Malignancies Post Adult to Adult Living Donor Liver Transplantation: Incidence, Risk Factors and Outcome

Original Article

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ABSTRACT

Background: Differential considerations for malignancies in the transplanted liver include recurrent primary liver tumours such as hepatocellular carcinoma (HCC) and de novo malignancies (DNM) such as lymphoproliferative disorder (PTLD), skin malignancy.

Aim: This study aimed to identify Incidence of malignancy post LDLT in Egyptian recipients including recurrent HCC and/ or DNM and to identify possible risk factors of malignancy post LDLT and outcome.

Patients and Methods: Combined retrospective and prospective cohort-cross sectional study that included all medical records of all patients who underwent LDLT, at Ain Shams Center of Organ Transplantation (ASCOT), during the period from 2008 till December 2023, recorded and analyzed then follow up till December 2024.

Results: 428 patients; subdivided into Group 1(152 patients) including all patients underwent LDLT due to HCC (subdivided into group 1a (20 patients) > patients who developed recurrent HCC after LDLT and group 1b > non-recurrence group. Group 2 (276 patients). (Subdivided into group 2a (12 patients)> group of DNM and group 2b > not developed DNM. Twenty patients developed recurrent HCC post-LDLT, with a percentage of 13.16% with 5-year survival of 35.7%. The recurrence of HCC after LDLT in our study (group 1a) was mainly extra-hepatic (70%) and early recurrence (65%). The incidence of DNM in our study was 4.3% with 5-year survival of 83.3% and PTLD was the most common DNM.

Conclusion: Prevalence of DNM was rare post LDLT (3.4%) and PTLD was most common. recurrence HCC was 13.16% and mainly extrahepatic.

Key Words: De novo malignancy, liver transplantation, recurrent HCC.

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INTRODUCTION

Liver transplantation is a life-saving procedure for patients with acute and chronic liver diseases[1]. In HCC patients, it represents 20-30% of liver transplant indications in the USA and Europe[2], while in Egypt, it accounts for 32%[3]. Immunosuppression increases post-LT cancer risk[4]. HCC recurrence occurs in 10%-15% of cases[5]. It is also apparent that factors beyond tumor size, number and alpha-fetoprotein (AFP) are associated with increasing the risk of HCC recurrence[5]. De novo malignancy (DNM) incidence after LDLT is 3.5% at 10 years and 18.4% at 20 years[6].

PATIENTS AND METHODS

This single-center study included all LDLT patients at Ain Shams Center of Organ Transplantation (ASCOT) from 2008 to December 2023, with follow-up until December 2024.

Inclusion Criteria:

All Egyptian recipients of LDLT during the defined study period.

Exclusion criteria:

non-Egyptian recipients, combined liver-kidney transplants, and those with absolute contraindications were excluded.

Study Procedures:

Records were reviewed for demographics, liver disease etiology, tumor markers, imaging, immunosuppression, and follow-up. Additional tests (CT, MRI, PET-CT) were performed when needed.

Study Population:

522 patients; 428 included.

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Group 1 (152 HCC): Group 1a>20 recurrent, Group 1b>132 non-recurrent.

Group 2 (276 non-HCC): Group 2a>12 with de novo malignancies, Group 2b>264 not developed DNM.

Our Protocol for Immunosuppression:

- **Non-HCC:** Cyclosporine-based therapy, MMF, steroid tapering, and infection-based adjustments.
- **HCC:** Tacrolimus monotherapy. Immunosuppression is adjusted for recurrence or switched to everolimus. Candidates are selected per Milan/University of California San Francisco criteria (no extrahepatic spread, no macrovascular invasion, AFP <400ng/ml) with bridging therapy on the waiting list and downstaging for those beyond Milan criteria before LDLT.

Our Protocol for Surveillance:

- **HCC:** Monthly AFP checks; Triphasic CT every 3–6 months (or earlier if AFP rises >15ng/ml/month), then every six months thereafter.
- **De Novo Malignancies:**
  - **Skin Cancer:** Use sun block, avoid direct sun exposure, wear protective clothing, and perform routine dermatological exams with biopsy for suspicious lesions.
  - **Colorectal Cancer:** Annual colonoscopy for IBD patients; screening every 3–5 years for PSC; five-year screening for NASH patients over 50; others follow general guidelines.
  - **Lung Cancer:** Annual low-dose CT scans for former smokers.
  - **Renal Cancer:** Annual abdominal CT imaging for patients with RCC or PCKD.

