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Original article

De novo malignancies after liver transplantation: A 30-year multicenter Brazilian cohort

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ABSTRACT

Introduction and Objectives: De novo malignancy (DNM) is a major late hazard after liver transplantation (LT), usually due to cumulative immunosuppression, viral oncogenesis, and host/environmental factors. Robust Brazilian multicenter data remain scarce. This study assessed burden, spectrum, timing, and post-cancer outcomes in a long-horizon national cohort.

Materials and Methods: Retrospective cohort of all orthotopic LT recipients from three Brazilian programs (1991–2022), with follow-up through June 1, 2024. Primary epidemiology used competing-risk methods (Aalen–Johansen with death as a competing event) for non-cutaneous DNM; Kaplan–Meier (KM) was reported for cross-study comparability. Overall survival (OS) was estimated from the first eligible DNM diagnosis in a prespecified clinical subset (excludes non-melanoma skin cancer [NMSC] and recurrent hepatocellular carcinoma; melanoma included).

Results: The analytic cohort comprised 1234 recipients; 142 developed post-LT malignancy, of whom 121 had ≥1 DNM. NMSC led the spectrum, followed by gastrointestinal neoplasms. Ten-year cumulative incidence of non-cutaneous DNM by Aalen–Johansen was 3.5% (95% CI 2.6–4.6); KM risks at 10 years were 9.8% for any DNM and 6.3% for non-cutaneous DNM. In the OS subset (n = 80), survival from first cancer diagnosis declined over time (primary: 1y 80.5%, 3y 69.8%, 5y 47.3%; sensitivity: 1y 78.0%, 3y 67.2%, 5y 44.0%). Temporal patterns showed sustained incidence beyond 5–10 years.

Conclusions: In a 30-year multicenter Brazilian cohort, DNM constituted a major late complication after LT with persistent risk into late survivorship and clinically meaningful attrition after non-cutaneous cancers. These findings support lifelong, risk-adapted and oncologically mindful immunosuppression, tailored to regional epidemiology and access to longitudinal care.

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1. Introduction

Liver transplantation (LT) has transformed the prognosis of end-stage liver disease. As survival improves, late complications, particularly de novo malignancies (DNM), have become increasingly consequential. Across solid-organ recipients and in LT specifically, overall cancer risk exceeds that of age- and sex-matched populations, reflecting cumulative immunosuppression, permissive viral oncogenesis, and host/environmental cofactors [1–3].

The hazard of de novo malignancy (DNM) is time-dependent: virus-associated entities—notably post-transplant lymphoproliferative disorder (PTLD) related to Epstein–Barr virus (EBV)—cluster earlier under higher immunosuppressive intensity, whereas solid tumors accumulate during long-term maintenance and ongoing exposures [2,3]. These patterns underpin contemporary approaches emphasizing risk-adapted surveillance and judicious minimization of calcineurin-inhibitor exposure, with mTOR-based regimens considered in defined settings (e.g., recurrent/de novo cutaneous malignancy) [4,5]. Despite extensive data from North America and Europe, Latin-American evidence, particularly multicenter series with extended follow-up, remains limited, constraining region-specific guidance [6,7].

Abbreviations: LT, liver transplantation; DNM, de novo malignancy; NMSC, non-melanoma skin cancer; HCC, hepatocellular carcinoma; CRC, colorectal cancer; ALD, alcohol-related liver disease; NASH, nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus; HPV, human papillomavirus; HHV-8, human herpesvirus 8; PTLD, post-transplant lymphoproliferative disorder; CNI, calcineurin inhibitor; mTOR, mechanistic target of rapamycin; mTORi, mTOR inhibitor; BMI, body mass index; OS, overall survival; CI, confidence interval

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To address this gap, a 30-year, multicenter Brazilian cohort from three LT programs was analyzed, aiming to quantify the burden and characterize the spectrum and timing of post-LT DNM, and to describe outcomes after first cancer diagnosis.

2. Materials and Methods

2.1. Study design and setting

A multicenter retrospective cohort study was conducted including all orthotopic liver transplants (LT) performed between September 1, 1991, and April 30, 2022, at three Brazilian centers: Instituto de Cardiologia e Transplantes do Distrito Federal (ICTDF), Brasilia; Hospital de Clinicas da Universidade Federal do Parana (HC-UFPR), Curitiba; and Hospital Nossa Senhora das Graças (HNSG), Curitiba. Follow-up was administratively censored on June 1, 2024. As a comprehensive cohort study including all eligible transplants, no formal sample size calculation was performed. Data were abstracted from institutional transplant registries and physical/electronic medical records. Reporting adheres to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE); the completed checklist is provided as Supplementary File S1.

2.2. Participants

Eligible participants were adult and pediatric recipients of orthotopic LT during the accrual window. Retransplants were counted once per patient. The primary time-to-event analyses excluded deaths occurring within 30 days after LT in order to avoid immortal-time and peri-operative bias. Pediatric recipients were defined as <18 years at LT.

2.3. Variables and data collection

Baseline covariates abstracted at the time of liver transplantation included age, sex, LT indication, body mass index (BMI), behavioral exposures (alcohol use and tobacco use), and history of pre-LT malignancy. Longitudinal data collection captured maintenance immunosuppression as recorded at 12 months post-LT (agents in use; not mutually exclusive), any documented episode of acute rejection during follow-up, and documented viral markers when available in the medical record (EBV, CMV, HPV, and HHV-8).

