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Mortality after lung transplantation: a single-centre cohort analysis

Jo Raskin[1]*, Arno Vanstapel[2,3]*, Eric K. Verbeken[3], Hanne Beeckmans[1], Bart M. Vanaudenaerde[2], Stijn E. Verleden[2], Arne P. Neyrinck[4], Laurens J. Ceulemans[2,5], Dirk E. Van Raemdonck[2,5], Geert M. Verleden[1,2], Robin Vos[1,2] & the Leuven Lung Transplant Group†

1 Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium
2 Division of Respiratory Diseases, Department of Chronic Diseases, Metabolism & Ageing (CHROMETA), KU Leuven, Leuven, Belgium
3 Department of Histopathology, KU Leuven, Leuven, Belgium
4 Department of Anesthesiology, University Hospitals Leuven, Leuven, Belgium
5 Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium

Correspondence
Dr. Robin Vos, Division of Respiratory Diseases, Lung Transplantation Unit, Department Chronic Diseases, Metabolism & Ageing (CHROMETA), KU Leuven, Herestraat 49, B-3000 Leuven, Belgium.
Tel.: +32 16 341548;
fax: +32 16 346803;
e-mail: robin.vos@uzleuven.be

SUMMARY

Detailed data on postoperative death in lung transplant (LTx) recipients are lacking. Therefore, we investigated all deaths after LTx in a large, single-centre, 25-year follow-up cohort. Prevalence, time, place and cause of death (COD) were retrospectively analysed for all patients undergoing primary LTx between July 1991 and December 2015 in our centre. Over subsequent years, postoperative survival significantly improved, with proportionally more patients surviving to 1-year post-LTx ($P < 0.0001$). A total of 347 (38.9%) LTx recipients died, of which 53.6% expired within 3 years post-LTx [median time to death 910 (236–2447) days]. Autopsy was performed in 34.8% of deaths. COD included CLAD in 27.1% (BOS 63.8% vs. RAS 36.2%); infection (26.5%); malignancy (15.6%); postoperative complication (11.2%); cardiovascular disease (4.6%) or other causes (6.9%). In 8.1%, no clear COD could be determined. COD significantly differed between the various LTx indications ($P = 0.047$). With longer follow-up, infection becomes a less prevalent COD, but CLAD and malignancies a more important COD. The majority of patients died on the intensive care unit (40.6%) or hospital ward (29.1%), but place of death varied depending on the underlying COD. The current study provides insights into the postoperative deaths of LTx recipients.

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Key words
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*Contributed equally.
†The Leuven Lung Transplant Group: This includes the following important collaborators of our lung transplant programme who were directly involved in the care of our lung transplant recipients during the past years: Laurent Godinas, MD, PhD; Jonas Yserbyt, MD, PhD; Lieven J. Dupont, MD, PhD; Anke Van Herck, MD; Annelore Sacreas, MSc; Janne Kaes, MSc; Tobias Heigl, MSc; Sofie Ordies, MD; Veronique Schaevers, MSc; Paul De Leyn, MD, PhD; Willy Coosemans MD, PhD; Philippe Nafteux, MD, PhD; Herbert Decaluwé, MD, PhD; Hans Van Veer, MD; Lieven Depypere, MD; Anna E. Frick, MD; Birgit Weynand, MD, PhD; Marie-Paule Emonds, MD, PhD.

Introduction

During the past half-century, lung transplant (LTx) surgery has become standard of care for selected patients with end-stage lung disease, such as cystic fibrosis, pulmonary fibrosis and emphysema. Survival after LTx has steadily improved due to better surgical techniques, perioperative management, optimization of

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immunosuppressive regimens, treatment of infections and management of chronic lung allograft dysfunction (CLAD). In 2018, median survival of adults who underwent primary LTx in the most recent era (2009-June 2016) was 6.5 years, which increased to 8.7 years for adult recipients surviving to 1 year after primary LTx [1]. Overall, better survival is seen in women, patients undergoing bilateral LTx, or with cystic fibrosis as indication for LTx. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), the main causes of death after adult LTx (reported from 1990 through June 2017) comprise infection and 'graft failure' in the first post-transplant year, whereas later, death from CLAD – mainly bronchiolitis obliterans syndrome (BOS) and to a lesser extent restrictive allograft syndrome (RAS) – predominates, next to lower death rates due to 'graft failure', malignancy and infection [1].

On the other hand, several transplant centres and social media platforms nowadays report LTx recipients surviving 20 years or more after transplantation [2,3], with 20-year post-LTx survival rates of 20–30% in experienced centres, again mainly patients who underwent bilateral LTx or were transplanted for cystic fibrosis [4–6]. The longest surviving LTx recipient in our institution is currently a woman who underwent heart–lung transplantation for Eisenmenger's syndrome 28 years ago. Some of these 'long-term survivors', however, required redo-transplantation (almost exclusively for prior CLAD) to prolong their life expectancy, which is performed in 4–10% of adults who underwent primary LTx [1].

Longer survival, with concurrent longer duration of immunosuppressive treatment and ageing of the patient, may lead to a shift in mortality causes after LTx, with malignancies occurring more frequently as cause of death (COD), next to CLAD. However, detailed analyses of prevalence, cause, place and time of death in large cohorts of LTx recipients are lacking. Therefore, the current study aims to investigate all deaths after LTx in a large, single-centre, 25-year follow-up cohort.

Patients and methods

Study design

Data were retrospectively assessed for all LTx recipients undergoing primary LTx between July 1991 and December 2015 at the University Hospitals Leuven, the main referral hospital for transplantation in Belgium. Patients receiving other solid organs, in addition to their lung allograft(s), during the same transplant procedure were also included (i.e. heart–lung, lung + liver, lung + kidney, heart–lung + liver transplant). All LTx recipients have lifelong, standardized 3–4 monthly post-transplant follow-up at our institution. The local Ethics Committee approved the study, and all patients had provided written informed consent at time of listing for LTx to access their clinical and biobanked data for research purposes (S51577).

Assessment of survival status and cause of death

Survival status, time, place and cause of the included patients' death were obtained from electronic medical records and postmortem reports and independently assessed by two experienced clinical physicians (JR, RV), subsequently reaching agreement on the most likely cause of death in case of initial inter-observer disagreement. Era of transplant surgery and of mortality (1991–1995, 1996–2000, 2001–2005, 2006–2010, 2011–2015) was determined for every patient. In case of redo-transplantation, no censoring was performed and time since first transplant surgery was used for analysis of patient survival, since immunosuppressive treatment had been initiated at the first procedure.