Analysis:

Kaplan-Meier survival analysis, Cox regression, and multivariate logistic regression using SPSS. $P<0.05$ was significant.

RESULTS

At Ain Shams Center of Organ Transplantation (ASCOT) (2008–2023; follow-up until Dec 2024), 428 LDLT patients were analyzed. Among 152 HCC patients, 20 (Group 1a) had recurrent HCC, and 132 (Group 1b) had no recurrence/malignancy. Of 276 non-HCC patients, 12 (Group 2a) developed de novo malignancy, and 264 (Group 2b) did not.

Table (1) In Group 1a (recurrence group, $n= 20$), the median pre-LT AFP was 33.7ng/ml (IQR: 8.3–74.1), nearly four times higher than in Group 1b (8.25ng/ml, IQR: 4.5–29; $P= 0.055$). Pre-transplant HCC interventions with no significant difference between groups, 55% of patients met the Milan criteria, while 45% were beyond Milan.

Table (2) CNI use was significantly higher in the recurrent HCC group (100.0% vs. 74.0%, $P= 0.000$). Tacrolimus was the predominant CNI in recurrence cases (70.0% vs. 19.8%), while Cyclosporine use was markedly lower (5.0% vs. 48.1%). These findings suggest a potential association between Tacrolimus use and HCC recurrence post-LDLT. Recurrent cases had a median explant tumor number of 2 (range: 1–7) and tumor size of 5.75cm (range: 2.5–14.3cm). Tumor differentiation differed significantly (95.0% moderate in recurrences vs. 62.1% in non-recurrences, $P= 0.034$), with Tacrolimus used in 70.0% of recurrences versus 19.8% in non-recurrences ($P= 0.000$), consistent with a higher mortality (70.0% vs. 26.5%, $P= 0.000$).

Figure (1) Kaplan-Meier analysis showed a highly significant survival difference ($P= 0.002$) compared to Group 1b (mean OS= 76.28 months), indicating markedly poorer long-term outcomes in Group 1a.

Table (3) in group 2a, PTLD was most common (33.3%), other malignancies included basal cell carcinoma, Kaposi sarcoma, mesothelioma, neuroendocrine carcinoma, pancreatic adenocarcinoma, rectal adenocarcinoma, and glioblastoma. The 5 cases of PTLD showed 2 cases regressing, 1 stationary, and 1 progressing (1 death among 4).

Table (4) There was significant difference between Group 2a and Group 2b regarding CNI and MMF.

Figure (2) Group 2a ($n= 12$) showed a mean OS of 183.14 months (95% CI: 131.26–235.02) with 1-, 3-, and 5-year survival rates of 91.7%, 83.3%, and 83.3%, respectively. Although this appears higher than Group 2b's OS (132.76 months), the difference was not statistically significant ($P= 0.090$).

Table 1: HCC pre-operative characteristics among the studied patients in group 1 (No= 152):

		Group 1b	Group 1a	Test value	*P*-value	Sig.
		No.= 132	No. = 20 (13.16%)			
AFP - before LT (ng/ml)	Median (IQR)	8.25(4.5–29)	33.7(8.3–74.1)	-1.918≠	0.055	NS
	Range	1.3–493.12	1.8–195			
HCC intervention before transplantation	No intervention	46(34.8%)	6(30.0%)	0.181*	0.671	NS
	RFA	20(15.2%)	3(15.0%)	0.000*	1.000	NS
	MW	3(2.3%)	1(5.0%)	0.504*	0.477	NS
	TACE	35(26.5%)	7(35.0%)	0.625*	0.429	NS
	TACE + RFA/MW /ethanol injection	20(15.2%)	3(15.0%)	0.000*	1.000	NS
	Ethanol injection	2(1.5%)	0(0.0%)	0.307*	0.579	NS
	TACE + TARE	3(2.3%)	0(0.0%)	0.464*	0.496	NS
	TACE + chemotherapy	1(0.8%)	0(0.0%)	0.153*	0.695	NS
	TACE + RF + chemotherapy	2(1.5%)	0(0.0%)	0.307*	0.579	NS
Criteria for transplantation (within Milan/beyond Milan)	Within Milan	58(43.9%)	11(55.0%)	0.857*	0.355	NS
	Beyond Milan	74(56.1%)	9(45.0%)			
Tumor number - before LT (imaging criteria)	Median (IQR)	2(1–3)	1(1–2)	-1.742≠	0.082	NS
	Range	0–6	1–5			
Overall tumour Size before LT (cm) imaging criteria)	Median (IQR)	3.4(1.97–5)	4.45(2.75–6.35)	-1.644≠	0.100	NS
	Range	0–12	1.5–8.4			

P>0.05: Non-significant; *P*<0.05: Significant (S); *P*<0.01: Highly significant (HS); *: Chi-square test; ≠: Mann-Whitney test.

