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Safety of Immune Checkpoint Inhibitors Prior to Liver Transplantation in Hepatocellular Carcinoma

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have emerged as promising agents for the management of advanced HCC. By reducing tumour burden, ICIs may serve as a downstaging/bridging tool to improve transplant candidacy. The aim of this study was to assess the safety of patients receiving pre-LT ICIs.

Methods: Multicenter, retrospective cohort study from January 2018 to December 2024, including 48 patients who received ICIs prior to LT (ICI cohort). A control cohort (non-ICI cohort) was built (1:3) using propensity score matching including 144 patients who underwent LT for HCC without prior ICI.

Results: Within the ICI cohort ($N = 48$) rejection occurred in 9 patients (18.8%), all biopsy-proven, with a median onset of 31 days post-LT (12.0–182.0). The median washout period was 60 days (13–96). Patients experiencing rejection had shorter washout periods ($p = 0.029$). All rejection episodes were successfully managed; two were steroid-resistant, one requiring re-transplantation. There were no rejection-related deaths. Of the 5 patients with HCC recurrence, 60% received ICI for < 90 days ($p = 0.027$). Comparison between the ICI and non-ICI cohort revealed no significant differences in rejection rates (18.8% vs. 19.4%, $p = 0.916$), graft failure, HCC recurrence, or overall mortality. Overall survival (OS) did not differ between ICI and non-ICI patients ($p = 0.625$) or

Abbreviations: ATG, anti-thymoglobulin; BCLC, barcelona cancer liver clinic; CTLA-4, cytotoxic T-lymphocyte associated protein 4; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; IVIG, intravenous immunoglobulin; LRT, locoregional therapy; LT, liver transplantation; OS, overall survival; PD-1, programmed death protein 1; PD-L1, programmed cell death ligand 1; PSM, propensity score matching; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

between those with and without rejection ($p = 0.119$). Rejection was not associated with increased mortality, with deaths primarily attributed to infection or HCC recurrence.

Conclusion: Our results demonstrate that rejection rates were similar in patients receiving ICIs pre-LT and it can be safely managed.

1 | Introduction

For selected patients with early-stage HCC, liver transplantation (LT) is the best treatment, achieving 5-year post-transplant survival rates exceeding 80% [1, 2]. Patient selection remains critical to optimise outcomes. The Milan criteria (single tumour < 5 cm or up to 3 tumours < 3 cm, without macrovascular invasion or extra-hepatic disease) are considered the standard of care in many centers [3]. However, several expanded criteria have been developed achieving excellent post-LT outcomes [4].

To further expand the number of patients who may benefit from LT, various strategies have been employed to either downstage tumours to meet transplant eligibility criteria or to maintain patients within criteria while on the transplant waiting list, known as bridging therapies. The current international guidelines recommend the use of locoregional therapies (LRT), including the different forms of ablation, trans-arterial treatments, and stereotactic body radiation therapy, among others [5–8].

In recent years, immune checkpoint inhibitors (ICIs), antibodies targeting the immune system—tumour interaction, have transformed the management of advanced HCC where combination approaches have been shown to improve survival [9, 10]. ICIs work by activating the immune system's ability to recognise and attack tumour cells, which occurs in the HCC setting mainly through the blockade of inhibitory pathways such as programmed death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4). By enhancing immune system activity, ICIs enable a better approach to control the tumour. This similar mechanism also enhances recognition of the allograft, exposing it to immune attack.

The use of ICIs has demonstrated the potential to reduce tumour burden, making them a promising tool for downstaging patients to meet transplant criteria or for bridging patients while awaiting transplantation. Despite promising results, it has not yet been incorporated into international guidelines due to concerns about rejection risk and the limited availability of long-term data [11–13]. Two phase 3 studies have demonstrated prolonged free survival and improved overall survival rate when integrating LRT plus ICI combinations in early stage or intermediate stage HCC (in the non-transplant setting) [14, 15], underscoring the potential combination in the pre-LT setting [16]. Additionally, the use of ICI prior to LT may have some long-term benefit as seen in clinical trials in the advanced setting. However, owing to immune hyperactivation, ICIs may introduce a significant challenge in the context of transplantation due to the potential increased risk of graft rejection, especially when compared with non-ICI patients. While research in this area is rapidly growing, data on the safety and efficacy of ICIs in the pre-transplant setting remain limited.