The type of malignancy was confirmed by pathology reports if available. Patients with active malignancy currently still alive, or successfully treated for prior (mostly skin) cancer, were not censored for survival analysis (end of follow-up 31/12/2016, i.e. 1 year after last included transplant procedure).

Cause of death was categorized as follows: early post-operative complication (e.g. lethal bleeding, perioperative shock, fatal suture dehiscence, severe primary graft dysfunction, etc.), infection, malignancy, cardiovascular disease (e.g. myocardial infarction, lethal arrhythmia, stroke), CLAD, other cause or unknown (no clear cause identifiable). Location of death was categorized as either in the operation room, surgical intensive care unit (ICU), medical ICU, regular ward, emergency room or at home.

Statistical analysis

All analyses were performed using GRAPHPAD PRISM 8.0.2 (San Diego, CA, USA). Results are expressed as mean (±standard deviation) or median (interquartile range) wherever appropriate. Groups were compared using *t*-test, Mann–Whitney test, Wilcoxon signed rank test, or one-way ANOVA, respectively, depending on normality

distribution and repeated measures. Fisher's exact or chi-square test was used to compare proportions, Kaplan–Meier curves and log rank test were used for survival analyses. All *P*-values are two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Transplant cohort and study population

A total of 893 LTx procedures were performed, including 683 (76.5%) double lung, 151 (16.9%) single lung, 47 (5.3%) heart–lung, 8 (0.9%) combined lung–liver, 2 (0.2%) combined heart–lung–liver and two combined lung–kidney transplants (0.2%). Only 33 (3.7%) of all procedures were redo-transplantations, almost exclusively performed for CLAD (30/33, 90.9%). Overall, our general transplant population comprised 52.2% males and 47.8% females, with a median age at transplant of 54 (41–59) years (mean 48.8 ± 13.5 years). The main indications for primary transplantation were emphysema (49%), followed by interstitial lung diseases (mainly IPF) (19%), cystic fibrosis (13%), pulmonary hypertension (idiopathic or secondary) (8%) or miscellaneous (11%) [such as obliterative bronchiolitis (4.4%), noncystic fibrosis bronchiectasis (2.5%) or lymphangioleiomyomatosis (1.0%)].

At the current time of analysis, a total of 347 (38.9%) patients had died, mostly middle-aged males transplanted for emphysema, which cohort was used for further analyses on prevalence, cause, place and postoperative time of death over the different transplant era.

Overall survival

Figure 1 depicts the annual number of primary LTx procedures ($n = 860$, exclusion of 33 s Tx procedures) and exponentially increasing cumulative number of post-transplant survivors over the study period. Figure 2 illustrates overall post-transplant survival per transplant era, as well as survival conditional on survival to 1-year post-transplant, demonstrating a significant improvement in post-LTx survival over the various eras of LTx.

One-year survival and median survival, respectively, increased from 54.3% and 200 (69.5–1225) days for patients transplanted during the initial 5 years [1991–1995] of our programme, to 86.5% and 1332 (480–3154) days for those transplanted during the [1996–2000] era; to 88.9% and 1951 (604.3–3625) days during the [2001–2005] era ($P < 0.0001$), reflecting the overall improved *early* (1-year) postoperative survival during the first 15 years of our transplant programme (Fig. 2a). Contemporary [2011–2015], 1-, 3- and 5-year overall survival after LTx is 93.4%, 86.8% and 80.7%, respectively.

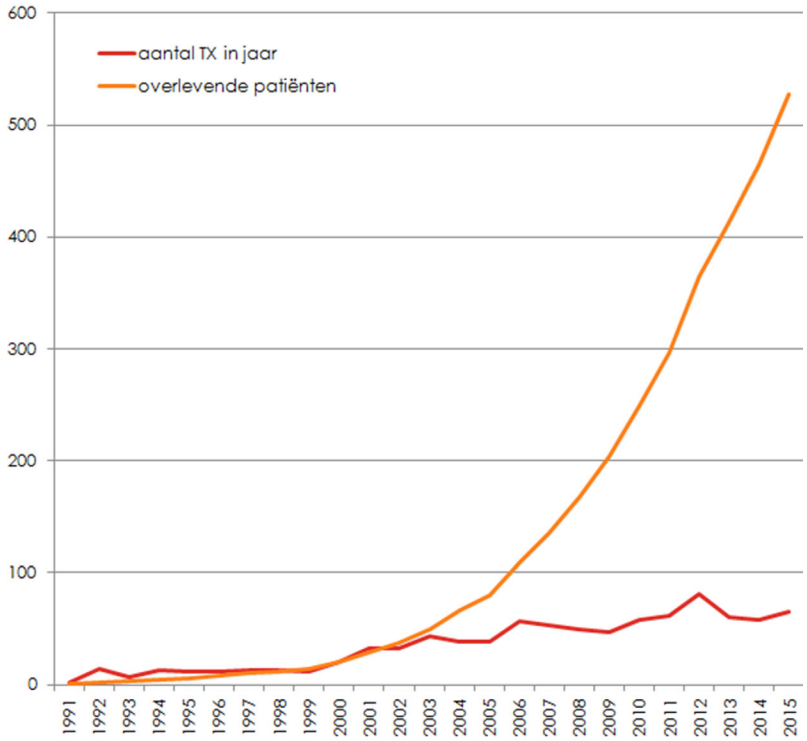

Figure 1 Annual number of lung transplant procedures and cumulative number of post-transplant survivors. Annual number of lung transplant procedures and cumulative number of post-transplant survivors in UZ Leuven (1991–2015, $n = 860$). The total number of deaths after first lung transplantation in our centre (1991–2015) was $n = 347$. No censoring at retransplantation and exclusion of second Tx ($n = 33$), follow-up until 31 December 2016 (minimal 1 year for patients transplanted in 2015).

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Median overall survival conditional on survival to 1-year post-transplant of all LTx recipients since 1991 (n = 860) was 11.8 years, which is considerably better than that of adult lung transplants in the ISHLT registry (1990–1998, n = 6.735: 7.2 years; 1999–2008, n = 16468: 8.7 years). Post-transplant survival conditional on survival to 1 year post-transplant (thus excluding early post-operative deaths), however, clearly also shows improved *late* survival outcome during the last 15 years of our transplant programme (Fig. 2b): that is 5-year survival conditional on survival to 1 year considerably increased from 60% in [1991–1995] to 67.2% in [1996–2000], 80.1% in [2001–2005], 84.7% in [2006–2010] and 86.4% [2011–2015].