2.4. Definitions

De novo malignancy was any incident histologically or radiologically confirmed malignant neoplasm diagnosed after LT in recipients surviving >30 days. Solid tumors included cutaneous lesions—basal-cell and squamous-cell carcinomas (grouped as non-melanoma skin cancer, NMSC) and melanoma—and non-cutaneous epithelial cancers; hematologic malignancies included post-transplant lymphoproliferative disorder, other lymphomas/leukemias, and multiple myeloma. Post-LT hepatocellular carcinoma (HCC) was classified as de novo only if no HCC existed pre-LT; otherwise, recurrent HCC was not considered as DNM. The primary analytic level for incidence and survival was the patient (first DNM per recipient). A prespecified event-level analysis was used only to describe the spectrum of DNM. Synchronous lesions at distinct anatomic sites on the same date and metachronous lesions on different dates were counted as independent events. Local recurrence/progression/metastasis of the same index tumor did not constitute a new DNM. In-situ lesions and dysplasias (e.g., actinic keratosis; intraepithelial neoplasia) were not considered DNM.

2.5. Outcomes

The primary epidemiologic endpoint was the cumulative incidence of non-cutaneous de novo malignancy after liver transplantation, estimated with the Aalen–Johansen method using death as a competing event. Secondary endpoints were: (i) cumulative incidence of any DNM (skin included), reported primarily with Kaplan–Meier to facilitate cross-study comparability; (ii) time-to-first DNM and distribution by tumor type/site; (iii) descriptive characterization of maintenance immunosuppression (agent-level presence at 12 months), overall and stratified by age group and maintenance-era (1991–2001, 2002–2012, 2013–2023; defined by the calendar year at the 12-month timepoint) and recorded viral serologies within the DNM-positive subset; and (iv) exploratory baseline comparisons within the analytic cohort, contrasting recipients who developed DNM with those without DNM, plus a prespecified BMI subset analysis. For clinical impact, overall survival (OS) in the DNM-positive subset was estimated from the date of first eligible DNM diagnosis, excluding NMSC and recurrent HCC (melanoma included), reflecting the distinct biology/prognosis of those exclusions. Time origins were endpoint-specific: LT date for incidence; first eligible DNM date for OS.

2.6. Statistical analysis

Descriptive statistics are reported as mean (SD) or median (IQR), as appropriate. For incidence, competing-risk methods (Aalen–Johansen) were applied with death as the competing event for the primary endpoint (non-cutaneous DNM). For cross-study comparability, Kaplan–Meier estimates are additionally presented (with acknowledgment of potential overestimation under competing mortality) for any DNM and for the prespecified non-cutaneous subset. Overall survival was analyzed with Kaplan–Meier and log-rank from the first eligible DNM (excludes NMSC and recurrent HCC; includes melanoma). Missing exact death dates flagged in the records were addressed in a sensitivity analysis by imputing the event time at the last documented contact. Two-sided α = 0.05. Analyses were conducted in R 4.3.3 (survival 3.5–8; cmprsk 2.2–11; mstate 0.3.2).

To complement the primary time-to-event framework, an exploratory baseline analysis was performed within the analytic cohort, comparing recipients with true DNM to those without DNM. Age distributions were summarized and compared with the Mann–Whitney U test; for age ≥60 years and male sex, crude risk ratios were estimated using Fisher's exact test. In a prespecified BMI subset (pre-LT BMI and age available), an age-adjusted logistic regression was fitted for the BMI–DNM association. Due to data-completeness and power constraints, no multivariable hazard modeling was undertaken in the primary analyses. Potential biases were mitigated through comprehensive case ascertainment (registries plus chart review), exclusion of deaths ≤30 days, and use of competing-risk estimators; residual confounding may persist given incomplete capture of lifestyle exposures, time-varying immunosuppression, inter-center surveillance differences, and evolving practice over three decades.

2.7. Ethical statement

The study protocol was approved by the Research Ethics Committees of the participating institutions, coordinated by the Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR), Curitiba, Brazil (CEP-HC-UFPR: CAAE 40,155,220.3.1001.0096; approval no 4.500.829; CEP-ICDF: CAAE 40,155,220.3.2001.0026; approval no 5.047.825). The requirement for written informed consent was waived due to the retrospective observational design of the study and the exclusive use of anonymized routinely collected data. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

3. Results

3.1. Study population

Between September 1, 1991, and April 30, 2022, 1342 liver transplantations were performed at three Brazilian tertiary centers. After excluding recipients who died within 30 days of surgery, 1234 patients constituted the analytic cohort, including 1163 adults (≥18 years; 94.2%) and 71 pediatric recipients (<18 years; 5.8%). During follow-up to June 1, 2024, 142/1234 (11.5%) developed ≥1 post-transplant malignancy. Of these, 121 (9.8%) had a de novo malignancy (DNM) (primary HCC included) and 24 (1.9%) had recurrent HCC; three recipients had both and were counted once in the overall malignancy tally. Across centers, crude DNM proportions ranged from 8.6 % to 10.8 %.