This study aims to validate the safety profile of pre-transplant ICIs when used as downstaging or bridging strategies in patients with HCC and clarify their impact on post-transplant outcomes.

2 | Methods

2.1 | Study Design, Patients and Data Collection

This is a multicentric cohort retrospective study which included 10 centers from North America (Canada and United States) and Europe (Spain, Switzerland and Austria); the list of participating centers can be found in Table 1. Center-wide transplant volumes were not uniformly available across participating institutions; therefore, the analysis focused only on patients meeting the study inclusion criteria. We collected all patients from participating centers who received at least one ICI infusion as treatment for HCC prior to LT, either alone or in combination with other locoregional treatment. These patients were matched in a 1:3 ratio using propensity score matching (PSM) with control patients who did not receive ICI as part of their pre-transplant HCC management. All included patients, regardless of ICI exposure, were adults (≥ 18 years of age at the time of transplant) who underwent liver transplantation for HCC between January 1st, 2018, and December 31st, 2023 (find the rational of the PSM described below). From the ICI cohort ($n = 48$), 41.7% (20/48) have been included in previous studies.

Each participating center independently determined the eligibility criteria for administering ICI as either bridging, downstaging, or palliative therapy prior to LT. Given the retrospective nature of the study, all patients who received ICI prior to transplantation were included, regardless of ECOG performance status or Child-Pugh classification. In some cases, patients initially received ICI with systemic intent and were subsequently considered for liver transplantation following successful downstaging.

For the control cohort (non ICI cohort), we selected adult patients with HCC with a Child Pugh A [5, 6] or B–7 transplanted at the Toronto General Hospital during the same time period. We matched the patients (3:1 ratio of controls for each patient in the ICI cohort) using a propensity score matching (see matching result in the Figure S1), ensuring that the control cohort was comparable to the ICI cohort in terms of relevant baseline characteristics (age, sex, underlying liver diseases, and year of transplantation).

We excluded paediatric transplant recipients under 18 years of age at the time of transplant and patients that received a multi-visceral transplant. The main objective of this study was to assess the safety of pre-transplant ICI therapy in relation to post-transplant outcomes, rather than the toxicity profile of the

TABLE 1 | Comparison between ICI cohort vs. non-ICI cohort.