Time of death

With regard to the cohort of deceased patients (n = 347), we noted that 53.6% of these patients had died within the first 3 years post-transplant, with a median time to death of 910 (236–2447) days. Only 12 of these patients (3.5%) had undergone redo-transplantation prior to death (median survival after redo-transplant was 433 (60–1101) days).

Table 1 illustrates the demographics of the cohort of deceased patients. Table 2 summarizes the proportion of deceased patients, stratified per transplant era and their median time to death. Figure 3 illustrates the cumulative number of deaths after the first LTx, both stratified per transplant era, per mortality era and per death burden during the previous years, demonstrating the multimodal distribution of deaths. Of the largest and most recently transplanted cohort [2011–2015], only 14.2% had died at end of follow-up (31/12/2016), with a median time to death of 433.5 (129–829) days, again reflecting improved *late* (>1-year) postoperative survival.

Cause and place of death

Causes of death of the 347 deceased patients (Table 1), in descending order of prevalence, included CLAD in 94 patients (27.1%) (BOS n = 60/94 or 63.8% vs. RAS n = 34/94 or 36.2%); infection in 92 patients (26.5%);

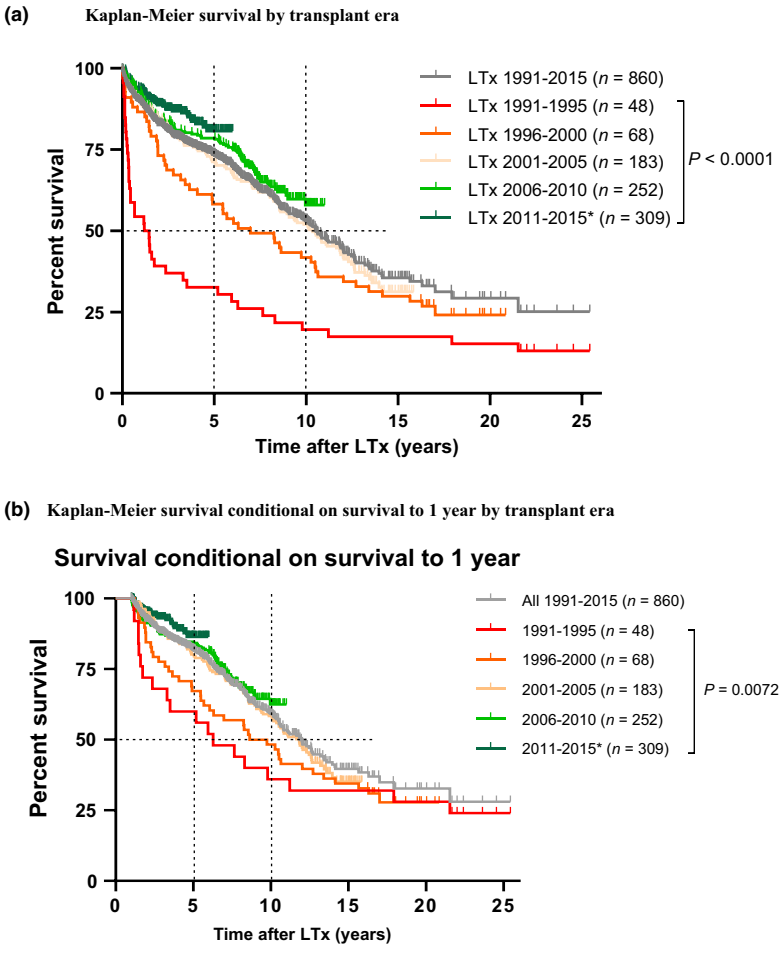

Figure 2 Overall survival after first lung transplantation per transplant era (LTx 1991–2015, n = 860). Kaplan–Meier curves of overall patient survival after first lung transplantation in UZ Leuven (1991–2015, n = 860) stratified per transplant era (a) and conditional on survival to 1 year stratified per era (b). No censoring at retransplantation and exclusion of second Tx (n = 33), follow-up until 31 December 2016 (*minimal 1 year for patients transplanted in 2015). Dotted lines represent the 5-year, 10-year or median survival cut-off. A significant difference in survival (Log rank test) is observed between the various eras during which lung transplantation was performed.

Table 1. Demographics of deceased lung transplant recipients

	Deceased (*n* = 347)
Year of first Tx	2008 (2003–2012)
Age at first Tx, years	55 (45–60)
Sex (M/F), *n*	196/151
Type of Tx, *n* (%)	
SSLTx	195 (56.2%)
SLTx	122 (35.2%)
HLTx	27 (7.8%)
HL + liverTx	1 (0.3%)
SSL + kidneyTx	2 (0.6%)
Underlying primary disorder, *n* (%)	
Emphysema	172 (49.6%)
Fibrosis	95 (27.4%)
Pulmonary Hypertension (prim or sec)	43 (12.4%)
Bronchiectasis (CF and non-CF)	32 (9.2%)
Obliterative bronchiolitis (non-CLAD)	3 (0.9%)
Other	2 (0.6%)
Time to death after first Tx, days	984 (277–2578)
Autopsy performed, *n* (%)	121 (34.8%)
Causes of death, *n* (%)	
Post-op complication	39 (11.2%)
Infection	92 (26.5%)
Cardiovascular	16 (4.6%)
CLAD	94 (27.1%)
Malignancy	54 (15.6%)
Other	24 (6.9%)
Unknown	28 (8.1%)
Place of death, *n* (%)	
Operation room	9 (2.5%)
Surgical ICU	73 (21.0%)
Medical ICU	68 (19.6%)
Ward	101 (29.1%)
Emergency room	6 (1.7%)
Home	90 (25.9%)
Unknown	0 (0%)

CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; F, female; HLTx, heart–lung transplantation; ICU, intensive care unit; M, male; SLTx, single-sided lung transplantation; SSLTx, bilateral lung transplantation; Tx, transplantation.

Data are expressed as total values, % or median (interquartile range) where appropriate.

malignancy in 54 patients (15.6%); postoperative complication in 39 patients (11.2%); cardiovascular disease in 16 patients (4.6%); whereas 24 patients (6.9%) died from various other causes (i.e. acute rejection $n = 6$, renal failure $n = 5$, encephalopathy/epilepsy $n = 4$, bleeding n = 2, unexplained bone marrow failure $n = 2$, intestinal failure/obstruction $n = 2$, euthanasia for psychologic reasons $n = 2$, tension pneumothorax of native lung $n = 1$). In 28 patients (8.1%), no clear COD could be established, mainly because these patients died at home ($n = 22/28$, 78.6%), no autopsy was performed following in-hospital death ($n = 4/28$, 14.3%), or autopsy could not reveal the actual COD ($n = 2/28$, 7.1%).