Table 2: Comparison of Post-Transplant Risk Factors and Mortality between Group 1a and Group 1b:

			Group 1b	Group 1a	Test value	*P*-value	Sig.
			No.= 132	No.= 20(13.16%)			
Pathological criteria	Microvascular invasion	No	108(87.8%)	15(75.0%)	2.345*	0.126	NS
		Yes	15(12.2%)	5(25.0%)			
	Explant tumour number	Median (IQR)	2(1–3)	2(1–4.5)	-1.120≠	0.263	NS
		Range	0–10	1–7			
	Explant tumour size (cm)	Median (IQR)	5(2.5–7)	5.75(4–8.8)	-1.926≠	0.054	NS
		Range	0–13.5	2.5–14.3			
	Differentiation of tumour in pathology	No differentiation	22(16.7%)	1(5.0%)	8.65*	0.034	S
		mild	16(12.1%)	0(0.0%)			
		moderate	82(62.1%)	19(95.0%)			
		severe	12(9.1%)	0(0.0%)			
	Tumour necrosis % in pathology	Median (IQR)	37.5(20–65)	65(25–80)	-0.870≠	0.384	NS
		Range	0–100	0–100			
Immuno-suppressive drugs	CNI	No	34(26.0%)	0(0.0%)	36.462*	0.000	HS
		Tacrolimus	26(19.8%)	14(70.0%)			
		Cyclosporine	63(48.1%)	1(5.0%)			
		Tacrolimus or cyclosporine	8(6.1%)	5(25.0%)			
	MMF	No MMF	56(42.4%)	6(30.0%)	1.110*	0.292	NS
		MMF	76(57.6%)	14(70.0%)			
	Everolimus	No everolimus	78(59.1%)	10(50.0%)	0.589*	0.443	NS
		Everolimus	54(40.9%)	10(50.0%)			
CMV infection		No cmv infection	119(90.2%)	19(95.0%)	0.488*	0.485	NS
		CMV infection	13(9.8%)	1(5.0%)			
Biopsy proven rejection (BPR)		No	126(95.5%)	17(85.0%)	3.408*	0.065	NS
		Yes	6(4.5%)	3(15.0%)			
Post-LT biliary obstruction		No	94(71.8%)	18(90.0%)	3.015*	0.083	NS
		Yes	37(28.2%)	2(10.0%)			
Post-LT bile leakage		No	124(94.7%)	20(100.0%)	1.121*	0.290	NS
		Yes	7(5.3%)	0(0.0%)			

		Group 1b	Group 1a	Test value	*P*-value	Sig.
		No.= 132	No.= 20(13.16%)			
Mortality post-transplant	No	97(73.5%)	6(30.0%)	15.035*	0.000	HS
	Yes	35(26.5%)	14(70.0%)			

P>0.05: Non-significant; *P*<0.05: Significant (S); *P*<0.01: Highly significant (HS); *: Chi-square test; ≠: Mann-Whitney test.

Table 3: Types, characteristics, different lines of treatment and outcome of de novo malignancy post LDLT:

Type of de novo malignancy	number	site	Time betweenLDLT&DNM(months)	Treatment of DNM (minimize immunosuppression)+	mortality	outcome
PTLD Non-Hodgkin lymphoma (41.7%) No. = 5	No.= 4 (33.3%)	Lymph node cervical (2 cases), mediastinal (1 case), and para-aortic (1case)	Median (42m) Range 36-50m	3 patients received chemotherapy/one patient with no treatment	Yes (1 of 4 patient)	2 cases>regression 1 case>stationary 1 case>progression
	No.= 1 (8.3%)	liver	28	no	Yes	progression
Basal cell carcinoma (8.3%)	No.= 1 (8.3%)	Face	60	surgical	no	regression
Kaposi sarcoma (8.3%)	No.= 1 (8.3%)	foot	72	Surgery/radiotherapy	no	regression
Mesothelioma (8.3%)	No.= 1 (8.3%)	pleura	84	Surgery/radiotherapy	yes	progression
Neuro-endocrine carcinoma (8.3%)	No.= 1 (8.3%)	lung	96	no	Yes	progression
Pancreatic adenocarcinoma (8.3%)	No.= 1 (8.3%)	pancreas	108	Chemotherapy/ radiotherapy	yes	progression
Rectal adenocarcinoma	No.= 1 (8.3%)	rectum	120	Chemotherapy/ radiotherapy	no	regression
Glioblastoma (8.3%)	No.= 1 (8.3%)	brain	132	surgical	no	stationary

