteration), and appendicitis were assessed. GERD was defined as clinically relevant reflux at any time in the post-transplant period. Once reflux was considered as persisting complaint despite optimal medical and conservative treatment, it was assessed by pH-manometry and barium swallow, and gastroscopy. As a consequence of this actual study, formal assessment of gastro-esophageal reflux, delayed gastric emptying, and bronchial aspiration has been introduced as a routine procedure. Of note, every patient routinely received prophylactic proton pump inhibitors. Gastroparesis was defined as persistent, clinically relevant nausea or vomiting in patients who reported the feeling of fullness and satiety over several months. These findings were in the majority of cases confirmed by endoscopy, pH-manometry, and gastric emptying scans. Of note, diarrhea was consistently present in almost all patients and was not retained as GI complication, since it was attributed to the well-known side effects of immunosuppressive therapy, in particular mycophenolate mofetil. All early postoperative GI complications (within 30-day post-transplantation) and long-term morbidity (>30 days after transplantation) were graded according to their severity on a validated therapy-orientated scale according to Dindo/Clavien et al. [12], assuming that more than one GI complication might have been identified per patient. Minor complications were defined as Dindo/Clavien grade I and II, major complications as grade III–V, while fatal complications represent a grade V.

**Table 1** Indications for lung transplantation in 227 patients during 1993–2010

	<i>n</i>	%
Chronic obstructive pulmonary disease	80	35.2
Cystic fibrosis	49	21.6
Pulmonary fibrosis	33	14.5
Alpha-1 antitrypsin deficiency	22	9.7
Primary pulmonary hypertension	19	8.4
Sarcoidosis	7	3.1
Bronchiolitis obliterans syndrome	6	2.6
Other	11	4.9

Major GI complications and complications requiring surgery were separately analyzed, and the three most commonly performed surgical procedures were described.

### Statistical analysis

Descriptive statistics are reported as median (range) or mean ( $\pm$ SD) for continuous variables and absolute or relative frequencies for categorical variables. Logistic regressions were used to test the effect of potentially influencing variables on the binary outcomes overall complications, severe complications, and surgery-requiring complications. Each outcome was analyzed separately. First, dependent variables were tested individually in simple regressions. Variables with *p* values  $\leq 0.2$  were then entered into a multiple logistic regression analysis to provide adjusted estimations of the odds-ratio (OR). All tests were two-tailed and a *p* < 0.05 was considered significant.

Data analysis was performed with Prism 5.2 (GraphPad<sup>®</sup> Software, Inc. 2236 Avenida de la Playa La Jolla, CA 92037 USA) and the Stata version 11.0 (Stata-Corp LP, College Station, TX).

## Results

During the 17-year study period, 227 lung transplantations including 10 re-transplantations have been performed (Table 1). Of these, 180 were double-lung, 40 single-lung, and 7 multiorgan transplantations (3 $\times$  liver–lung, 2 $\times$  heart–lung, and 2 $\times$  kidney–lung). Seventy (33.2 %) patients required extracorporeal circulation. One hundred and eighteen men and 99 women were included with a mean ( $\pm$ SD) age of 46.4 years ( $\pm$ 14.9 years) at the time of transplantation. The mean ( $\pm$ SD) length of hospital stay was 43 days ( $\pm$ 24 days), and the median follow-up time was 48.5 months (3–84 months). Patients with re-transplantation or multiorgan transplantation were excluded as

well as five patients with incomplete charts leaving 205 patients for final analysis.

### Overall GI complications

There were 263 GI complications of any degree in 127 (62 %) patients. Forty-four (21.5 %) patients had only minor (grade I–II) and 83 patients (40 %) had also major (grade III–V) complications. Table 2 shows the type and incidence of the most common GI complications, with their repartition in major or minor complications.

GERD was the most commonly encountered GI complication in both major and minor complication groups. The time point of onset of GERD symptoms varied considerably between patients (median 3.5 months, range 1–22 months). Medical treatment was successful in 39 patients (83 %), while 8 patients (17 %) needed elective surgery.

Endoscopically confirmed peptic ulcer disease was found in 18 patients (8.8 %) and occurred in most of the affected patients (78 %) during long-term follow-up beyond 30 days after transplantation. Endoscopic and medical treatment was efficient in all patients but two who needed emergency surgery for ulcer perforation.

Colitis, either infectious or inflammatory, represented the second most important complication group (42 patients, 20.5 %). Diverticulitis occurred in eleven patients (5.4 %) as long-term complication. Of these, six patients required resection, three as elective surgery and three as an emergency procedure due to bowel perforation. The postoperative course was uncomplicated, both after primary anastomoses (two patients) and Hartmann procedures (four patients). Infectious colitis was observed early within 30-day post-transplantation in 12 patients (38.7 %), and eight of them required emergency colectomy for perforation or toxic megacolon with stoma procedures being performed in all patients except one. One of those patients died within 2 weeks after lung transplantation from multiorgan failure.