Figures 4 and 5 summarize the COD per mortality era and per postoperative survival time. With increasing post-transplant survival time a shift in mortality causes is seen, with mortality due to infection being more prevalent in the first 3 years post-transplant and mortality due to malignancy or CLAD becoming increasingly prevalent from 3 years on. A same trend, albeit less prevalent, is seen for cardiovascular causes of death.

Figure 6 summarizes COD in relation to the underlying pretransplant disease, demonstrating a significant difference in COD for the major indications (emphysema, fibrosis, pulmonary hypertension and bronchiectasis) (chi-square $P = 0.047$): patients transplanted for emphysema primarily died of CLAD (30.2%), fibrosis patients mainly of infection (24.2%), those with pulmonary hypertension predominantly of postoperative complications (30.2%) and those transplanted for bronchiectasis mostly of CLAD (37.5%). Kaplan–Meier survival analysis also demonstrated that mainly patients with pulmonary hypertension demonstrated increased early postoperative mortality compared to the other transplant indications ($P = 0.056$).

Overall, the majority of patients died, in descending order of frequency, on the ICU (40.6%: surgical ICU 21.0%, medical ICU 19.6%), hospital ward (29.1%) or at home (25.9%) (Table 1). Place of death in relation to underlying COD is depicted in Fig. 7, demonstrating that most patients dying from a postoperative complication expired in the surgical ICU (61.5%), patients who died of infection mostly expired on the medical (34.8%) or surgical ICU (32.6%), patients dying from a cardiovascular cause, CLAD or other COD most frequently died on the hospital ward (respectively, 31.3%, 43.6% and 37.5% of patients in each group), while patients dying from malignancy or with an unknown COD mostly expired at home (respectively, 48.1% and 78.6% of patients in each group) (chi-square $P < 0.0001$).

Infections

A total of 92 patients' deaths (26.5% of all deaths) were directly related to infection/sepsis, most frequently due to fungal infection (36.9%, *Aspergillus fumigatus* $n = 26$, other fungi $n = 8$), followed by bacterial infection (34.8%, *Pseudomonas aeruginosa* $n = 18$, other bacteria $n = 14$), viral infection (9.8%, *cytomegalovirus* [CMV] $n = 5$, *Influenza* $n = 3$, *varicella zoster virus* $n = 1$) or a combination of microorganisms (6.5%, CMV + *A. fumigatus* $n = 3$,

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Table 2. Summary of lung transplant procedures per era

Transplant era*, years	Transplant procedures (incl. retransplants), *n* (%)	Retransplants, *n* (%)	Deceased, *n* (%)	Alive, *n* (%)	Median time to death†, days (IQR)
1991–1995	48	0	42 (87.5%)	6 (12.5%)	200 (68–1244)
1996–2000	70	2 (2.9%)	51 (72.9%)	19 (27.1%)	1332 (531–3154)
2001–2005	186	3 (1.6%)	117 (62.9%)	69 (37.1%)	2159 (699.5–3539)
2006–2010	264	12 (4.5%)	91 (34.5%)	173 (65.5%)	986 (382–2353)
2011–2015	325	16 (4.9%)	46 (14.2%)	279 (85.8%)	433.5 (129–829)
Overall	893	33 (3.7%)	347 (38.9%)	546 (61.1%)	910 (236–2447) days

Summary of the proportion of deceased patients stratified per transplant era and their median time to death. Data are expressed as total values or %, or median (interquartile range, IQR) where appropriate.

*Period during which (first – in case of multiple) lung transplant surgery was performed.

†Median time to death of the cohort of deceased patients only; surviving patients not included, no censoring at redo-transplantation. Follow-up until 31 December 2016 (minimal 1-year follow-up for patients transplanted in 2015).

CMV + bacteria $n = 1$, *P. aeruginosa* + *A. fumigatus* $n = 2$). In $n = 11/92$ patients (11.9%), despite clinical suspicion and empirical treatment of infection, no specific microorganism could be identified. Median survival of patients dying from infection was 464 (166–1139) days.

Malignancies

A total of 54 patients (15.6% of all deaths) died due to malignancy, most frequently primary lung cancer ($n = 22/54$, 40.7%), followed by post-transplant lymphoproliferative disorder/lymphoma ($n = 11/54$, 20.4%), urogenital cancer ($n = 5/54$, 9.3%: renal 1, bladder 3, endometrium 1), gastrointestinal tract cancer ($n = 4/54$, 7.4%: colon 3, oesophagus 1), head/neck cancer ($n = 3/54$ 5.6%), brain cancer ($n = 2/54$, 3.7%), skin cancer ($n = 2/54$, 3.7%, both malignant melanoma), and the remaining five patients (9.3%) died due to other cancer/cancer of unknown primary origin.

The majority of patients who died from malignancy expired at home (48.1%), or died on the hospital ward (35.2%). Median survival of the patients dying from malignancy was 223.6 (812.8–3261) days post-LTx; patients dying of lung cancer demonstrated a 1.6 year shorter survival compared to patients dying of other malignancies: 1802 (610.3–2792) vs. 2406 (867.8–3524) days (log rank $P = 0.065$). However, only two patients dying of lung cancer in our cohort deceased within 6 months post-LTx (both of metastasized adenocarcinoma discovered in their explant lungs, leading to death after 65 and 123 days post-transplant, respectively), whereas most other patients dying of lung cancer died considerably later post-transplant (i.e. after a median of 2083 (773.3–2985) days post-transplant).

A total of $n = 12/22$ (54.5%) primary lung cancers developed in the remaining native lung after prior single-sided LTx (performed for emphysema in $n = 7$ patients and pulmonary fibrosis in $n = 5$ patients); $n = 4/22$ (18.2%) cancers were incidentally diagnosed in the explanted lung and characterized by metastatic disease, while $n = 6/22$ (27.3%) cancers developed late post-transplant in the donor allograft (none were present at the transplant procedure). Lung cancer histology was nonsquamous/adenocarcinoma in $n = 8/22$ (36.4%) cases, squamous carcinoma in $n = 8/22$ (36.4%) cases, undifferentiated large-cell carcinoma in $n = 3/22$ (13.6%) cases, large-cell carcinoma with neuroendocrine features (LCNEC) in $n = 1$ (4.5%) case and small-cell carcinoma (SCLC) in $n = 2$ (9.0%) cases.