3.2. Incidence of de novo malignancy

Using competing-risk methods (Aalen–Johansen) with death as a competing event, the 10-year cumulative incidence of non-cutaneous DNM was 3.5% (95% CI 2.6–4.6). For cross-study comparability, 10-year Kaplan–Meier risks were 9.8% (95% CI 8.1–11.8) for any DNM (skin included) and 6.3% (95% CI 4.9–8.0) for non-cutaneous DNM (Fig. 1). The analytic cohort (n = 1234) accumulated 14,624 person-years of follow-up, with median follow-up of 7.8 years (IQR 3.8 –18.8; range 0.1–32.6 years). The overall incidence rate of any de novo malignancy was 8.3 per 1000 person-years (95% CI 6.9–9.8), corresponding to an annual risk of approximately 0.83%.

3.3. Recipient characteristics

Among DNM-positive recipients (n = 121), adults predominated (n = 115; 95.0%) and pediatric recipients accounted for 5.0% (n = 6). Pediatric DNM-positive recipients were predominantly female (5/6, 83.3%), with PTLD and cervical cancer as the most prevalent DNMs, and a longer median time from LT to first DNM than adults (86.8 vs. 62.8 months) (Table 1). Overall, males accounted for 72.0% and median age at LT was 54.0 years (range 2–73). In crude complete-case comparisons, recipients aged ≥60 years had a higher DNM risk than those <60 (12.8% vs. 8.8%; RR 1.45, 95% CI 1.02–2.06; p = 0.04), whereas male sex showed only a small, non-significant excess risk (10.1% vs. 9.2%; RR 1.10, 95% CI 0.75–1.60; p = 0.68). In an exploratory analysis constrained by data availability, pre-LT BMI was slightly lower in DNM versus non-DNM recipients (median 25.4 vs. 26.7 kg/m^2; Mann–Whitney U p = 0.028) (Table 2) and was inversely associated with DNM, with a relatively small effect size, in an age-adjusted logistic model (p = 0.027).

A prior malignancy was documented in 37/121 (30.6%), exclusively among adult DNM-positive recipients, and consisted predominantly of HCC (34/121; 28.1%) and non-melanoma skin cancer (3/121; 2.5%). Underlying liver disease among DNM-positive recipients was most often alcohol-related liver disease (ALD, 38/121, 31.4%), followed by HCV (26/121, 21.5%), HBV (19/121, 15.7%), and NASH (10/121, 8.3%); PBC (4/121, 3.3%) and PSC (2/121, 1.7%) were less frequent. Age-stratified prevalent etiology distributions are detailed in Table 1. No CRC occurred among PSC recipients in this cohort.

Viral markers were recorded to a limited extent; within the DNM subset, the available counts were CMV 23/121 (19.0%), EBV 3/121 (2.5%), HPV 5/121 (4.1%), and HHV-8 2/121 (1.7%). Among 4 LT recipients with documented HPV infection who subsequently developed cutaneous or anogenital squamous cell carcinoma (SCC), 3/4 were female (75.0%) and 1/4 was male (25.0%).

Maintenance immunosuppression at 12 months post-LT (agents not mutually exclusive) was predominantly CNI-based, with tacrolimus in 95/121 (78.5%) and cyclosporine in 23/121 (19.0%); adjunct agents included mycophenolate in 41/121 (33.9%), prednisone in 19/121 (15.7%), and mTOR inhibitors in 7/121 (5.8%). Age- and era-stratified distributions and documented acute rejection (35/121, 28.9%) are outlined in Table 3.

3.4. Spectrum of de novo malignancies

At the patient level (first DNM per recipient; n = 121), the distribution was: non-melanoma skin cancer 42/121 (34.7%), solid tumors

