Archivos de Bronconeumología 62 (2026) 536–541

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Sociedad Española
de Neumología y
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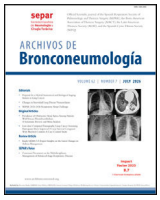

Original Article

Comparison of Lung Cancer Screening Programs in Liver Transplant Recipients and the General Population

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ARTICLE INFO

Article history:
Received 2 December 2025
Accepted 27 March 2026
Available online 9 April 2026

Keywords:
Centrilobular emphysema
Liver transplantation
Low-dose computed tomography
Lung cancer
Smoking

ABSTRACT

Objectives: The objectives of this study are to analyse whether liver transplant recipients (LTR) have a higher incidence of lung cancer (LC) compared to a population of high risk smokers enrolled in a LC screening program and to evaluate if LC screening results allow an early diagnosis in LTRs.
Methods: We conducted a retrospective study comparing LC screening outcomes using low-dose computed tomography (LDCT) in 124 LTRs and 485 matched non-immunosuppressed controls. Matching criteria included age, sex, smoking history, active smoking status, and presence of emphysema. Tumour characteristics, staging, treatment, and survival were analysed.
Results: LC was diagnosed in 9.7% of LTRs and 4.5% of controls ($p = 0.11$). LTRs more frequently presented with squamous cell carcinoma, while adenocarcinoma predominated in controls. Early-stage diagnosis (stage IA) was more common in LTRs (83.4% vs. 50%, $p = 0.056$). Survival after diagnosis was comparable between groups in the first three years, although LTRs showed reduced long-term survival. Multivariate analysis identified cumulative tobacco exposure > 35 pack-years (HR = 3.0; $p = 0.003$), and centrilobular emphysema (HR: 2.8; $p = 0.004$) as independent risk factors for LC, liver transplantation showed an association close to significance (HR: 1.9; $p = 0.08$).
Conclusions: LTRs have a higher incidence of LC than matched non-immunosuppressed individuals. LDCT screening enables early detection and favourable outcomes. These findings support routine LC screening in high-risk LTRs, particularly those with significant smoking histories, and centrilobular emphysema.
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Introduction

De novo neoplasms are among the leading causes of late mortality in liver transplant recipients (LTRs) [1,2]. Within this group of diseases, lung cancer (LC) is one of the most frequent non-cutaneous tumors [3,4]. LTRs have a risk of LC that is twice as high as that of the general population [5–7], and their prognosis is worse due to competing mortality risks [8].

The risk of LC is higher after liver transplantation than after kidney transplantation [5]. Although immunosuppression plays a significant role in the development of *de novo* neoplasms [9], no studies have demonstrated that LTRs have a higher incidence of LC than non-immunosuppressed individuals when other risk factors are equal.

The main risk factor for LC in both, general population and LTRs, is smoking [10]. Smoking cessation is associated with a reduced

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https://doi.org/10.1016/j.arbres.2026.03.010
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Table 1
Comparison between both cohorts of patients.

	Liver transplant recipients	Controls	*p* value
Number	124	485	
Male	110 (88.7%)	429 (88.4%)	0.94
Female	14 (11.3%)	56 (11.6%)	
Age[a]	59.8 ± 8.8	58.8 ± 9.4	0.15
Smoking history (pack-years)[b]	36.5 (23.5–50)	36.9 (22.5–52.5)	0.79
Active smoking	65 (52.4%)	255 (52.6%)	0.97
Chronic obstructive pulmonary disease	51/123 (41.5%)	129/393 (32.8%)	0.08
Paraseptal emphysema	32 (25.8%)	108 (22.3%)	0.40
Centrilobular emphysema	24 (19.3%)	129 (26.6%)	0.06
Time since liver transplant (months)[b]	36 (12.8–75)		
Indication of liver transplantation			
Alcoholic liver disease	75 (60%)		
Hepatitis C	33 (26%)		
Other indications[c]	16 (14%)		

[a] Mean ± standard deviation.
[b] Median and interquartile range.
[c] Hepatitis B (6 patients), primary biliary cholangitis (2 patients), primary sclerosing cholangitis (2 patients), metabolic-associated steatotic liver disease (1 patient), hereditary hemochromatosis (1 patient), familiar amyloidotic polineuropathy (1 patient), nodular regenerative hyperplasia (1 patient), metastases of neuroendocrine tumor (1 patient).

risk of LC in both groups [6,11]. Other risk factors include female sex [12] and pulmonary centrilobular emphysema [13].