In our cohort, one patient died from secondary lung cancer, that is donor-derived pulmonary metastasis of a glioblastoma 2.3 years post-LTx, which highlights the unfortunate possibility of donor-transmitted malignancy.

Discussion

The current study assessed cause, place and postoperative time/era of death in a large, single-centre cohort of LTx recipients. With increasing time of follow-up, infection as a COD (26.5% of our cohort) becomes less prevalent, but CLAD (27.1%), malignancy (15.6%) and to a lesser extent cardiovascular diseases (4.6%) become a more prevalent COD after LTx, which may be due to longer post-transplant survival, associated longer exposure to side-effects of immunosuppressive treatment (i.e. arterial hypertension, diabetes) and ageing. In recent years, this is becoming ever more evident as the cumulative number of patients surviving longer after

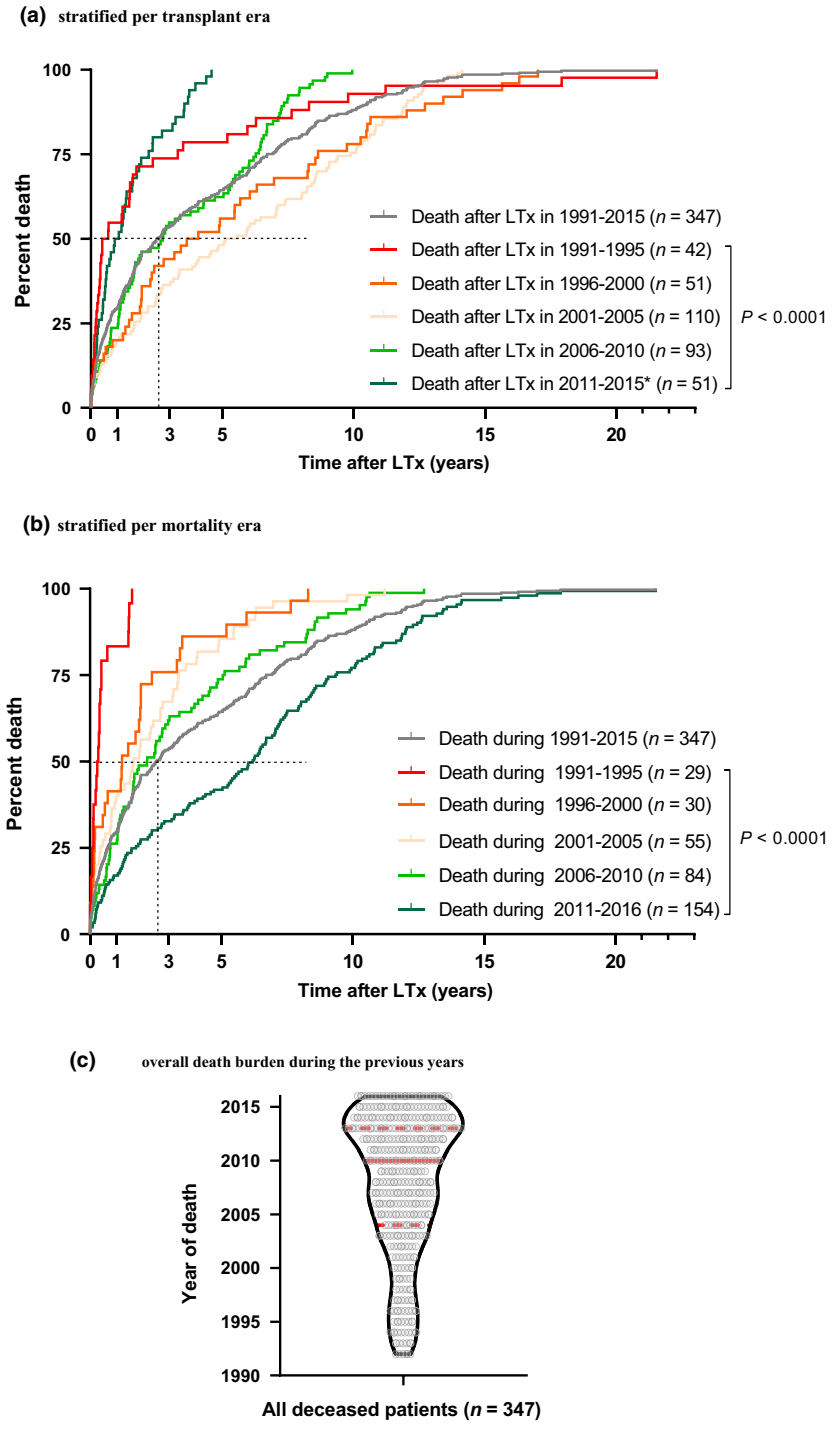

Figure 3 Cumulative number of deaths (LTx 1991–2015, *n* = 347). Kaplan–Meier curves of cumulative number of deaths after first lung transplantation in UZ Leuven (1991–2015, *n* = 347) stratified per transplant era (a) or per mortality era (b). Dotted lines represent the median survival cut-off. A significant difference in deaths ($P < 0.0001$, Log rank) is observed between the various eras during which lung transplantation was performed. Violin plot depicting the death burden during the previous years (c). Dotted lines represent median and interquartile range of the included patients' year of death (1991–2015, *n* = 347). No censoring at retransplantation and exclusion of second Tx (*n* = 33), follow-up until 31-12-2016 (*minimal 1 year for patients transplanted in 2015).

LTx has exponentially increased, which may pose an increased burden on the healthcare system in the very near future. This is comparable to the current challenges of the 'baby boom' generation on economy and health care in the general population. Indeed, many long-term survivors of the ever-increasing cohort of ageing LTx recipients suffer from comorbidities, such as CLAD, malignancies or ageing-related disease, requiring intensified care; and many of these patients may finally die in hospital, on a regular ward or medical ICU, as is evidenced by our data. Of course, local practice and healthcare coverage systems may differentially impact the location of patients' death in other countries/centres, yet many transplant centres are nowadays likely increasingly faced with these key challenges.