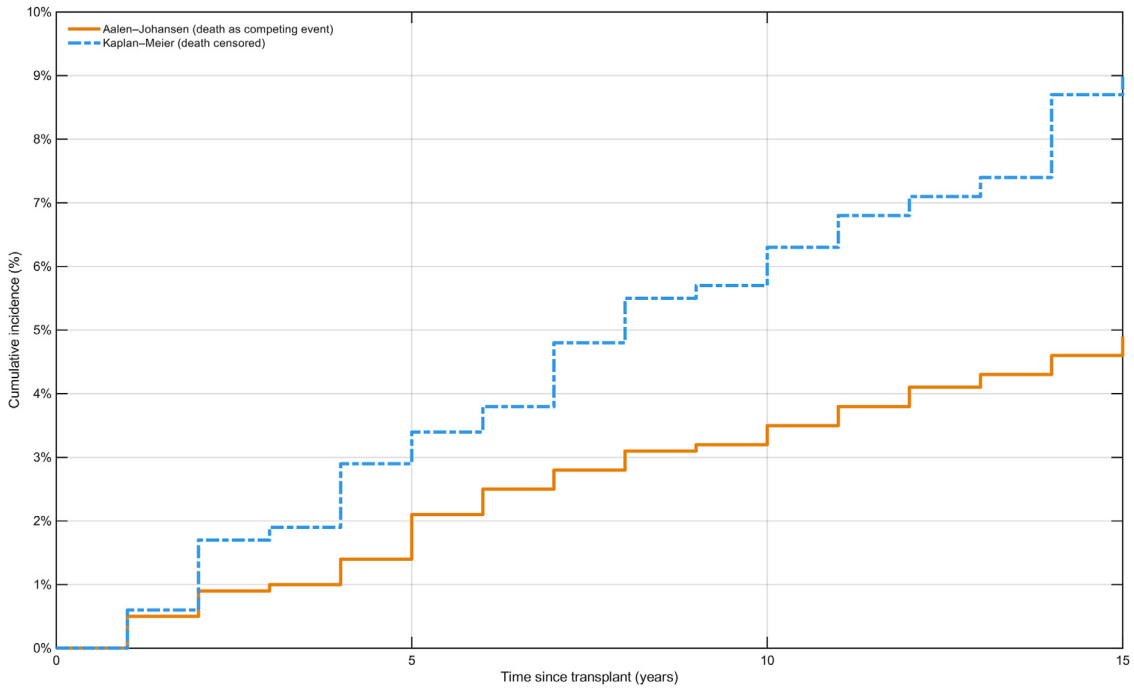


Fig. 1. Non-cutaneous de novo malignancy after liver transplantation: cumulative incidence by Aalen–Johansen vs. Kaplan–Meier. Cumulative incidence of first non-cutaneous de novo malignancy from the date of liver transplantation, comparing Aalen–Johansen estimates with death as a competing event (solid line) and Kaplan–Meier with deaths censored (dashed line).

Table 1
Profile of adult and pediatric DNM-positive liver transplant recipients.

Variable	Adult DNM-positive recipients (n = 115)	Pediatric DNM-positive recipients (n = 6)
Age at LT (years)	Mean 54.1; Median 55; Range 20–73	Mean 12.8; Median 14; Range 2–17
Sex	Female 29 (25.2%); Male 86 (74.8%)	Female 5 (83.3%); Male 1 (16.7%)
Prevalent etiologies at LT	ALD 38 (33.0%); HCV 26 (22.6%); HBV 19 (16.5%); NASH 10 (8.7%); Other 22 (19.1%)	Cryptogenic (16,7%); Biliary atresia (16,7%); PSC (16,7%); Autoimmune Hepatitis (16,7%); Alpha-1 Antitrypsin Deficiency (16,7%); Alagille syndrome (16,7%)
Prevalent Neoplasia Types*	NMSC 42 (36.5%); Colorectal cancer 13 (11.3%); Prostate cancer 10 (8.7%); Cervical cancer 5 (4.3%); Pancreatic cancer 4 (3.5%); PTLD 4 (3.5%); Other 37 (32.2%)	PTLD 2 (33.3%); Cervical cancer 2 (33.3%); NHL 1 (16.7%); HL 1 (16.7%)
Latency LT → first DNM (months)*	Median 62.8; Range 1.2–305.2	Median 86.8; Range 4.3–174.2

Notes: Pediatric defined as age <18 years at LT; adults defined as age ≥18 years at LT. DNM-positive defined as recipients with at least one eligible de novo malignancy after LT (excluding recurrent HCC-only cases).
Abbreviations: LT, liver transplantation; DNM, de novo malignancy; NMSC, non-melanoma skin cancer; PTLD, post-transplant lymphoproliferative disorder; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; ALD, alcohol-related liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
*Prevalent etiologies refer to the underlying liver disease at the time of LT. Prevalent neoplasia types and latency refer to the first eligible post-LT DNM per patient (earliest diagnosis date).

Table 2
Baseline characteristics by de novo malignancy status (DNM vs no DNM).

Variable	DNM (n = 121)	No DNM (n = 1113)	Effect size	p-value
Age ≥60 years	43 (35.5%)	293 (26.3%)	RR 1.45 (95% CI 1.02–2.06)	0.036
Male sex	87 (72.0%)	776 (69.7%)	RR 1.10 (95% CI 0.75–1.60)	0.677
BMI, median (kg/m^2)	25.4	26.7	Δ −1.3	0.028

Notes: Data are n (%) or median. Categorical variables were compared with Fisher's exact test and the continuous variable (BMI, kg/m^2) with the Mann–Whitney U test. Effect sizes are reported as risk ratios (RR) with 95% CI for categorical variables and as median differences (DNM - no DNM) for BMI. Two-sided, unadjusted p values are shown. Percentages use non-missing data. **Abbreviations:** BMI, body mass index; CI, confidence interval; DNM, de novo malignancy; RR, risk ratio.

Table 3
Maintenance immunosuppression at 12 months post-LT among DNM-positive recipients, stratified by age group and maintenance-era.

Variable	Adult (≥18 years)			Pediatric (<18 years)		
Era (n = 121)	1991–2001 (n = 15)	2002–2012 (n = 21)	2013–2023 (n = 79)	1991–2001 (n = 4)	2002–2012 (n = 2)	2013–2023 (n = 0)
Prevalent agent at 12 months	Cyclosporine	Tacrolimus	Tacrolimus	Cyclosporine	Tacrolimus/ Prednisone	NA
Immunosuppression agents at 12 months (non-mutually exclusive)						
Tacrolimus	2/15 (13.3%)	18/21 (85.7%)	73/79 (92.4%)	0/4 (0.0%)	2/2 (100.0%)	NA
Cyclosporine	13/15 (86.7%)	3/21 (14.3%)	3/79 (3.8%)	4/4 (100.0%)	0/2 (0.0%)	NA
Mycophenolate	5/15 (33.3%)	9/21 (42.9%)	25/79 (31.6%)	1/4 (25.0%)	1/2 (50.0%)	NA
Prednisone	7/15 (46.7%)	4/21 (19.0%)	5/79 (6.3%)	1/4 (25.0%)	2/2 (100.0%)	NA
mTORi	0/15 (0.0%)	0/21 (0.0%)	7/79 (8.9%)	0/4 (0.0%)	0/2 (0.0%)	NA
Therapy intensity at 12 months						
Monotherapy (CNI)	5/15 (33.3%)	9/21 (42.9%)	49/79 (62.0%)	2/4 (50.0%)	0/2 (0.0%)	NA
Dual therapy	8/15 (53.3%)	11/21 (52.4%)	26/79 (32.9%)	2/4 (50.0%)	1/2 (50.0%)	NA
Triple therapy	2/15 (13.3%)	1/21 (4.8%)	4/79 (5.1%)	0/4 (0.0%)	1/2 (50.0%)	NA
Graft outcomes						
Acute rejection (ever documented)	6/15 (40.0%)	8/21 (38.1%)	18/79 (22.8%)	2/4 (50.0%)	1/2 (50.0%)	NA