	ICI cohort ($n=48$)	No ICI cohort ($n=144$)	p[a]
Male, *n* (%)	41 (85.4)	128 (88.9)	0.521
Age (years)	60.2 (56.8–64.8)	60.3 (55.4–64.0)	0.738
Multifocal HCC, *n* (%)	30 (62.5)	107 (74.3)	0.117
Largest lesion (cm)	3.9 (2.9–5.2)	2.7 (19.2–40.8)	0.007
Macrovascular invasion, *n* (%)	9 (18.8)	0 (0.0)	<0.001
Locoregional therapy, *n* (%)	38 (79.2)	142 (98.6)	<0.001
Milan criteria, *n* (%)	18 (37.5)	95 (66.0)	<0.001
Barcelona Cancer Liver Clinic (BCLC)			
A, *n* (%)	17 (35.4)	97 (67.4)	<0.001
B, *n* (%)	22 (45.8)	47 (32.6)	0.099
C, *n* (%)	9 (18.8)	0 (0.0)	<0.001
Aetiology of liver disease			
Autoimmune vs. others, *n* (%)	1 (2.1)	2 (1.4)	1.000
Metabolic Associated Steatotic Liver Disease vs. others, *n* (%)	5 (10.4)	21 (14.6)	0.465
Viral vs. others, *n* (%)	28 (58.3)	82 (56.9)	0.866
Deceased donor, *n* (%)	46 (95.8)	132 (91.7)	0.336
Induction (with ATG), *n* (%)	8 (16.7)	0 (0.0)	<0.001
Rejection, *n* (%)	9 (18.8)	28 (19.4)	0.916
Steroid-resistant rejection, *n* (%)	2 (22.2)	1 (3.6)	0.141
Time from transplant to rejection (days)	31.0 (13.0–96.0)	48.0 (10.2–196.0)	0.085
Graft failure, *n* (%)	2 (4.2)	3 (2.1)	0.600
Re-transplantation, *n* (%)	2 (4.2)	0.0 (0.0)	0.062
HCC recurrence, *n* (%)	5 (10.4)	15 (10.4)	1.000
Time to recurrence (months)	18.2 (4.1–26.0)	14.4 (6.5–19.4)	0.583
Death, *n* (%)	7 (14.6)	21 (14.6)	1.000
Death due to recurrence, *n* (%)	2 (4.2)	8 (5.6)	0.543
Follow-up (since transplant), years	2.6 (1.4–3.7)	3.2 (1.9–4.2)	0.067
Type of ICI			
Atezolizumab-bevacizumab, *n* (%)	10 (20.8)		
Nivolumab, *n* (%)	34 (70.8)		
Pembrolizumab, *n* (%)	1 (2.1)		
Durvalumab, *n* (%)	1 (2.1)		
Combination, *n* (%)	1 (2.1)		
PD1 inhibitor –Trial, *n* (%)	1 (2.1)		
Cycles (number)	9.0 (5.2–18.0)		
Months on ICI	8.0 (3.8–13.7)		
Washout (days)	60 (22.0–196.0)		
Washout range			
0–30 days, *n* (%)	14 (29.2)		
31–60 days, *n* (%)	10 (20.8)		
> 60 days, *n* (%)	24 (50.0)		

(Continues)

TABLE 1 | (Continued)

	ICI cohort ($n=48$)	No ICI cohort ($n=144$)	p[a]
Histopatological response to Immune checkpoint inhibitors (ICI)			
Non-response, *n* (%)	13 (27.1)		
Partial, *n* (%)	17 (35.4)		
Complete, *n* (%)	18 (37.5)		
Time from ICI to rejection (months)	3.8 (2.4–6.1)		
ICI treatment objective			
Downstaging, *n* (%)	13 (27.1)		
Bridging, *n* (%)	18 (37.5)		
Systemic/palliative treatment, *n* (%)	17 (35.5)		

Note: Continuous variables are expressed as median (P_{25}–P_{75}).
[a]Comparisons between cohorts for continuous variables were performed using student's *t*-test and for categorical variables using chi-square test or Fisher's test, when appropriate (if expected frequencies in any cell were < 5).

treatment itself. Consequently, patients who received ICIs but dropped out of the waiting list were not included, and adverse events occurring during ICI therapy prior to transplantation were not captured, as they fell outside the scope of this analysis.

All the patients were followed up until the last recorded clinical visit or death. Clinical epidemiological data, HCC characteristics as well as details on treatment and follow-up data were recorded. Please find in Table S2 a detailed list of the variables collected to capture the rejection risk.

This multicentric retrospective cohort study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2 | Safety Assessment and Definitions

The safety of ICI pre-LT was assessed by the rate of post-LT rejection in the follow-up period. Rejection was diagnosed when patients demonstrated a rising trend in liver enzymes over two consecutive days after excluding other potential causes (as per standard practice in each centre). Rejection was confirmed either by liver biopsy, evaluated according to the Banff criteria [9], or by a clinical response to empirical high-dose steroids administered for at least 3 days, with subsequent improvement in liver biochemistry. Patients requiring escalation of treatment such as anti-thymoglobulin, plasmapheresis, or IVIG were classified as having steroid-resistant rejection.