Although earlier studies did not show that chest X-ray screening reduced LC mortality [14–16], since the 1990s, low-dose computed tomography (LDCT) has demonstrated a reduction in LC mortality [17–19]. Given the higher incidence of LC in LTRs, screening in this population is particularly important. A recent study by our group showed that LDCT screening enables early diagnosis in a high percentage of LTRs [20].

The present study aims to analyse whether LTRs have a higher incidence of LC than a high-risk matched control group enrolled in a LC screening program. We compared screening results in LTRs with a matched cohort of non-immunosuppressed patients and analysed tumour characteristics and post-diagnosis outcomes in both groups.

Methods

Patients

Two cohorts were included in this study. The first cohort consisted of all LTRs at Clínica Universidad de Navarra who participated in the LC screening program between 2007 and 2021. The second cohort included matched controls who also participated in the screening program and were matched by sex, age at screening entry (±10 years), cumulative tobacco exposure (±10 pack-years), smoking status at screening entry, and presence of emphysema on baseline LDCT. Four controls were selected for each LTR.

Inclusion criteria for both groups were: (1) age over 40 years, (2) cumulative tobacco exposure > 10 pack-years, (3) active smoking or cessation within the past 10 years, and (4) absence of symptoms suggestive of LC.

Screening program

All patients underwent initial LDCT using a 64-row multidetector CT scanner (SOMATON Sensation 64; Siemens Healthineers, Farcheim, Germany), following a previously reported protocol [20]. Images were reviewed by a single radiologist blinded to the final diagnosis. The diagnostic algorithm and follow-up procedures have been previously described [21]. After the initial LDCT scan, patients without pulmonary nodules or with nodules of less than 5 mm underwent a new scan every year. Patients with nodules between 5 and 9 mm underwent a 3-month follow-up LDCT, and further evaluation if growth was detected. Patients with nodules larger than 10 mm underwent a PET-CT scan and a fine needle aspiration or intraoperative biopsy if malignancy was suspected.

Statistical methods

Continuous variables were expressed as mean ± standard deviation or median and interquartile range, depending on distribution. Categorical variables were presented as counts and percentages. Comparisons were made using the Mann–Whitney test for continuous variables and the Chi-square test for categorical variables.

LC incidence and post-diagnosis survival were estimated using the Kaplan–Meier method. Comparisons between incidence and survival curves were performed using the log-rank test. Variables with $p < 0.2$ in univariate analysis were included in a multivariate Cox regression to identify independent predictors of LC. The variables that were studied as potential risk factors of LC were: gender, age, liver transplantation, smoking history, smoking status, and paraseptal and centrilobular emphysema. Age and cumulative tobacco exposure were dichotomized around the median.

Statistical analysis was performed using SAS Enterprise Guide 8.3 (32-bit) and SPSS 5.0. A p-value < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in the LC screening program and for the use of their clinical data for research. The study was approved by the Ethics Committee for Research of Universidad de Navarra, Spain (CEI-UN 2021.141).

Results

Baseline comparison between cohorts

The LTR cohort included 124 patients. The control cohort included 485 patients; 11 controls were excluded due to poor LDCT image quality. Some controls were reclassified as having emphysema based on image review, using a visual analysis adapted from the Fleischner Society criteria [22], despite the absence of this finding in the original report. Baseline characteristics of both cohorts are shown in Table 1.