Table 4: Comparison between group 2b and group 2a regarding post-transplant mortality and risk factors for DNM:

		Group 2b	Group 2a	Test value	*P*-value	Sig.
		No. = 264 (95.65 %)	No. = 12 (4.3 %)			
CNI	No	109(41.3%)	0(0.0%)	55.479*	0.000	HS
	Tacrolimus	26(9.8%)	3(25.0%)			
	Cyclosporine	128(48.5%)	6(50.0%)			
	Tacrolimus or cyclosporine	1(0.4%)	3(25.0%)			
MMF	No	153(58.0%)	3(25.0%)	5.072*	0.024	S
	Yes	111(42.0%)	9(75.0%)			
Everolimus	No everolimus	177(67.0%)	7(58.3%)	0.392*	0.531	NS
	Everolimus	87(33.0%)	5(41.7%)			
Post LDLT CMV infection	No cmv infection	243(92.0%)	11(91.7%)	0.002*	0.962	NS
	CMV infection	21(8.0%)	1(8.3%)			
Biopsy proven rejection	No	253(95.8%)	11(91.7%)	0.479*	0.489	NS
	Yes	11(4.2%)	1(8.3%)			
Banff score of biopsy proven rejection	(3/9)	2(66.7%)	1(100.0%)	0.444*	0.505	NS
	(5/9)	1(33.3%)	0(0.0%)			
Benign biliary stricture (obstruction) post LT	No	259(98.1%)	9(75.0%)	21.773*	0.000	HS
	Yes	5(1.9%)	3(25.0%)			
Biliary leak post LT	No	256(97.0%)	10(83.3%)	6.112*	0.013	S
	Yes	8(3.0%)	2(16.7%)			

		Group 2b	Group 2a	Test value	*P*-value	Sig.
		No. = 264 (95.65 %)	No. = 12 (4.3 %)			
Vascular complications post LT	No	252(95.5%)	11(91.7%)	0.367*	0.545	NS
	Yes	12(4.5%)	1(8.3%)			
Mortality	No	181(68.6%)	8(66.7%)	0.019*	0.890	NS
	Yes	83(31.4%)	4(33.3%)			

P>0.05: Non-significant; *P*<0.05: Significant (S); *P*<0.01: Highly significant (HS); *: Chi-square test.

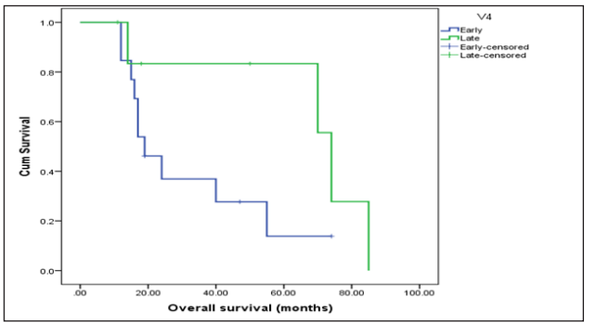

Fig. 1: Comparison between patients with early and late in group 1a regarding O.S. (months) using Kaplan-Meier analysis.

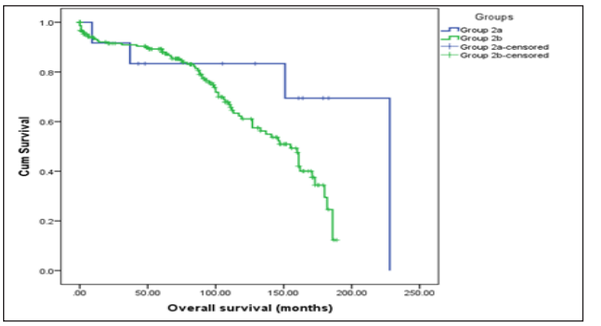

Fig. 2: Comparison between group 2a and group 2b regarding O.S. (months) using Kaplan-Meier analysis.