Graft failure was defined as either (a) the need for re-transplantation due to a non-functional graft or (b) early death resulting from a non-functional graft, regardless of the underlying cause, including rejection.

2.3 | Propensity Score Matching (PSM)

We used PSM (1:3 ratio) to adjust for differences in baseline characteristics and minimise confounding between cohorts. PSM was performed using an optimal matching algorithm to minimise the overall distance in propensity scores between treated and control subjects, thereby achieving the best possible covariate balance across groups. From an initial cohort of 266 patients, we applied a 1:3 matching ratio, pairing each patient who received pre-transplant ICI therapy ($n=48$) with up to three controls who did not. Post-matching covariate balance was assessed by calculating absolute standardized mean differences (SMDs), all of which were below the predefined threshold of 0.05, indicating excellent balance between groups (Figure S1).

Matching was based on variables known or potentially associated with post-transplant rejection: (a) age, (b) sex, (c) underlying liver disease (autoimmune which include autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis vs. non-autoimmune, which include the rest of the underlying liver diseases) and (d) year of transplant to ensure comparable follow-up periods. Covariate balance before and after matching was evaluated using standardized mean differences, as shown in Figure S1.

Variables such as Child-Pugh score and tumour burden were not included in the matching process, as they are not directly associated with the primary outcome of interest (safety of pre-transplant ICI in relation to post-transplant rejection). Furthermore, the immunosuppression regimen was not included as a covariate in the PSM due to substantial heterogeneity in protocols across centers, which precluded reliable adjustment for this variable.

2.4 | Statistical Analysis

Patient baseline characteristics were expressed as events and percentages (%) for categorical variables, and as medians with interquartile range for continuous data. The relationship between qualitative variables was assessed by the chi-squared test, or Fisher's exact test, as appropriate. Comparisons of quantitative data were performed using Student's *t*-test for

normally distributed variables and Mann–Whitney *U* test for non-normally distributed data. A *p*-value of <0.05 was considered statistically significant. A univariate analysis was conducted to identify associations between variables and outcomes. A Kaplan Meier analysis was done to assess the graft and overall patient survival. Propensity score matching was performed with a 1:3 ratio with replacement and a calliper of 0.05. Missing data were treated as missing and were not imputed. Cases with missing key variables were excluded from the analysis. All statistical tests were two-tailed, and a *p*-value of 0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY).