Notes: (1) Age group defined by age at liver transplantation (LT): pediatric <18 years; adult ≥18 years. (2) Immunosuppression reflects the maintenance regimen recorded at 12 months post-LT. (3) Agents are not mutually exclusive. (4) Therapy intensity counts the number of concurrent agents among tacrolimus, cyclosporine, mycophenolate mofetil, prednisone, and mTOR inhibitor (everolimus/sirolimus). (5) Acute rejection reflects any documented episode in the registry. (6) Transplant eras are defined by the calendar year at the 12-month timepoint (LT date + 12 months): 1991–2001, 2002–2012, 2013–2023.

(non-NMSC) 66/121 (54.5%) and hematologic malignancies 13/121 (10.7%).

At the event level (140 DNMs), NMSC accounted for 57 events. Among non-NMSC solid tumors, there were 19 gastrointestinal, 17 genitourinary, 10 breast and gynecologic, and 9 hepatopancreatobiliary tumors; head and neck tumors numbered 6 and respiratory 3. Other solid tumors totaled 5 events—2 angiosarcomas, 1 malignant peripheral nerve sheath tumor and 2 melanomas. Hematologic malignancies comprised 14 events, including 6 cases of PTLD in 6 patients (Supplementary File S2).

3.5. Timing and survival

Among DNM-positive recipients (n = 121), 47.1% of first DNMs occurred within ≤5 years, 38.0% at 5−10 years, and 14.9% >10 years after LT; the median time to first DNM was 65.3 months (range ~1.2 months−25.4 years). For NMSC, the median time from LT to first lesion was 5.1 years (IQR 4.1−7.1). In the prespecified clinical subset (n = 80; excluding NMSC and recurrent HCC; melanoma included), overall survival (OS) from first cancer diagnosis was 80.5% at 1 year, 69.8% at 3 years, 47.3% at 5 years, and 43.4% at 10 years when events were limited to deaths with recorded dates (34 deaths; median OS ~4.9 years) (Fig. 2). A conservative sensitivity that treated flagged undated deaths as events at last contact yielded OS estimates of 78.0%, 67.2%, 44.0%, and 39.6% at 1/3/5/10 years, respectively (36 deaths; median OS ~4.6 years).

4. Discussion

4.1. Epidemiological context and incidence

Long-term survivorship after liver transplantation (LT) has brought de novo malignancies (DNM) to the forefront. In this multicenter Brazilian cohort (n = 1234), 142 (11.5%) developed at least one post-LT malignancy; 121 (9.8%) met criteria for DNM, a frequency within international ranges (3.1−14.4%) and consistent with the 2−4-fold excess cancer risk versus matched populations [2,3]. The 10-year cumulative incidence of non-cutaneous DNM by Aalen−Johansen was 3.5% (95% CI 2.6−4.6); for cross-study comparability, Kaplan−Meier estimates were 9.8% for any DNM (skin included) and 6.3% for non-cutaneous DNM. These values are lower than those reported in a recent multicenter European cohort (10-year non-cutaneous DNM risk, 11.6%), likely reflecting differences in endpoints and case-mix, as well as heterogeneous screening intensity across centers and over three decades of practice evolution, without linkage to a national cancer registry in our setting, which may have reduced case ascertainment [8]. Although absolute risks differed, a long-term single-center series including 1616 LT recipients reported 10-year risks of 12.9% for any de novo cancer and 7.8% for non-cutaneous solid tumors (hematologic 2.3%) and demonstrated a continued rise without plateau—an overall pattern also suggested by our data [9].

Clinical impact extends beyond incidence. In another large transplant−cancer cohort, overall survival after first de novo cancer was 54% at 5 years and 43% at 10 years versus 89% and 70% in matched LT controls [10]. In our predefined subset (DNMs only, excluding NMSC and recurrent HCC; n = 80), Kaplan−Meier survival from diagnosis was 80.5%, 69.8%, 47.3% at 1, 3, and 5 years (primary; 34 dated deaths), with a conservative sensitivity of 78.0%, 67.2%, 44.0% (36 events). Coupled with transplant-specific immune dysfunction, oncogenic viral reactivation, and altered repair on top of population risks, these findings underscore the disproportionate burden of skin cancers, lymphomas, and gastrointestinal tumors in LT recipients and the need for lifelong surveillance and judicious immunosuppression stewardship [3,11].