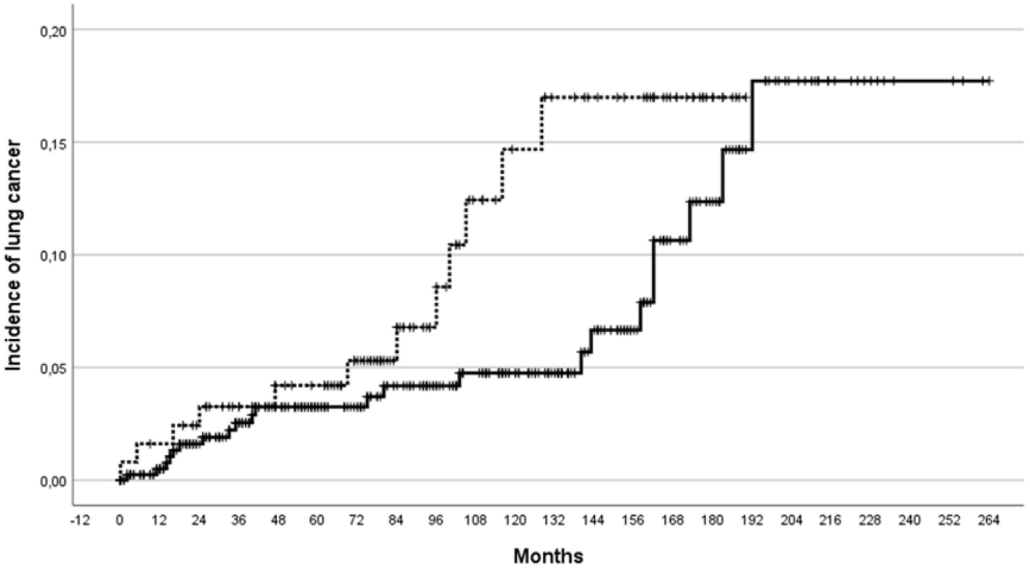

Fig. 1. Incidence of lung cancer in liver transplant recipients (dotted line; *N* = 124) and in matched controls (*N* = 485) (*p* = 0.11).

Table 2
Histological types of lung cancer in liver transplant recipients and in matched controls.

	Liver transplant recipients *N* = 10[a]	Controls *N* = 21[a]
Adenocarcinoma	3 (30%)	14 (66.6%)
Large cell carcinoma	2 (20%)	1 (4.8%)
Squamous cell carcinoma	5 (50%)	4 (19.1%)
Small cell carcinoma	0	2 (9.5%)

[a] Histology of lung cancer in two liver transplant recipients and one control is unknown.

Table 3
Lung cancer staging at diagnosis in liver transplant recipients and matched controls.

Stage	Liver transplant recipients	Controls
IA	10 (83.4%)	11 (50%)
IB	0	1 (4.5%)
IIB	0	2 (9.1%)
IIIA	1 (8.3%)	2 (9.1%)
IIIB	0	2 (9.1%)
IVA	1 (8.3%)	0
IVB	0	4 (18.2%)
Total	12 (100%)	22 (100%)

Lung cancer incidence and comparison

LC was diagnosed in 12 LTRs (9.7%) and 22 controls (4.5%) (*p* = 0.11). Incidence of LC in both cohorts is shown in Fig. 1. The actuarial risk factors of lung cancer 3, 5, and 10 years after inclusion in the LC screening program were 2.5%, 3.2% and 4.8% for the controls and 3.3%, 4.2% and 14.7% for the LTRs). The median number of LDCT scans per patients (including the initial one) was 3 (interquartile range: 2–7). Two of the LC in each group were detected in the basal LDCT, the rest of them were detected at follow-up.

Histological subtype was unknown in two LTRs and in one control. Squamous cell carcinoma was most frequent among LTRs (50%), while adenocarcinoma predominated in controls (66.6%). This difference approached statistical significance (*p* = 0.055). Histological types are shown in Table 2.

Tumour stage at diagnosis was IA in 83.4% of LTRs and 50% of controls (*p* = 0.056). Staging details are presented in Table 3.

In the study period (2007–2021), approximately 450 LTRs were followed in our center. Three patients not undergoing the LDCT screening program were diagnosed of LC. One of them, who had ceased smoking 18 years before was diagnosed a stage IV lung adenocarcinoma; another one was diagnosed a stage IV small cell lung cancer 20 years after ceasing smoking. The third patient was currently smoking and had been transplanted for a hepatocellular carcinoma. He was diagnosed a stage Ib lung adenocarcinoma one year after LT after doing a CT scan for the follow-up of his liver cancer.

Treatment and survival

Treatment in LTRs included surgery (8 cases, 66.7%), radiotherapy (2 cases), and chemotherapy (1 case). One LTR declined treatment. Among controls, 14 patients (63.7%) underwent surgery, and 7 received chemotherapy or combined chemoradiotherapy. Treatment data were unavailable for one control.

Survival after LC diagnosis is shown in Fig. 2. Three LTRs (25%) and five controls (22.7%) died due to tumor progression.