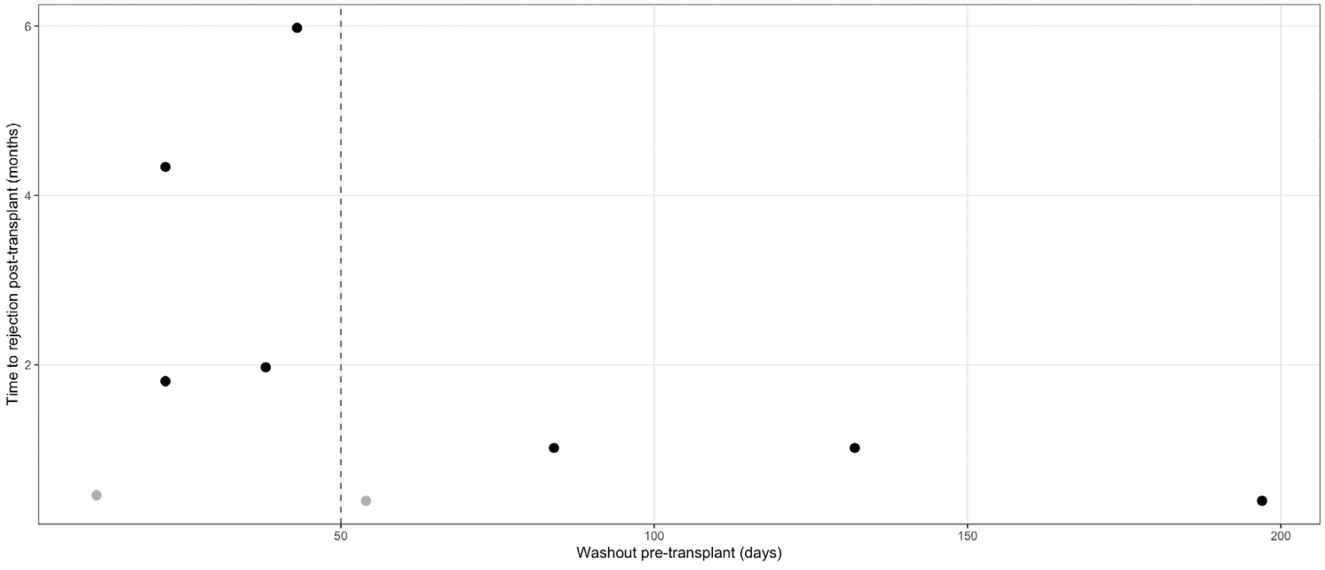
3 | Results

A total of 192 patients were included in our study, 48 patients received ICI prior to transplant (ICI cohort) and 144 did not receive ICI prior to LT (non-ICI cohort). 88% of patients were males with a median age of 60.7 (55.6–64.2) years; 57.3% of patients had a viral cause for their underlying liver disease, followed by 13.5% metabolic associated liver diseases and 8.9% alcohol related. From an HCC perspective at the diagnosis time, 71.4% were multifocal, the median largest lesion was 3.0 (2.0–4.5) cm, 113/192 (58.9%) were within Milan criteria, 59.4% were Barcelona Cancer Liver Clinic (BCLC) A, and more than 90% received bridging/downstaging LRT.

3.1 | ICI Cohort

A total of 48 patients were treated with ICI pre-LT. 37.5% (18/48) fulfilled the liver transplant Milan criteria [3], 17 were Barcelona Cancer Liver Clinic (BCLC) A, 22/48 B and 9 were BCLC C. Nivolumab was the most common drug administered in 70.8% of patients, followed by atezolizumab-bevacizumab in 20.8%. In 15 patients (31.3%) ICIs were given to try and downstage their HCC; in 18 (37.5%) it was given as bridging therapy, and in 19 (39.6%) it was administrated as destination therapy and time after patients became transplant candidates due to a positive response. The median exposure to ICI was 9 cycles per patient, with a median treatment duration of 8.0 (3.8–13.7) months. The wash-out period prior to transplant ranged from 2 to 814 days, with a median of 60 (IQR 22.0–196.0) days. Notably, 8/48 patients received induction therapy with anti-thymoglobulin (ATG) to reduce the chance of rejection not as per any centre protocol.

Out of the 48 patients, 9 (18.8%) developed rejection, all of which were biopsy-proven (find in Figure 1 the detailed data of the rejection episodes). The median time between the last ICI infusion and the rejection was 3.8 (2.4–6.1) months. The median time to rejection after transplant was 31 days, ranging from a minimum of 12 days to 182 (13.0–96.0). None of the patients who received ATG developed rejection. Only 2 patients experienced steroid-resistant rejection; one of the patients had graft failure and required re-transplantation. There were no rejection-related deaths.



Days	10	20	30	40	50	60	70	80	90	≥100
Accumulative rejection episodes	0	1	3	5	5	6	6	6	7	9

FIGURE 1 | Distribution of rejection episodes according to washout duration from last ici dose to liver transplantation. Each dot represents a post-transplant rejection episode, plotted by washout duration (days) on the x-axis and follow-up time (months) on the y-axis. The vertical dashed line marks the 50-day threshold. Lighter grey markers indicate steroid-resistant rejection episodes, whereas darker markers indicate steroid-responsive episodes.