According to the ISHLT registry, mortality after the first year post-transplant, especially in long survivors (>10 years), is mainly attributable to CLAD (22.2%)

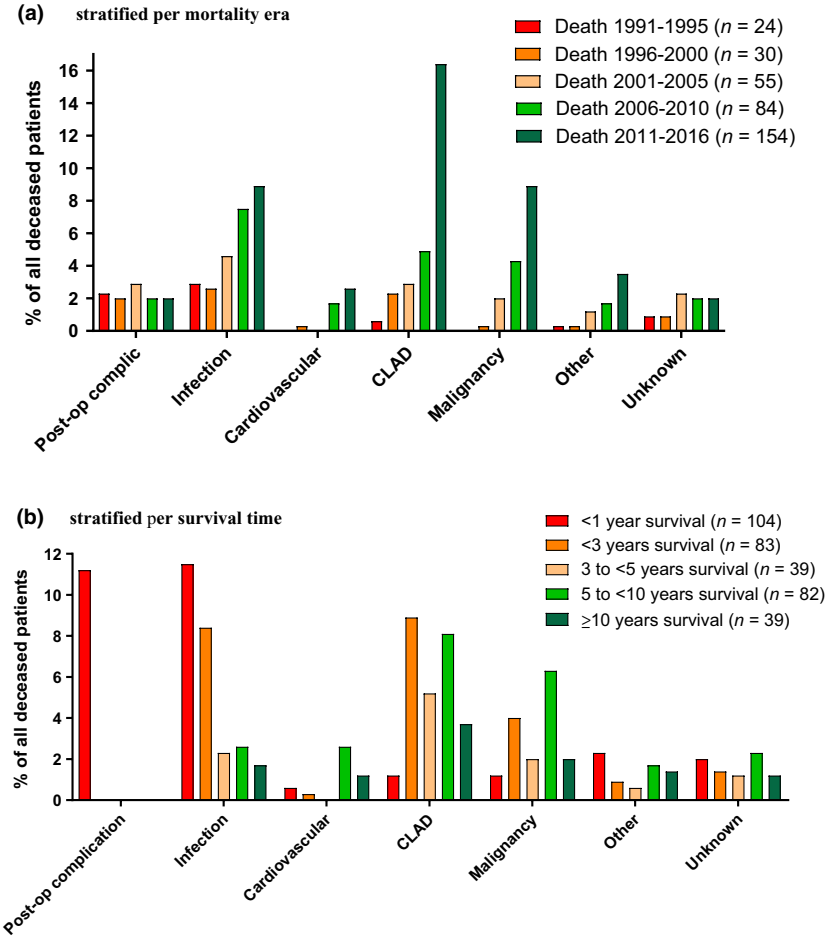

Figure 4 Cause of death in percentage of total deaths (LTx 1991–2015, *n* = 347). Summary of causes of death in percentage of total deaths after first lung transplantation in UZ Leuven (1991–2015, *n* = 347) stratified per transplant era (a) or per mortality era (b). No censoring at retransplantation and exclusion of second Tx (*n* = 33), follow-up until 31 December 2016 (minimal 1 year for patients transplanted in 2015).

and (noncytomegalovirus) infections (16.5%), but malignancy is emerging as an important COD (nonlymphoma 14.0%, lymphoma 3.0%), being the third most common COD in LTx recipients surviving >5 years [1]. Overall malignancy rate has been shown to increase with longer follow-up after LTx: respectively, 23.7%, 43.5% and 57.4% of LTx recipients will have developed any cancer at 5, 10 and 15 years post-transplant [1]. This increased cancer prevalence may be due to development of age-associated neoplastic disease [7–9], besides resulting from the undesirable effects of chronic inflammation, immune activation, DNA damage and loss of immune surveillance due to immunosuppressive treatment [10–12].

The most common malignancies according to the ISHLT registry are nonmelanoma skin cancer (mostly associated with prior UV exposure and/or voriconazole use) [13,14] and PTLD [1]. In our study, lung cancer was the most common lethal cancer, representing 40% of all malignancy-related deaths. Overall, in solid organ transplant (SOT) recipients, the most common malignancies are cancers of lung, liver, kidney and non-Hodgkin's lymphoma, which comprised 43% of all malignancies, compared with 21% in the U.S. general population, in a landmark study including 175 732 American SOT recipients (median 47 years old; kidney, liver, heart and lung transplant) [7]. Overall standardized incidence ratio (SIR) (i.e. observed/expected cases) of malignancy was 2.1 (95% CI, 2.06–2.14) in SOT recipients compared to the general population, which corresponds to an excess absolute risk of 0.7% per year. Of note, overall SIR in LTx recipients was much higher compared to other SOT recipients, probably due to more intense immunosuppression required in LTx [7]. A part from non-Hodgkin's lymphoma [SIR, 18.73 (95% CI, 15.59–22.32)], lung cancer risk [SIR, 6.13 (95% CI, 5.18–7.21)] was most elevated in LTx recipients [7], confirming data from prior single-centres studies in thoracic transplant recipients [15]. This may be associated with smoking-related lung diseases (e.g. chronic obstructive pulmonary disease, interstitial lung disease) being an indication for LTx. As in our study, most malignancies occurred in (generally older) emphysema or fibrosis patients and most lung cancers arose in the remaining native lung.