4.2. Temporal patterns and spectrum

DNM accrued steadily across follow-up, without evidence of a late plateau. The median interval from LT to the first DNM was 65.3 months (~5.4 years) (range ~1.2 months−25.4 years); 47.1% of first DNMs occurred within ≤5 years, 38.0% between 5 and 10 years, and 14.9% beyond 10 years, consistent with long-horizon reports of continued rise under chronic immunosuppression [9]. Early events in this cohort were chiefly NMSC, whereas between 5 and 10 years events were predominantly epithelial/solid (including non-melanoma skin, gastrointestinal and hepatopancreatobiliary tumors). Overall, these dynamics support durable, risk-adapted surveillance that extends well past the early post-transplant period [9].

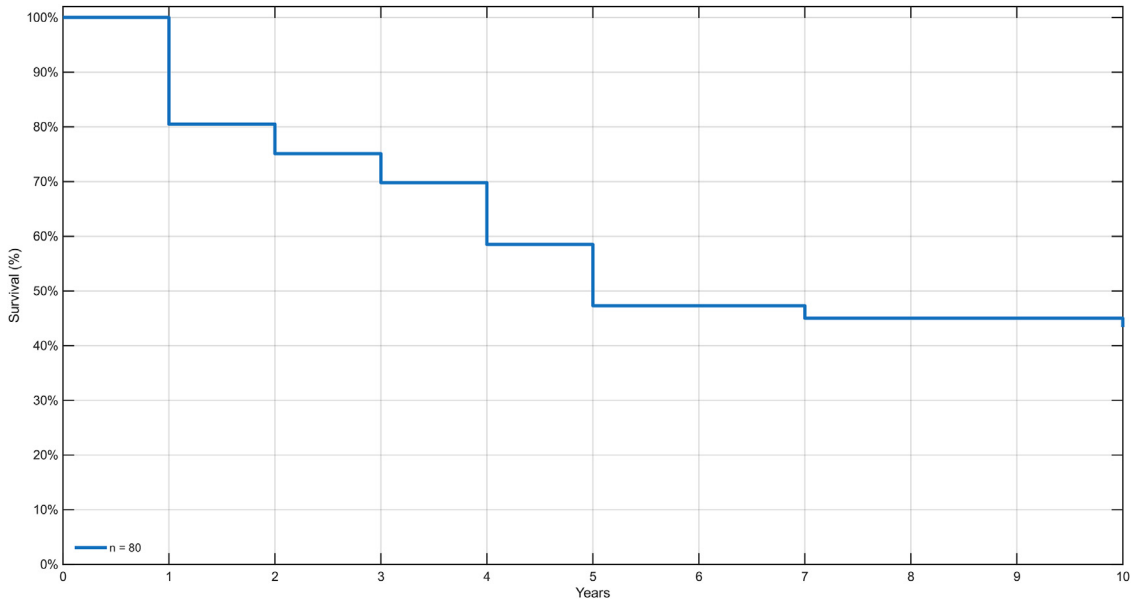


Fig. 2. Overall survival after first de novo malignancy diagnosis. Kaplan−Meier overall-survival curve from the date of the first eligible DNM diagnosis (n = 80); non-melanoma skin cancers and recurrent HCC are excluded, melanoma is included. Follow-up is displayed through 10 years. **Abbreviations:** DNM, de novo malignancy; HCC, hepatocellular carcinoma.

The spectrum mirrored western series, with NMSC as the most prevalent subtype: 40.7% of all DNM events (57/140) and the first DNM in 34.7% of recipients (42/121). Median time to first NMSC was 5.1 years (IQR 4.1–7.1), highlighting a long-term complication whose frequency increases with cumulative immunosuppressive exposure [4].

4.3. Risk factors and patient characteristics

Older recipient age tracked with a higher crude DNM risk (≥60 years: 12.8% vs. 8.8% <60; RR 1.45, 95% CI 1.02–2.06), while *a* ≥ 50-year threshold showed a similar but non-significant pattern. This directionality is concordant with US/European series in which older age at LT commonly predicts post-transplant cancer, plausibly via immunosenescence and accumulated genotoxic exposure layered on chronic immunosuppression [12,13]. Prior malignancy was frequent among DNM-positive recipients (30.6%) and associated with older age at LT, yet neither earlier time-to-DNM nor higher mortality within the DNM subset was observed, compatible with shared exposures and the pro-oncogenic effect of sustained immunosuppression over time [12]. Male sex was common (72%) but mirrored the baseline cohort; after accounting for that distribution, the crude excess was modest and non-significant (RR 1.10, 95% CI 0.75–1.60; $p = 0.68$), aligning with reports in which sex is not a consistent independent predictor once age, indication, and exposures are modeled, and no sex-related heterogeneity in survival has been consistently demonstrated [10,12].

Underlying liver disease also shaped risk: among DNM-positive recipients, ALD (31.4%), HCV (21.5%), and HBV (15.7%) predominated, consistent with guidance identifying ALD as a higher-risk substrate (often compounded by tobacco) while PSC carries a distinct colorectal cancer (CRC) hazard in the presence of IBD [4]. In this cohort, PSC was infrequent (∼4% of all LT) and contributed 1.7% of DNM-positive cases, with no CRC events among PSC recipients—most likely reflecting low local prevalence rather than contradicting established biology; intensified colonoscopic surveillance at PSC-IBD diagnosis remains warranted [14,15]. Autoimmune hepatitis comprised ∼7.5% of indications and 6.5% of AIH recipients developed a de novo malignancy; numbers were small, but tumor heterogeneity mirrored prior AIH reports, and post-LT cancer care should follow disease-specific guidance [5,16]. Briefly, because pre-LT HCC was the most common prior cancer, and late recurrences are not rare, prolonged HCC-specific surveillance remains appropriate [17].