DISCUSSION

In our study, the recurrence rate of 13.16% observed and was consistent with previous reports. Kaido *et al.*, (2011)[7] documented a 14% recurrence rate following living donor liver transplantation (LDLT), while Giuliani *et al*., (2024)[8] reported a slightly higher rate of 15.4%. These similarities suggest that our findings are broadly representative of global trends in HCC recurrence post-LDLT. The mean age of patients with recurrent HCC in our study (54.10±8.14 years) matches that reported by Na *et al*., (2016)[9], who noted a mean age of 52.0±8.1 years, reinforcing the idea that HCC recurrence predominantly affects middle-aged individuals. However, the male predominance in our cohort 95% exceeds that reported by Na *et al*., (2016)[9] (85.5%), possibly reflecting gender-specific risk profiles in our population.

The main etiology for HCC in Group 1a in our study was HCV (80%), differing from Na *et al*., (2016)[9], where HBV (85.2%) had been the most common etiology. Pelizzaro *et al*., (2024)[10] had indicated that the main etiology for hepatocellular carcinoma (HCC) recurrence post- LDLT was often linked to underlying liver disease, particularly chronic viral hepatitits, which had contributed to tumor development and recurrence risk after transplantation.

In group 1a in the current study, according to the criteria of transplantation, the patients who underwent transplantation within Milan criteria were 55%, and 45% were beyond Milan. In Na *et al*., (2016)[9], 29.6% were within Milan criteria and 70.4% beyond Milan criteria. In Maccali *et al*., (2021)[11], 86.4% were within Milan criteria and 13.6% beyond Milan criteria. In El-Domiaty *et al*., (2021)[12], 69% were within Milan criteria and 31% beyond Milan criteria. In our study, there was no significant difference between group 1a (group of HCC recurrence) and group 1b (control group) regarding criteria of transplantation. This may be attributed by strict criteria in selection of patients of HCC for LDLT in our unit. Our results were in accordance with another study conducted in Egypt by Khalil *et al*., (2018)[13]. As regards recurrence, 7 patients from the Milan group had recurrence with a recurrence rate of 15.1%, while for the beyond Milan group but within UCSF criteria, 4(28.6%) patients had recurrence, with no statistically significant difference between the two groups. The study reported that the Milan criteria can be safely expanded to UCSF with comparable results if responding well to downstaging and with low AFP.

In the current study, there was a highly significant difference between group 1b (control group) and group 1a (group of recurrence HCC) regarding CNI drugs use. Tacrolimus as a CNI drug was used in 70% of group 1a. Tacrolimus or cyclosporin was used in 25% of group 1a (*P*-value 0.0). Rodríguez-Perálvarez *et al*., (2013)[4] reported that an increased risk of HCC recurrence occurs with a higher early exposure to CNI, and immunosuppression protocols with reduced CNI, with or without concomitant drugs when needed, should be preferred for LT patients with HCC, even if the tumor fulfills Milan criteria in the explanted liver.

Locoregional therapy before LDLT in Group 1a was 70%, which had been lower than 88.9% in Na *et al*., (2016)[9] and higher than 43.3% in Mahmoud *et al*., (2022) [14]. The recurrence rate had been lowered in patients who underwent LRT (11.5%) compared to those who did not (35.3%) in Mahmoud *et al*., (2022)[14].

The most common sites of extrahepatic HCC recurrence in our study were the bone and adrenal gland (30% and 20%, respectively) that was nearly consistent with Maccali *et al*., (2021)[10], in which the sites of extrahepatic recurrence were the lungs and bones (34.3% and 31.4%, respectively).

Recurrence of HCC post-LDLT (group 1a) was classified into early recurrence (<24 months) and late recurrence (>24 months). The early recurrence rate was 65%, while the late recurrence rate was 35% in our study, which was nearly consistent with the results in El-Domiaty *et al*., (2021)[11], which were 61.3% and 38.7%, respectively.

The incidence of de novo malignancy in our study was 4.3% (12 out of 264 patients), which falls within the range reported by other studies. Kobayashi *et al*., (2024)[6] reported that the incidence of DNM after LDLT was 3.5% at 10 years and 18.4% at 20 years post-LDLT. Similarly, Tajima *et al*., (2024)[15] found that the overall incidence of DNMs was around 7.4%.