Gastroparesis was observed in 22 patients (10.7 %). It occurred early in the postoperative period in 67 % of affected patients and was treated by prokinetic medication alone in 84 %, whereas 16 % required an anti-reflux procedure.

Calculous cholecystitis was another frequently observed pathology in the post-transplant period (8.3 % of patients) and was treated by surgery or medical treatment (including percutaneous drainage) in 78 and 22 % of the patients, respectively. When occurring in the early postoperative period (35.3 % of cases), cholecystitis was characterized by severe illness, while late occurrence presented as normal biliary stone disease with classic clinical presentation. Of

**Table 2** Type and severity<sup>a</sup> of GI complication in 205 patients undergoing lung transplantation during 1993–2010

	Total <i>n</i> = 263	%	Grade I–II <i>n</i> = 147		Grade III–V <i>n</i> = 116	
			III	IV–V	III	IV–V
GERD	47	22.9	25	22	0	0
Infectious colitis	31	15.1	22	3	6	6
Gastroparesis	22	10.7	17	5	0	0
Peptic ulcer disease	18	8.8	9	9	0	0
Cholecystitis	17	8.3	3	11	3	3
Hepatitis	16	7.8	16	0	0	0
Diverticulitis	11	5.4	5	6	0	0
Pancreatitis	7	3.4	4	1	2	2
Other	94	45.8	46	46	2	2

<sup>a</sup> Dindo/Clavien complication grading: grade I and II: minor, III–V: major, V: fatal

note, the vast majority of patients (88.4 %) did not undergo cholecystectomy before lung transplantation.

Hepatitis was found in 7.8 % of the patients during follow-up and was mainly drug related and without further clinical relevance. Pancreatitis was observed in 3.4 % of the patients during follow-up and was mainly (71 %) acalculous and probably related to immunosuppression. Two of these patients needed intensive care support, and one patient died of uncontrollable sepsis due to necrotizing pancreatitis, 3 years after double-lung transplantation. The two patients with gall stone pancreatitis were treated by endoscopic gallstone extraction and sphincterotomy, followed by laparoscopic cholecystectomy in a 6-week interval. The large group of other post-transplant GI complications included diarrhea, obstruction syndromes, i.e., bowel obstruction in patients with cystic fibrosis, pancreatic insufficiency, or PEG leakage. The only univariate risk factor for overall GI complications identified in this study was the period of transplantation. The most recent (2004–2010) transplantation period revealed a significantly higher overall GI complication rate than the earliest (1993–1998) period (OR 2.16; 95 % CI 1.08–4.32,  $p = 0.03$ ) (Table 3).

### Major GI complications

Major GI complications were observed in 83 patients (40.5 %) and were fatal in four affected patients (4.8 %). One patient died of fulminant colitis, one of necrotizing pancreatitis, and two of massive bleeding from esophageal varices in the context of liver failure due to liver cirrhosis 5 and 8 years after bilateral lung transplantation, respectively. Univariate analysis identified double-lung

transplantation as a risk factor for major GI complications; patients with bilateral transplantation revealed more severe GI complications than those with an unilateral procedure ( $p = 0.02$ ) (Table 3). Multivariate analysis identified bilateral lung transplantation ( $p = 0.012$ ) and early (1993–1998) transplantation period ( $p = 0.008$ ) as independent risk factors for severe GI complications (Table 4).

### GI complications requiring surgery

Forty-three (21 %) patients presented complications requiring surgery such as colectomy in 14 patients (6.8 %), cholecystectomy in 13 patients (6.3 %), and an anti-reflux procedure in eight patients (3.9 %). Seventeen patients (49 %) underwent interventions in an elective setting, mainly for GERD or gallstone disease, while 18 patients (51 %) required emergency surgery for bowel perforation, complicated cholecystitis, or severe infectious colitis. The 30d-mortality in this series was 2.3 %. Multivariate analysis revealed a Charlson comorbidity index of  $\geq 3$  as an independent risk factor for developing surgery-requiring GI complications ( $p = 0.015$ ) (Table 5).

Many factors, such as indication to lung transplantation, preoperative prednisone therapy, preexisting comorbidities, use of extracorporeal circulation, and immunosuppressive regimen, were not identified as risk factors for any of the three primary and secondary outcomes.