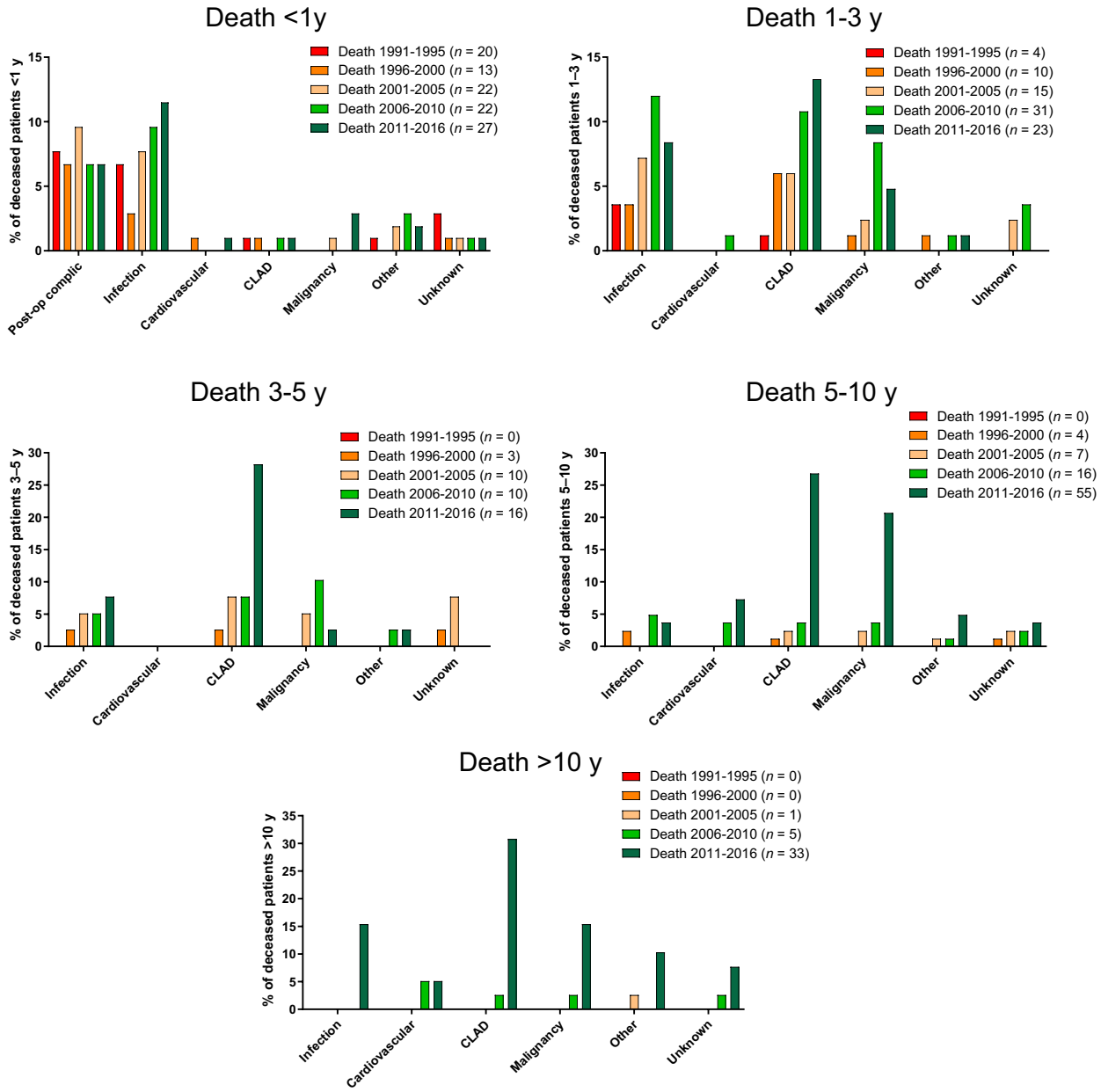

Figure 5 Cause of death (stratified per era of death) according to postoperative time of death (LTx 1991–2015, *n* = 347). Summary of causes of death in percentage of deaths after first lung transplantation in UZ Leuven (1991–2015, *n* = 347) stratified per era of death. No censoring at retransplantation and exclusion of second Tx (*n* = 33), follow-up until 31 December 2016 (minimal 1 year for patients transplanted in 2015).

Interestingly, the incidence of lung cancer showed a biphasic pattern in LTx recipients with a very high incidence rate in the first 6 months post-transplant [SIR 11.17 (95% CI, 7.48–16.04)] and a somewhat lower incidence rate thereafter [SIR 5.53 (95% CI, 4.58–6.63)], likely reflecting either early donor-transmitted malignancy [16], (undiagnosed) systemic spread of occult malignancy in the explant lung(s), or progression of undiagnosed cancer in the remaining native lung after single-sided LTx, as was also seen in our LTx recipients dying of lung cancer.

Chronic lung allograft dysfunction (mostly BOS) is a well-known cause of late mortality after LTx [1,17]. Overall, almost 90% of LTx recipients experienced either BOS or death within 10 years after primary LTx, as recently demonstrated in an analysis of 15 268 (mostly North American) LTx recipients over a 18-year study period [18]. Of note, nearly 50% of all LTx recipients (mostly