The study found a highly significant association between the use of calcineurin inhibitors (CNIs) and de novo malignancies. Univariate analysis showed a very high association (p<0.001, OR ~87.7), which further increased in the multivariate model (p= 0.002, OR ~244.4). Specifically, tacrolimus was used in 25% of the de novo malignancy group, and either tacrolimus or cyclosporine was used in 25% of the group (p<0.001). This finding aligns with Erard *et al*., (2024)[16], which reported that discontinuation of CNIs has been associated with a reduced risk of DNMs. Additionally, Colmenero *et al*., (2022)[17] illustrated that CNIs, such as tacrolimus and cyclosporine, are associated with an increased risk of developing DNMs due to their immunosuppressive effects, which impair the body's ability to detect and destroy cancer cells.

In our study, there was highly significant difference between group 2a and group 2b regarding history of smoking with (p value= 0011). The univariate analysis demonstrated that history of smoking is significantly associated with an increased risk of de novo malignancies post-LDLT, with an odds ratio of 3.48 (p= 0.041), when adjusted for confounding factors in the multivariate analysis, the effect size slightly decreased to an OR of 2.92 (p= 0.048), This was consistent was single-center study by Chmelova *et al*., (2018)[18], involving 1,295 liver transplant recipients which reported that 10.5% developed de novo malignancies, with lung and head/neck cancers being among the most common. The study identified smoking as an independent risk factor for cancer development in the post-transplant population. Although the cohort included various underlying liver diseases, the significant association between smoking and increased cancer risk highlights the necessity for targeted interventions, such as smoking cessation programs, to mitigate this risk.

Biliary stricture (obstruction) was significantly more common in the de novo malignancy group (group 2a) (25.0%) compared to the control group (group 2b) (1.9%), with a p-value of <0.001. Biliary stricture post-LDLT was highly significant in univariate analysis (p<0.001, OR ~17.3) and remained significant after adjusting for other variables (p= 0.018, OR ~64.2). Additionally, biliary leak was more common in the de novo malignancy group (16.7%) compared to the control group (3.0%), with a p-value of 0.013. These findings suggest that the cumulative effects of persistent inflammation (e.g., from biliary complications) may predispose LDLT recipients to DNMs. Jang and Lee; (2022)[19] reported that the incidence of benign biliary strictures is notably higher in LDLT compared to deceased donor liver transplantation, primarily due to the anatomical and technical complexities involved in the procedure. However, no study has explicitly established a correlation between biliary complications and de novo malignancy post-LDLT, highlighting the need for further research in this area.

In our study, the most common type of de novo malignancy was non-Hodgkin lymphoma (PTLD) (41.7%), followed by various other malignancies such as basal cell carcinoma (8.3%), Kaposi sarcoma, mesothelioma, and adenocarcinomas. Colmenero *et al*., (2022)[17] reported a broader spectrum of de novo malignancies. Non-melanoma skin cancers (NMSC) were frequently observed; however, the incidence of hematologic malignancies such as post-transplant lymphoproliferative disorders (PTLD), which included NHL, was also notably high. Kobayashi *et al*.; 2024 reported that lung cancer was the most frequent DNM after LDLT (50%), followed by PTLD (37.5%) and skin cancer (12.5%).

Patients with de novo malignancy (group 2a) underwent different lines of treatment, including systemic chemotherapy (41.7%), surgical treatment (33.3%), and radiotherapy (33.3%), with no intervention or immunotherapy treatment. The most common treatment was systemic chemotherapy, which corresponded with the most common de novo malignancy in our study (PTLD). Similarly, Wahab *et al*., (2021)[20] showed that PTLD is one of the more common and aggressive de novo malignancies in liver transplant recipients, with chemotherapy being the principal line of treatment. Kobayashi *et al*., (2024) and Wahab *et al*., (2021)[6,20] reported that R0 resection (complete tumor removal) significantly improves survival outcomes and achieves a better prognosis.

STUDY LIMITATIONS

Finally, our study has some limitations. It was a single-center study, which may introduce selection bias, and it included only adult LDLT recipients. Future multicenter studies are needed to further evaluate the disease burden among Egyptian recipients.

CONCLUSION

Recurrent HCC and de novo malignancies post-LDLT pose significant challenges. HCC recurrence occurred in 13.16% of cases, predominantly in males with HCV ,CNIs exposure was major risk factor. Early recurrence (<24 months) was more aggressive with higher mortality. De novo malignancy (4.3%) developed later (median: 83 months) and was linked to HBV/HCV co-infection, smoking, biliary complications, and chronic immunosuppression.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics committee of the Faculty of Medicine, Ain Shams University, Egypt (assurance no. FWA 000017585). All participants signed an informed consent before taking any data or doing any investigations and after explaining the study aim

CONFLICT OF INTERESTS

There are conflicts of interest.

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