Risk factors for lung cancer development

Univariate analysis showed no significant association between sex or active smoking and LC risk. Factors associated with increased LC risk included age > 60 years (HR = 2.2; 95% CI: 1.1 -4.3; *p* = 0.047), tobacco exposure > 35 pack-years (HR = 3.9; 95% CI: 1.9 -8.1; *p* < 0.001, Fig. 3), centrilobular emphysema on baseline LDCT (HR: 3.2; 95% CI; 1.6-6.2; *p* < 0.001, Fig. 4), and being a LTR (HR: 1.8; 95% CI: 0.9 -3.6; *p* = 0.11, Fig. 1). Paraseptal emphysema was not associated to a higher risk of LC.

Multivariate analysis identified tobacco exposure > 35 pack-years (HR: 3.0; 95% CI: 1.4–6.3; *p* = 0.003) and centrilobular emphysema (HR = 2.8; 95% CI: 1.4–5.5; *p* = 0.004) as significant independent predictors of LC. Being an LTR showed a trend toward increased risk (HR = 1.9; *p* = 0.08) (Table 4).

Discussion

This study compares two cohorts participating in an LC screening program: LTRs and non-immunosuppressed controls. Both cohorts were comparable in key LC risk factors: age, sex [12], cumu-

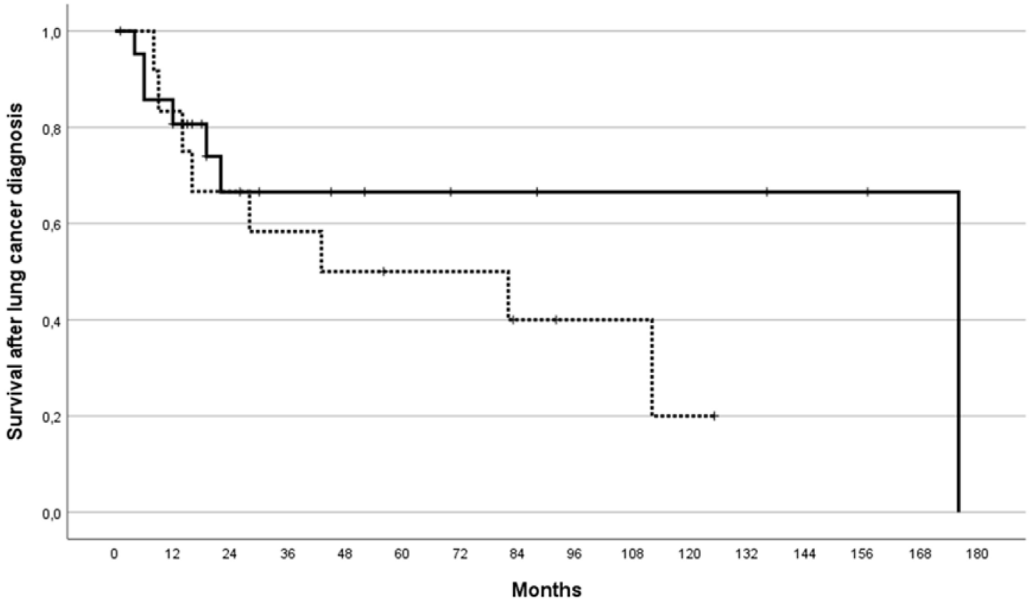

Fig. 2. Survival after lung cancer diagnosis in liver transplant recipients (dotted line; $N = 12$) and matched controls ($N = 22$) diagnosed in a screening program ($p = 0.27$).