### Discussion

In this study, the incidence and type of GI complications after lung transplantation during a 17-year period were assessed. In addition, possible risk factors were analyzed among various patient-related characteristics, as well as pre-, intra-, and postoperative items. With 61.5 %, GI complications after lung transplantation were frequent. The reported GI complication rates in the literature vary widely and range from 21 to 59 % [8, 13, 14] which may be explained by different definitions of GI complications, the focus on one particular complication, and different patient groups [8, 13, 15]. For instance, some studies only included GI complications requiring surgery and others focused on a particular disease such as cystic fibrosis. This disease causes specific GI complications such as exocrine pancreatic insufficiency, malnutrition, and constipation, which are not necessarily related to the transplantation procedure [16]. In addition, retrospective series may underreport minor complications treated medically only [17]. Our results revealed more minor complications in recently transplanted patients. This latter finding may be explained by enlarged indications for lung transplantation, less-strict patient selection related to the increasing number of

**Table 3** Predictors for the development of overall, severe, and surgery-requiring GI complications in 205 patients undergoing lung transplantation during 1993–2010 (adjusted by time of transplantation)

Predictor	Patients with GI complications								
	Overall			Major			Surgery requiring		
	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>
COPD	56	58	0.54	41	43	0.54	21	22	0.79
Cystic fibrosis	28	68	0.18	15	40	0.46	9	22	0.79
Pulmonary fibrosis	17	53	0.31	10	31	0.25	6	19	0.77
PPH	8	50	0.47	6	38	0.69	2	13	0.43
Charlson index $\geq 3$	35	66	0.4	23	43	0.6	16	30	0.06 <sup>a</sup>
Diabetes	19	58	0.62	10	30	0.21	7	21	0.99
Mild or severe liver disease	19	68	0.37	12	43	0.83	6	21	0.89
Cardiovascular disease	28	56	0.39	19	38	0.69	9	18	0.55
Preoperative prednisone	39	59	0.48	26	39	0.57	12	18	0.55
Type of transplantation									
Double lung	104	62		74	44		39	24	
Single lung	21	58	0.98	9	25	0.02 <sup>a</sup>	4	11	0.12 <sup>a</sup>
Extracorporeal circulation	35	39	0.8	22	37	0.65	14	24	0.52
Tacrolimus	84	67	0.89	53	42	0.18 <sup>a</sup>	30	24	0.63 <sup>a</sup>
Mycophenolate mofetil	28	62	0.55	23	51	0.96	9	20	0.87
Azathioprine	22	61	0.84	18	50	0.81	5	14	0.19 <sup>a</sup>
Ciclosporin	84	64	0.34	56	42	0.34	32	24	0.25 <sup>a</sup>
Period of transplantation									
1993–1998	27	51		25	47		10	19	
1999–2003	33	57	0.53	25	43	0.67 <sup>a</sup>	10	17	0.82
2004–2010	65	69	0.33	33	35	0.15 <sup>a</sup>	23	25	0.44

COPD chronic obstructive pulmonary disease, PPH primary pulmonary hypertension

<sup>a</sup> Retained for multivariate analysis

**Table 4** Independent predictors<sup>a</sup> for major GI complications in 205 patients undergoing lung transplantation during 1993–2010

Predictor	Patients with major GI complications				
	<i>n</i>	%	OR	95 % CI	<i>p</i>
Type of transplantation					
Double lung	74	44	1		
Single lung	9	25	0.3	0.12–0.77	0.012
Period of transplantation					
1993–1998	25	47	1		
1999–2003	25	43	0.42	0.17–1.06	0.067
2004–2010	33	35	0.26	0.09–0.7	0.008

<sup>a</sup> Multivariate analysis

**Table 5** Independent predictors<sup>a</sup> for surgery-requiring GI complications in 205 patients undergoing lung transplantation during 1993–2010

Predictor	Patients with major GI complications				
	<i>n</i>	%	OR	95 % CI	<i>p</i>
Charlson index					
1–2	27	18	1		
>3	16	30	2.64	1.21–5.67	0.015
Type of transplantation					
Double lung	39	24	1		
Single lung	4	11	0.3	0.08–1.10	0.069

<sup>a</sup> Multivariate analysis

performed transplantations worldwide, and a more focused pre- and postoperative work-up, i.e., in patients with GERD [2].

With 5 %, the mortality related to GI complications was rather low in our cohort, which allows for a nuanced

attitude with respect to prophylactic GI surgery, as outlined below. Some series revealed an increased mortality rate of 9 % up to 35 % after emergency GI surgery after lung transplantation and favored prophylactic elective surgery if indicated [8, 18]. The only predictors for developing major

GI complications were bilateral lung transplantation and early experience (1993–1998).

Major GI complications occurred in 40 % of the patients and about half of them required surgery, which highlights the impact of GI complications on the post-transplant course. About half of these surgical procedures could be performed in an elective setting, while the other half required an emergency procedure, often within the 30-day post-transplant period. This further endorses the necessity of a compulsive attitude toward careful postoperative GI surveillance and evaluation. In this respect, our results indicated that comorbidity (Charlson index  $\geq 3$ ) was a significant predictor for developing major GI complications after lung transplantation.