When comparing patients who developed rejection with those who did not, patients with rejection had a shorter washout period (median 43.0 days; 22.0–108.0) compared to those without rejection (88.0, 19.0–205.0) ($p = 0.029$). When stratifying the washout by 10-day periods > 50% of the rejection occurred within the first 50 days (Figure 1). Among patients who developed rejection, those treated with PD-L1 inhibitors ($n = 2$) had longer washout periods (median 164.5132–197 max-min) compared to patients treated with PD-1 inhibitors ($n = 7$) (median 32 IQR 38) ($p < 0.001$). Patients who did not develop rejection had a shorter course of ICI treatment (< 12 months; $p = 0.044$). A comparison between patients who developed rejection vs. those who did not is detailed in Table 2.

Regarding the histopathological features, 13 patients showed no pathological response to treatment, 8 (61.5%) of them were BCLC B and 3 (23.1%) BCLC C. From the ICI cohort, 11/13 (84.6%) were outside the Milan criteria; among those, 53.8% ($n = 7/13$)

TABLE 2 | ICI cohort comparison between rejection and non-rejection.

	Rejection ($N = 9$)	Non-rejection ($N = 39$)	p[a]
Male, *n* (%)	7 (77.8)	34 (87.2)	0.601
Age (years)	60.1 (48.6–66.2)	61.8 (57.9–64.5)	0.265
Multifocal HCC, *n* (%)	2 (22.2)	28 (71.8)	0.009
Largest lesion (cm)	3.3 (2.1–5.2)	4.1 (3–0-5.3)	0.346
Macrovascular invasion, *n* (%)	2 (22.2)	7 (17.9)	1.000
Milan criteria, *n* (%)	4 (44.4)	13 (33.3)	0.701
Barcelona Cancer Liver Clinic (BCLC)			
A, *n* (%)	4 (44.4)	13 (33.3)	0.701
B, *n* (%)	3 (33.3)	19 (48.7)	0.478
C, *n* (%)	2 (22.2)	7 (17.9)	1.000
Locoregional therapy, *n* (%)	7 (77.8)	31 (79.5)	1.000
Aetiology of liver disease—Autoimmune vs. rest, *n* (%)	1 (11.1)	0 (0.0)	0.188
Induction (with ATG), *n* (%)	0 (0.0)	8 (20.5)	0.322
Type of ICI: PD-L1 inhibitor, *n* (%)	2 (22.2)	9 (23.2)	1.000
Type of ICI: PD-1 inhibitor, *n* (%)	7 (77.8)	30 (76.8)	
Cycles (number)	18 (9.0–22.0)	9 (4.0–14.0)	0.624
Months on ICI	13.2 (8.3–19.9)	7.4 (3.7–12.9)	0.674
Exposure ICI < 1 year, *n* (%)	3 (33.3)	29 (74.4)	0.044
Expousure ICI < 6 months, *n* (%)	1 (11.1)	15 (38.5)	0.238
Washout (days)	43.0 (22.0–108.0)	88.0 (19.0–205.0)	0.029
0–30 days, *n* (%)	3 (33.3)	11 (28.2)	1.000
31–60 days, *n* (%)	3 (33.3)	7 (17.9)	0.370
> 60 days, *n* (%)	3 (33.3)	21 (53.8)	0.461
Response to the treatment			
Non-response, *n* (%)	1 (11.1)	12 (30.8)	0.410
Partial, *n* (%)	3 (33.3)	14 (35.9)	1.000
Complete, *n* (%)	5 (55.6)	13 (33.3)	0.265
Graft failure, *n* (%)	1 (11.1)	1 (2.6)	0.343
Re-transplantation, *n* (%)	1 (11.1)	1 (2.6)	0.343
HCC recurrence, *n* (%)	0 (0.0)	5 (12.8)	0.568
Death, *n* (%)	1 (11.1)	6 (15.4)	1.000

Note: Continuous variables are expressed as median (P_{25}–P_{75}).
[a]Comparisons between cohorts for continuous variables were performed using student's *t*-test and for categorical variables using chi-square test or Fisher's test, when appropriate (if expected frequencies in any cell were < 5).