Modifiable exposures remain central. Descriptively, 30.6% of DNM-positive recipients had a smoking history and 44.6% had alcohol use disorder, consistent with literature linking tobacco and alcohol to higher post-LT cancer risk—particularly head/neck and lung for smoking—and risk amplification under chronic immunosuppression; systematic capture across the full cohort was limited, underscoring the need for routine documentation and cessation counseling [12,13]. Metabolic factors likely contribute as well: in this dataset, DNM-positive recipients showed a slightly lower pre-LT BMI than cancer-free comparators and an age-adjusted BMI–DNM association, findings tempered by single-time-point BMI and potential sarcopenia/post-LT weight gain. Still, meta-analytic evidence implicates metabolic-syndrome components in oncogenesis, and a 5-year LT cohort reported ∼38% metabolic syndrome—signals that support structured metabolic surveillance and risk modification after LT [18,19].

4.4. Immunosuppression and oncogenesis

The central paradox of transplantation—preventing rejection while limiting oncogenic harm—was evident in this CNI-dominant cohort, in which tacrolimus was used by 95/121 (78.5%) and cyclosporine by 23/121 (19.0%) at 12 months post-LT. Mechanistically, chronic immunosuppression can foster cancer through loss of immune surveillance, facilitation of oncogenic viral activity, impaired DNA-damage responses, and pro-angiogenic/pro-fibrogenic signaling [13,20]. Observational evidence indicates that exposure intensity matters: in a large multicenter LT cohort, cumulative tacrolimus exposure was the only immunosuppression-related exposure independently associated with post-LT malignancy after adjustment, with consistent effects when recurrent HCC and NMSC were excluded [21]. Across solid-organ series, agent-specific signals have varied (e.g., higher hazards with azathioprine/cyclosporine, lower adjusted rates with tacrolimus), illustrating heterogeneity within and across drug classes and providing biological plausibility for epidemiologic patterns [20].

Beyond any single drug, total immunosuppressive load appears pivotal [22]. In the present data, mycophenolate was commonly combined with a CNI, precluding isolation of an independent effect; in time-dependent analyses elsewhere, the number of agents predicted malignancy, and agent-specific associations varied—again supporting exposure sparing over reliance on a “protective” agent [22]. In contrast to CNIs, mTOR inhibitors (sirolimus/everolimus) offer antiproliferative/anti-angiogenic activity; liver-transplant cohorts and meta-analyses suggest reduced HCC recurrence under mTOR-based strategies, and conversion series report lower NMSC burden with sirolimus [22–25]. Still, whole-cohort time-varying analyses have shown heterogeneous associations, likely reflecting confounding by indication and era effects [22].

Across the three participating centers, maintenance immunosuppression is broadly structured around CNI-based regimens, with tacrolimus preferentially adopted in the contemporary era. A core, shared principle is CNI minimization through stepwise lowering of tacrolimus exposure over time, complemented—when clinically indicated—by CNI-sparing adjuncts such as mycophenolate and/or mTOR inhibitors. Early corticosteroid tapering is routine, and mycophenolate is introduced selectively to mitigate renal dysfunction, accommodate lower CNI targets, or address heightened rejection risk. Overall, inter-center variability appears to reflect feasibility and era-related access patterns rather than fundamentally divergent therapeutic concepts.

With respect to mTOR inhibitors (sirolimus/everolimus), the centers describe a convergent, scenario-driven strategy in which conversion or incorporation is reserved for specific indications, most commonly progressive CNI-related nephrotoxicity/renal dysfunction and oncologic risk. When feasible, this includes lymphoproliferative disease (PTLD/lymphoma) and Kaposi sarcoma, typically alongside broader immunosuppression reduction and tacrolimus maintained at the lowest acceptable levels when continued. In routine practice, conversion is generally deferred beyond the immediate postoperative period (often after ∼3–6 months once early surgical and hepatic stability is achieved), although earlier introduction (∼1–6 months) may occur in selected cases driven by renal dysfunction or compelling oncologic considerations. Consistent with this targeted approach, mTORi use at the standardized 12-month timepoint was uncommon (7/121, 5.8%) and confined to the contemporary era (7/79, 8.9% in 2013–2023), supporting that uptake was selective and largely a late-era phenomenon [26], aligning with broader national implementation following the Brazilian Ministry of Health Joint Ordinance No 5/2017 [27], which approved the national Clinical Protocol and Therapeutic Guidelines for adult LT immunosuppression and delineated Brazil’s public health system (SUS) pathways for access to protocol-listed immunosuppressants.