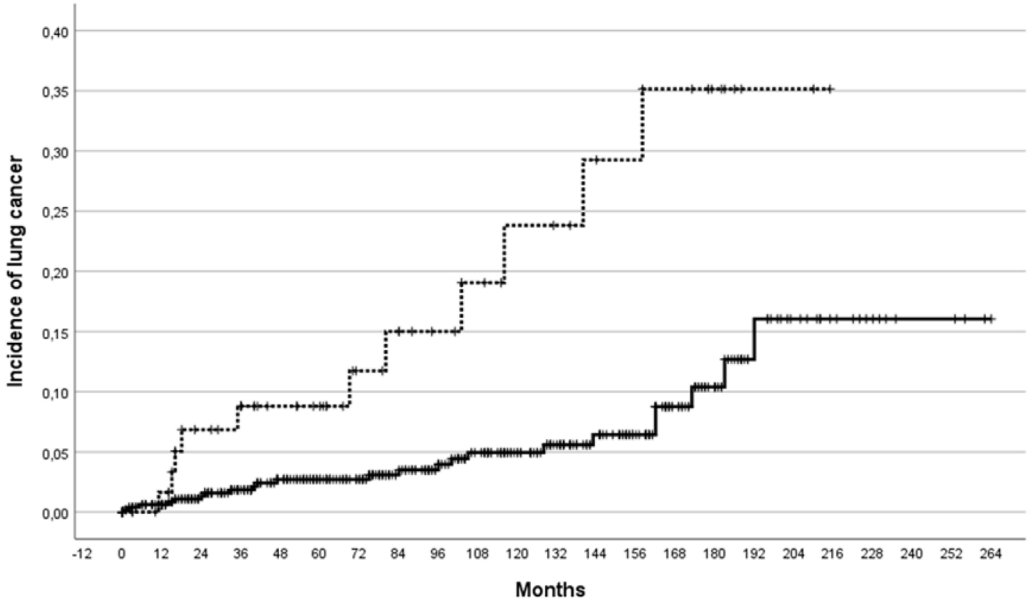

Fig. 3. Incidence of lung cancer in 124 liver transplant recipients and 485 matched controls, according to their cumulative smoking history above (dotted line) or below 35 pack-years ($p < 0.001$).

lative smoking history [23,24], current smoking status [11], and emphysema.

A key finding is the higher LC incidence in LTRs compared to non-transplanted patients. Previous studies have shown increased LC incidence in LTRs [5–7], but did not account for differences in tobacco exposure. Given that alcohol-related liver disease is a major indication for liver transplantation and is associated with tobacco use [25], the higher LC incidence may reflect a greater proportion of smokers among LTRs. Our control group consisted of smokers with comparable tobacco histories. Thus, our findings reinforce the increased risk of LC in LTR, making them a vulnerable population, especially if they have a heavy smoking history or centrilobular emphysema.

Another important result is that LDCT screening enabled early diagnosis in a comparable or even higher proportion of LTRs than controls. This aligns with findings by Sigel et al. [8], who reported earlier LC stages at diagnosis in solid organ transplant recipients. This may be due to more intensive medical follow-up in transplant patients. Previous studies, such as Jiménez et al. [10], found that most LTRs were diagnosed at advanced stages and were associated to poor short term survival rates. In our series, early diagnosis led to better survival outcomes in LTRs than in other series and comparable to non-transplanted patients. However, survival curves showed reduced survival in LTRs after three years, likely due to higher comorbidity burden, despite similar cancer-specific survival [8].

Finally, histological differences were observed: LTRs had more squamous cell carcinomas, consistent with Sigel's findings [8]. Recent studies show increasing adenocarcinoma incidence [26], as seen in the NLST and NELSON trials [27,28]. These tumour types have distinct genomic profiles [29], influencing treatment response. Immunosuppression, particularly calcineurin inhibitors,

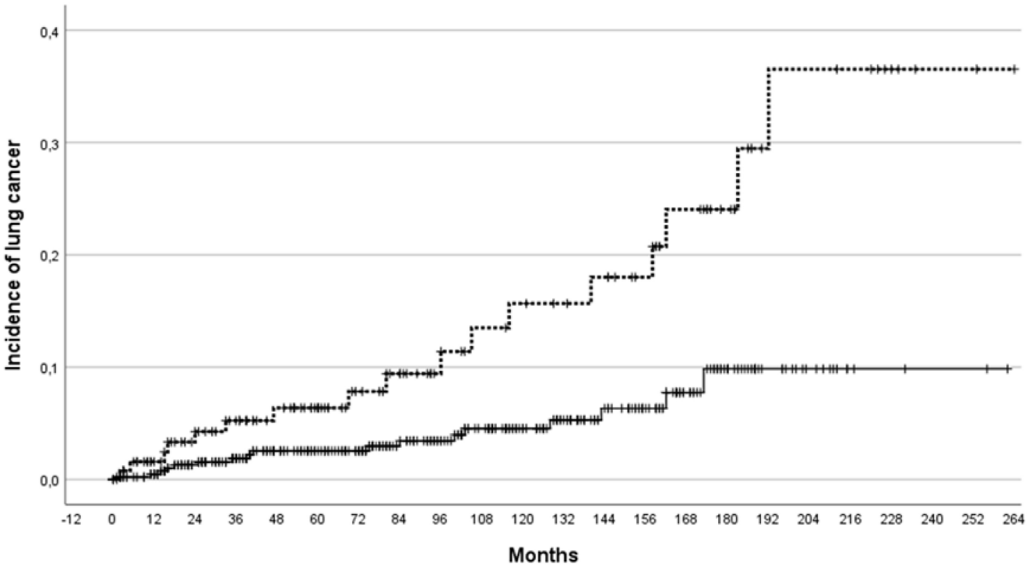

Fig. 4. Incidence of lung cancer in 124 liver transplant recipients and 485 matched controls, in patients with centrilobular emphysema (dotted line) or without it in the basal computed tomography scan ($p < 0.001$).