had received treatment for less than six months. In contrast, 50% of the patients who responded to ICIs had been exposed to treatment for more than a year ($p = 0.058$). Patients who received ICI treatment for less than 90 days had a higher recurrence rate of HCC (37.5%; 3/8) compared to those who were treated for 90 days or longer (5%; 2/40), $p = 0.027$. Among patients who received ICI treatment for less than 90 days, 75% were outside the Milan criteria; 5 out of 8 patients were classified as BCLC B, and 1 patient as BCLC C. In the group treated for 90 days or longer, 62.5% were outside the Milan criteria; 17 patients were BCLC B, and 8 were BCLC C. There were no significant differences between groups in terms of tumour burden. Additionally, there were no significant differences between these longer/shorter exposure cohorts in terms of post-transplant overall rejection or early rejection (< 3 months). None of the patients who developed recurrence received induction therapy.

The one-year post-LT survival rate was 91.7%, with 4/48 deaths in the first year (due to cardiovascular events, sepsis, and one due to HCC recurrence). During follow-up, a total of 7 patients died, primarily due to cardiovascular events or sepsis, with 2 deaths resulting from post-LT HCC recurrence (both HCCs were within Milan criteria at LT). A summary of all data is presented in Table 1.

3.2 | Comparison Between the ICI Cohort vs. the Non-ICI Cohort

When comparing both cohorts, no statistically significant differences were observed between the cohorts in terms of age, sex, underlying liver disease (autoimmune vs. non-autoimmune), or year of transplant when adjusted by the propensity score matching (PSM). Notably, 18.8% of patients in the ICI cohort presented with macrovascular invasion, compared to 0% in the non-ICI cohort. Most patients (98.6%) in the non-ICI cohort received LRT prior to transplantation, compared to 79.2% in the ICI cohort.

From the overall cohort a total of 37 patients (19.3%) developed rejection with a median time from transplant to rejection of 45.0 (12.0–169.5) days. Furthermore, 3 patients developed a steroid-resistant rejection, 1 developed graft failure (34 days after the transplant) related to rejection requiring re-transplantation. HCC recurrence was diagnosed in 10.4% of the patients with a median time to recurrence of 15.0 (6.7–22.4) months. 75% of the recurrences were extra-hepatic, and 50% of them were treated with systemic therapy (tyrosine kinase inhibitor). Twenty-eight (14.6%) patients died during follow-up, with sepsis and multi-organ failure being the most common cause of death. There were no rejection-related deaths.

After a median follow-up of 36.5 (21.0–50.0) months, there were no significant differences in rejection rates between the two cohorts (see Table 3), with 18.8% ($N = 9$) in the ICI cohort and 19.4% ($N = 39$) in the non-ICI cohort ($p = 0.916$). All patients ($n = 8$) who received induction with ATG were in the ICI cohort, whereas none of the patients in the non-ICI cohort received induction. The only patient who required re-transplantation due to rejection was in the context of ICI-related rejection. No significant differences were observed in the time from transplant to rejection, although rejection tended to occur later in the non-ICI cohort ($p = 0.085$). Similarly, no differences were observed between the two cohorts for graft failure, HCC recurrence, or overall mortality.

There were no deaths related to rejection. All cases of rejection were successfully treated with adjustment of the immunosuppression regimen and corticosteroid pulses. In two cases, additional treatments such as ATG, plasmapheresis, and/or IVIG were required, with one patient requiring re-transplantation.

3.3 | Subgroup Analysis: Macrovascular Invasion

There were 9/48 patients with macrovascular invasion, with a median tumour size at baseline of 42.5 mm (28.8–77.5). Treatment regimens included nivolumab in 4/9 (44.4%) and atezolizumab–bevacizumab in 5/9 (55.6%). Patients received a median of 14 ICI cycles (IQR 7.5–21.5), with a median total treatment duration of 378 days (IQR 185.5–458.5). Regarding radiologic response, 3/9 (33.3%) had no response, 1/9 (11.1%) achieved a partial response, and 5/9 (55.6%) achieved a complete response. Two patients (2/9, 22.2%) experienced post-transplant rejection, none requiring re-transplantation. No cases of post-LT HCC recurrence were observed. There was one death (1/9, 11.1%), which was unrelated to ICI exposure.