### Emergency surgery

GI complications occurring early after transplantation are accompanied by a high mortality rate, mainly related to emergency procedures [7]. In a recently published analysis, 7 % of patients required emergency surgery for the treatment of GI complications occurring early after lung transplantation [18]. In the present study, an emergency procedure was mainly indicated due to bowel perforation or complicated acute cholecystitis. There is an ongoing debate on whether colon resection is safe in the post-transplant setting and whether primary anastomosis should be performed in case of resection. Although pneumoperitoneum and pneumatosis intestinalis might be nonspecific clinical findings after bilateral lung transplantation and not necessarily related to ischemic bowel or perforation [19], a high index of suspicion is warranted in this context since the clinical presentation of bowel perforation might be masked in immunosuppressed patients [20]. Any clinical suspicion of bowel perforation requires therefore an immediate and aggressive diagnostic approach with a low threshold for exploratory surgery [18]. In our cohort, stoma procedures or, alternatively, primary anastomoses with protective ileostomy have been performed without particularly complicated postoperative course. These procedures were performed by specialized, experienced colorectal surgeons, which might be one reason to explain this rather encouraging outcome. Noteworthy, it has been demonstrated that colon resection in immunocompromised patients, performed by specialized colorectal surgeons, is related with less complications and a better postoperative outcome [20].

### Prophylactic surgery

Candidates for lung transplantation may reveal GI diseases in the preoperative work-up such as symptomatic cholelithiasis, GERD, and colon diverticulosis. In the

severely immunocompromised patient due to high levels of immunosuppression, GI complications such as cholecystitis or diverticulitis are more frequent than in the general population and might present with a complicated disease course [21–23]. So far, it remains controversial whether such pre-existent diseases should be treated routinely by prophylactic surgery [8, 18]. The presented data do not allow drawing final conclusions concerning this issue. The high incidence of calculous cholecystitis observed in the post-transplantation period in patients with preexisting gall stones merits an individualized approach for prophylactic cholecystectomy before lung transplantation [7]. In contrast, the role of prophylactic colon surgery has not yet been assessed. Nevertheless, diverticulitis does not usually occur immediately after transplantation and surgical management can thus be performed safely, even in an emergency setting. Similar to our observations, Larson et al. described an incidence of diverticulitis of 4.5 % in their cohort of 314 lung transplantation recipients, and more than half required surgical management [24]. Infectious colitis cannot be prevented by prophylactic surgery; aggressive diagnostic procedures and management are important [18]. GERD was the most commonly encountered GI complication after lung transplantation in our patient cohort, and 17 % of patients with GERD underwent anti-reflux surgery during follow-up. Its pathophysiology is multifactorial, i.e., functional pylorus stenosis and gastroparesis due to injury of the vagus nerve during surgery or by ice cooling, or impaired esophageal and gastric motility due to the underlying disease (cystic fibrosis) or related to side effects of medical treatments [25]. GERD plays an important role since it might deteriorate transplant function and lead to CLAD [25, 26]. Recent studies have demonstrated the safety of laparoscopic anti-reflux surgery in the post-transplant setting [27] and its efficiency in preserving lung function [28–30]. So far, preventive fundoplication is not recommended unless preoperative work-up demonstrates severe preexisting GERD, which might jeopardize the function of the transplanted lung. More evidence will be available from an ongoing clinical trial (ClinicalTrials.gov, NCT 01982968) on the role of laparoscopic fundoplication in patients with idiopathic pulmonary fibrosis.

Several limitations of this study need to be addressed. First, although the study relies on a prospectively generated database, the data analysis is retrospective. Minor complications tend to be underestimated and may not have been reported which may interfere with the application of the Dindo/Clavien classification. With regard to the definition of GERD as a clinical entity, asymptomatic reflux might have been missed, especially in the earlier periods (1999–2004). Further, a wide range of GI complications have been described, occurring at different time points,

which might impede with the identification of risk factors as an associative model. However, this approach was chosen to truly reflect the reality in our series over the past 17 years. A retrospective analysis over such a long study period is vulnerable to alterations, i.e., medical evolution, change of staff, or technological progress. The division in three periods is an attempt to provide for this shortcoming. Generally, the attempt to identify independent risk factors for developing GI complications after lung transplantation may underestimate their potential interactions in such a complex domain, which requires careful interpretation of the presented results.

In conclusion, GI complications after lung transplantation are frequent and various and specific types of complications may arise during follow-up. Besides comorbidity, no specific risk factors for developing GI complications could be identified. A high level of suspicion, a compulsive attitude toward careful postoperative surveillance, thorough evaluation by a multidisciplinary team, and surgical management by specialized GI surgeons are mandatory.

**Acknowledgment** The authors thank Pierluigi Ballabeni for his valuable help in statistical analyses.

**Conflict of interest** No conflict of interest or funding source to declare.

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