Table 4
Multivariate analysis of factors related to the diagnosis of lung cancer in 124 liver transplant recipients and 485 non-transplanted matched controls.

	HR[a]	CI[b] 95%	*p* value
Liver transplantation	1.9	0.9–3.9	0.08
Centrilobular emphysema	2.8	1.4–5.5	0.004
Age ≥ 60 years	1.7	0.9–3.5	0.12
Smoking > 35 pack-years	3.0	1.4–6.3	0.003

[a] HR, hazard ratio.
[b] CI, confidence interval.

may affect oncogene activation differently. In the same way, the proportion of histological subtypes of skin cancer is different in LTR and in general population. Basal cell carcinoma is the predominant skin cancer in general population (70% of them), while squamous cell carcinomas are more frequent than basal cell carcinomas in LTR [30]. Recently, a mutational signature has been found in tumours from patients on chronic immunosuppressive therapy (solid organ or allogeneic stem cell transplant recipients). This signature was not found in tumour from non-transplanted patients [31]. Specific mutational signatures, such as this, may explain in part these differences in the histological subtypes of malignancies between transplanted and non-transplanted patients.

Our study also identified cumulative tobacco exposure above 35 pack-years and centrilobular emphysema as significant LC risks factors. These high-risk patients may benefit from closer monitoring and stricter immunosuppression management [9]. In fact, the criteria for entering the LC screening program in our center (age above 40 years and cumulative smoking above 10 pack-years) [21] are less strict than the recommendations suggested by other groups such as the United States Preventive Services Task Force, that focus LC screening in patients between 55 and 80 years with a cumulative smoking history above 20 pack-years [32]. The use of the current stricter criteria may serve to do the LDCT screening more cost-effective. Despite our inclusion criteria, that were less strict than current recommendations, the cumulative incidence of LC in the control group was comparable or even higher than in other studies [17,33]. This reinforces the idea of the high risk of LC in LTR.

The main limitation of this study is its retrospective design, that may introduce information bias and carries the risk of missing variables that could be of relevance. Another limitation is the relatively small cohort size, which limits statistical significance. Nevertheless, this is the largest series evaluating LDCT screening in LTRs and the first to compare LTRs with matched controls. As with any single center study, the conclusions of this paper cannot be extrapolated to other centers in other geographical areas. Although carried out in a single centre, the study followed the screening protocol of the International Early Lung Cancer Action Project guidelines. Thus, their findings could be easily generalizable. Another important issue is the role of the cumulative exposure to immunosuppression [9], and its duration on the risk of LC. Unfortunately, due to the retrospective design and the limited sample size, this aspect could not be further explored.

In conclusion, LTRs have a higher risk of LC than the general population. LDCT screening enables early diagnosis in most cases and yields survival outcomes comparable to non-transplanted patients. Future multicenter studies are needed to confirm these findings. These studies should be prospective and include both transplanted and non-immunosuppressed patients. They could also be useful for individualizing LC screening programs according to risk factors and for further investigation of the potential role of different immunosuppressive therapies on the risk of LC.

Contribution of each author

Study conception: MCL, GB, JJZ, JP de-T, LS, JIH.
Data collection: MCL, PRPL, MI, AE, MS, FR.
Data analysis and interpretation: MCL, PRPL, GB, JIH.
Drafting of the manuscript: MCL, GB, JIH.
Critical review of the manuscript: All the authors.
Final approval of the manuscript: All the authors.

Artificial intelligence involvement

The authors have used Copilot for helping in the translation of the manuscript to English language and Notebook LM for the generation of the visual abstract.

Funding of the research

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Conflicts of interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

Acknowledgements

The authors express their gratitude to all the clinicians, surgeons, radiologists, and nurses of the liver transplant and the I-ELCAP programs at the Clínica Universidad de Navarra, and to all the patients that have participated in the I-ELCAP program.

CIBERehd is funded by the Instituto de Salud Carlos III, Spain.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2026.03.010.

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