4.5. Viral-associated malignancies in liver transplant recipients

Oncogenic viruses remain integral to post-transplant carcinogenesis, with risk amplified by chronic immunosuppression [28–30]. In this cohort, hematologic neoplasms (including PTLD) comprised 10.7% of first DNM (13/121), while documented EBV positivity was

sparse (2.5%, 3/121). PTLD as first DNM was rare (6/121, 4.96%) and showed marked temporal heterogeneity, with time from LT to diagnosis ranging from approximately 4 to 305 months. The earliest-onset case occurred in a pediatric EBV-seronegative recipient, whereas the later-onset PTLD cases occurred predominantly in adult recipients and most had recorded EBV negativity, a pattern broadly consistent with reports of early EBV-driven disease in EBV-naïve recipients and late, often EBV-negative monomorphic PTLD [30], although EBV ascertainment was incomplete in our series. Mechanistic links (e.g., LMP1/EBNA2-mediated B-cell activation) support these phenotypes [28]. Prevention is best anchored in risk-stratified EBV-DNA monitoring with pre-emptive immunosuppression reduction [31]; prior meta-analysis found no consistent benefit of routine antiherpesvirus prophylaxis against EBV-PTLD, although newer analyses suggest potential benefit in select subgroups (especially pediatric/high-risk) [29,32].

In addition to EBV, CMV may contribute indirectly via sustained antigenemia and immune modulation, consistent with biological plausibility [33]; however, large cohort data have not shown a consistent association with most cancers in solid organ transplantation [34]. In the present DNM subset, 19.0% (23/121) were CMV-positive, and 7/40 gastrointestinal/skin tumors events after year five occurred in CMV-positive recipients (exploratory signal). HHV-8 was uncommon (≈1.7% in the first-DNM subset) and no Kaposi sarcoma was observed; nonetheless, donor-derived infection and reactivation are recognized, and immunosuppression tailoring (CNI minimization/consideration of mTOR) is central when HHV-8−driven disease is suspected [35−37]. Targeted testing is reasonable in compatible clinical scenarios and higher-risk donors [35].

HPV underlies much of the excess anogenital squamous neoplasia (with a more limited role in subsets of cutaneous SCC) [38,39]. Here, five recipients had documented HPV, four of whom later developed cutaneous or anogenital SCC—consistent with the elevated incidence reported in transplant cohorts and with the >5-year latency seen in over half of first DNMs [38]. For HBV/HCV, inflammation-mediated and virus-specific mechanisms (e.g., HBV integration/HBx, HCV epigenetic/metabolic reprogramming) sustain hepatocarcinogenesis [40]. Correspondingly, recurrent HCC clustered in virus-related cirrhosis (HCV 45.8%, HBV 16.7% of recurrences), reinforcing the need for continued, etiology-aware surveillance even with virologic control [17,40].

4.6. Brazilian context and healthcare implications

The multicenter design captures real-world heterogeneity across Brazil's transplant landscape, with crude DNM proportions varying modestly by center (8.6−10.8%). Brazil's Unified Health System finances ∼95% of liver transplants, but faces disparities in long-term follow-up capacity [41,42]. These structural differences likely translate into uneven access to comprehensive post-transplant cancer screening, as transplant activity and resources are disproportionately concentrated in major urban centers, while resource-limited facilities may face barriers to early detection and timely management [42,43].

Against this backdrop, the participating centers describe similar principles for post-LT cancer surveillance; however, implementation is feasibility-driven and varies in intensity across sites and patient subgroups. Gynecologic surveillance is generally ensured through specialist care with annual evaluation, whereas prostate screening is incorporated into routine outpatient practice using PSA-based assessment (commonly from age 50), with urology referral when abnormal. For other solid tumors, surveillance typically includes annual abdominal ultrasound, age-based breast imaging (mammography and/or breast ultrasound from age 40), and colonoscopy at routine intervals (e.g., every 5 years from age 45, or earlier when clinically indicated). For PSC and/or IBD recipients, all centers endorse colonoscopic surveillance, but recommended intervals differ (annual vs. every 2 years), underscoring protocol variation. Skin cancer surveillance follows a similar pattern: rather than universal scheduled dermatology visits, follow-up is predominantly lesion-triggered (photoprotection counseling plus referral for suspicious lesions), with one center additionally reporting annual dermatology assessment for higher-risk patients (e.g., prior suspicious lesions or prior skin cancer).

Collectively, these center-level practices suggest that within a publicly financed system marked by uneven specialist availability, post-LT cancer screening in Brazil may be systematically non-uniform. This may influence detection timing and case-mix in real-world multicenter cohorts.

4.7. Study limitations

As is inherent to retrospective registries, granularity regarding lifestyle exposures and the completeness of viral serology data was variable, potentially tempering some subgroup inferences. In exploratory, unadjusted analyses within the primary analysis cohort, older age showed a consistent signal, whereas sex did not; etiologic patterns mirrored the cohort's case-mix. Non-uniform ascertainment of vital status and key survival endpoints over the 30-year period (including death and graft failure) limited time-to-event inference, precluding multivariable competing-risk modeling and robust 5- and 10-year patient and graft survival estimates for the full cohort without substantial risk of bias.

5. Conclusions

This 30-year multicenter Brazilian experience demonstrates that de novo malignancy affects 1 in 10 liver transplant recipients, led by NMSC and characterized by sustained long-term risk. The findings support risk-stratified surveillance, careful CNI exposure minimization, and selective mTOR-based strategies in appropriate candidates, while emphasizing the need for workflow-integrated approaches adaptable to regional resource variability. As liver transplantation transitions to chronic disease management, addressing de novo malignancies remains central to optimizing long-term outcomes and quality of life in this growing population.

Authors' contributions

LMSG contributed to the conception and design of the study, data curation and wrote the original draft. JCUC administered the project and revised the manuscript. ACTF supervised the study. AW contributed to data curation and supervision. All authors approved the final version of the manuscript.

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Declaration of interests

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2026.102181.

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