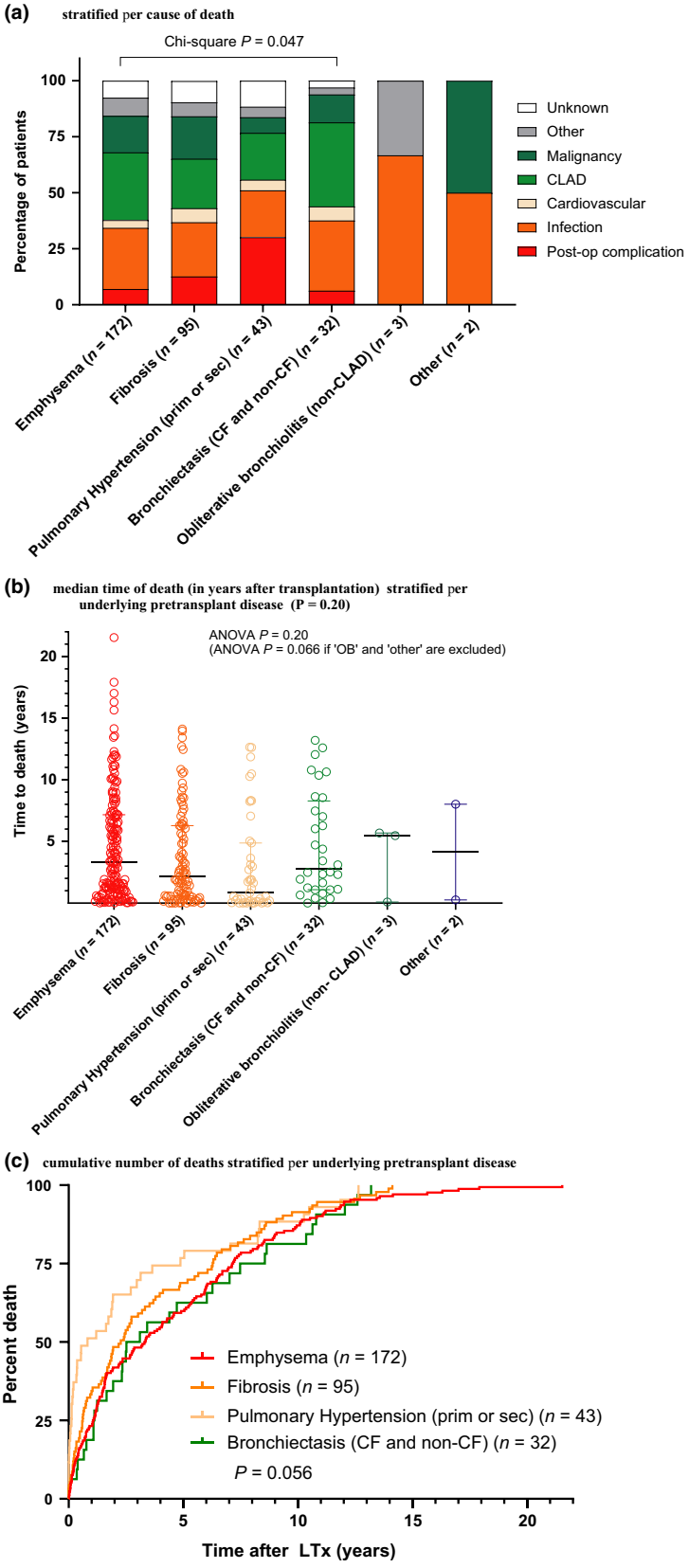

Figure 6 Death according to underlying pretransplant disease (LTx 1991–2015, *n* = 347). Summary of all deaths according to underlying pretransplant disease after first lung transplantation in UZ Leuven (1991–2015, *n* = 347): (a) stratified per cause of death. There was a significant difference in COD for the major indications (emphysema, fibrosis, pulmonary hypertension and bronchiectasis) (chi-square *P* = 0.047). (b) Median time of death stratified per underlying pretransplant disease (*P* = 0.20). (c) Cumulative number of deaths stratified per underlying pretransplant disease (*P* = 0.056). Only the most important indications were given for Kaplan–Meier survival analysis, that is patients with OB (*n* = 3) or other indication for LTx (*n* = 2) were omitted because of low n-values. No censoring at retransplantation and exclusion of second Tx (*n* = 33), follow-up until 31 December 2016 (minimal 1 year for patients transplanted in 2015).

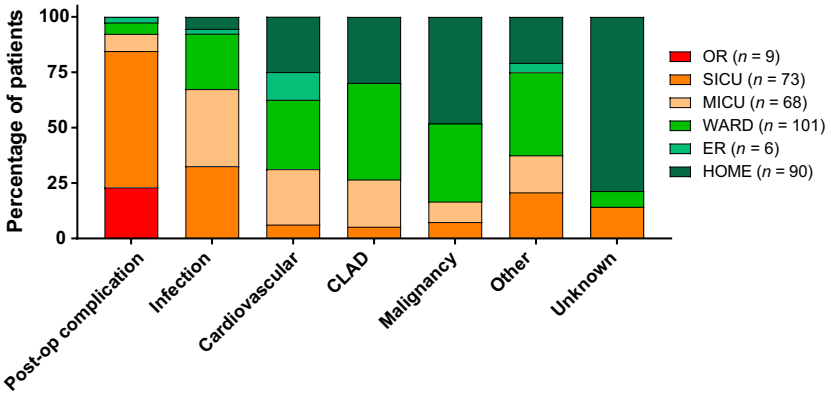

Figure 7 Place of death according to cause of death (LTx 1991–2015, *n* = 347). Summary of place of death according to cause of death, in percentage of total deaths after first lung transplantation in UZ Leuven (1991–2015, *n* = 347). No censoring at retransplantation and exclusion of second Tx (*n* = 33), follow-up until 31 December 2016 (minimal 1 year for patients transplanted in 2015). There was a significant difference in place of death for the different causes of death (chi-square $P < 0.0001$).

from outside North America) had no data available on their BOS status, since BOS is considered as optional (Tier 2) for reporting to the ISHLT Registry, in contrast to patient survival status (Tier 1). Nevertheless, our current data are in line with CLAD (BOS) as most important COD in patients surviving the first 1–3 years post-LTx.

However, it may sometimes be a difficult clinical differential diagnosis between 'dying of CLAD' (i.e. fatal respiratory insufficiency, palliative sedation) and 'dying with CLAD' of another cause, for instance respiratory sur infection, which clinical interpretation inevitably may have biased our findings to some extent. Yet, a recent study of LTx patients requiring admission to a medical ICU could similarly differentiate COD among nonsurvivors (*n* = 44) between infection (57%), respiratory insufficiency secondary to BOS (18%), or other causes during index admission (*n* = 13/44) and the ensuing 6 months following admission (*n* = 31/44) [19]. Moreover, in this cohort, no clear COD could be identified in some 16% of deaths, which is much higher than in our study (8.1%). Besides possible inter-observer variability regarding the final COD, other limitations of our study are inherent to its design, being a single-centre, retrospective study; inclusion of patients undergoing redo-transplantation (however, this was a very low proportion of only 3.5%); and the large study period spanning several decades, during which different prophylactic and therapeutic strategies have been applied. Also, changes in the perioperative workup over the years may possibly have influenced mortality; however, this is very unlikely since our perioperative workup (by means of a standardized pretransplant evaluation) has been unchanged since the nineties. Nevertheless, both recipient and donor acceptance criteria have been liberalized over the past decades, as in most transplant centres worldwide, which may have led to transplantation of more difficult/frail recipients and/or transplantation of more lungs from extended criteria donors (including donors with a more extensive smoking history) during the most recent era, which may have impacted on mortality. Unfortunately, it was impossible to correct for this possible bias in the current analysis, and in a previous report from our group, we furthermore demonstrated that lung transplant recipients from extended criteria donors have similar long-term outcomes compared to standard criteria donors [20].

Nevertheless, our current study is – to our knowledge – the largest to date describing in detail prevalence, cause, place and postoperative time of death in LTx recipients over the different transplant era, with autopsy reports available in one-third of all patients. Therefore, it provides additional insights into mortality after LTx. Infection as a COD becomes less prevalent, but CLAD and malignancies have become more important causes of death in the recent era of transplantation, with most patients dying in hospital, which may pose an increased burden on the healthcare system.

Authorship

JR and AV: performed the research/study, collected the data and wrote the paper. EKV, HB, BMV, SEV, APN, LJC, DEVR and GMV: collected the data, critically revised the data and the study. RV: designed the research/study, collected the data and wrote the paper.

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Conflict of interests

None of the authors of this manuscript have any conflicts of interest to disclose in relation to this manuscript. The authors confirm that that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form in English or in any other language, without the written consent of the copyright holder. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. All authors contributed in an important manner to the study design, data collection and analysis, or writing of the paper according to the guidelines of the International Committee of Medical Journal Editors (ICMJE). All authors have read and approved the manuscript, all authors take responsibility for the manuscript, and the submitting author has permission from all authors to submit the manuscript on their behalf.

Take-home message

With longer post-transplant survival, a shift in mortality causes towards CLAD and malignancies is seen in lung transplant recipients.

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