3.4 | Post-LT Survival

There were no significant differences in overall survival between patients who received ICI treatment versus those who did not ($p = 0.625$) (Kaplain–Meyer curve showed in Figure 2A). There were also no significant differences in overall survival between patients who developed rejection and those who did not ($p = 0.119$) (Figure 2B). 21.6% of the patients who experienced rejection died; however, none of these deaths were related to acute rejection: Two deaths were attributed to chronic cholestatic complications that culminated in septic shock, five to acute infections, and one to HCC recurrence.

4 | Discussion

Our study demonstrates no differences in post-transplant rejection rates between the ICI and non-ICI cohorts supporting the use of ICI as a safe approach for downstaging and bridging in selected patients with HCC prior to LT. As previously demonstrated [11, 12], our findings found rejection rates of 18.8%, lower than previously published rates and akin to the control population [13, 17].

This study highlights that rejection management in the context of pre-LT ICI administration is feasible and successful with one graft lost due to acute rejection. This might be explained by the increasing clinical experience, with early recognition and detection of rejection emerging as key factors for successful management of these individuals. In our study, none of the patients who received induction therapy with ATG developed rejection. In non-ICI patients, ATG has demonstrated to be a good tool to treat acute cellular rejection [18, 19]. The use of ATG prior to LT needs to be further explored.

TABLE 3 | ICI cohort comparison between PD1 and PDL1.

	PD-1 inhibitor ($n=37$)	PD-L1 inhibitor ($n=11$)	p[a]
Male, *n* (%)	30 (81.1)	11 (100)	0.179
Age (years)	61.1 (56.2–64.6)	62.2 (59.0–65.5)	0.562
Multifocal HCC, *n* (%)	24 (64.9)	6 (54.5)	0.535
Largest lesion (cm)	3.9 (2.8–5.1)	4.9 (3.1–6.7)	0.177
Macrovascular invasion, *n* (%)	4 (10.8)	5 (45.5)	0.020
Locoregional therapy, *n* (%)	32 (86.5)	6 (54.5)	0.022
Aetiology of liver disease—Autoimmune vs. rest, *n* (%)	1 (2.7)	0 (0.0)	1.000
Induction (with ATG), *n* (%)	7 (18.9)	1 (9.1)	0.661
Cycles (number)	9.0 (4.5–19.5)	9.0 (6.0–13.0)	0.347
Months on ICI	8.3 (3.7–15.3)	6.2 (4.2–9.0)	0.176
Washout (days)	43.0 (18.0–156.5)	132.0 (88.0–203.0)	0.224
Washout (days) in patients who developed rejection	38.0 (22.0–54.0)	164.50 (132.0–197.0)	<0.001
Washout range			
0–30 days, *n* (%)	13 (35.1)	1 (9.1)	0.139
31–60 days, *n* (%)	9 (24.3)	1 (9.1)	0.416
>60 days, *n* (%)	15 (40.5)	9 (81.8)	0.036
Response to ICI			
Non-response, *n* (%)	7 (18.9)	6 (54.5)	0.020
Partial, *n* (%)	14 (37.8)	3 (27.3)	0.723
Complete, *n* (%)	16 (43.2)	2 (18.2)	0.171
Time from ICI to rejection (days)	98.0 (66.0–154.0)	21.5 (12.0–31.0)	0.350
Rejection steroid-resistant, *n* (%)	2 (28.6)	0.0 (0.0)	1.000
Graft failure, *n* (%)	1 (2.7)	1 (9.1)	0.410
Re-transplantation, *n* (%)	1 (2.7)	1 (9.1)	0.410
HCC recurrence, *n* (%)	4 (10.8)	1 (9.1)	1.000
Death, *n* (%)	6 (16.2)	1 (9.1)	1.000

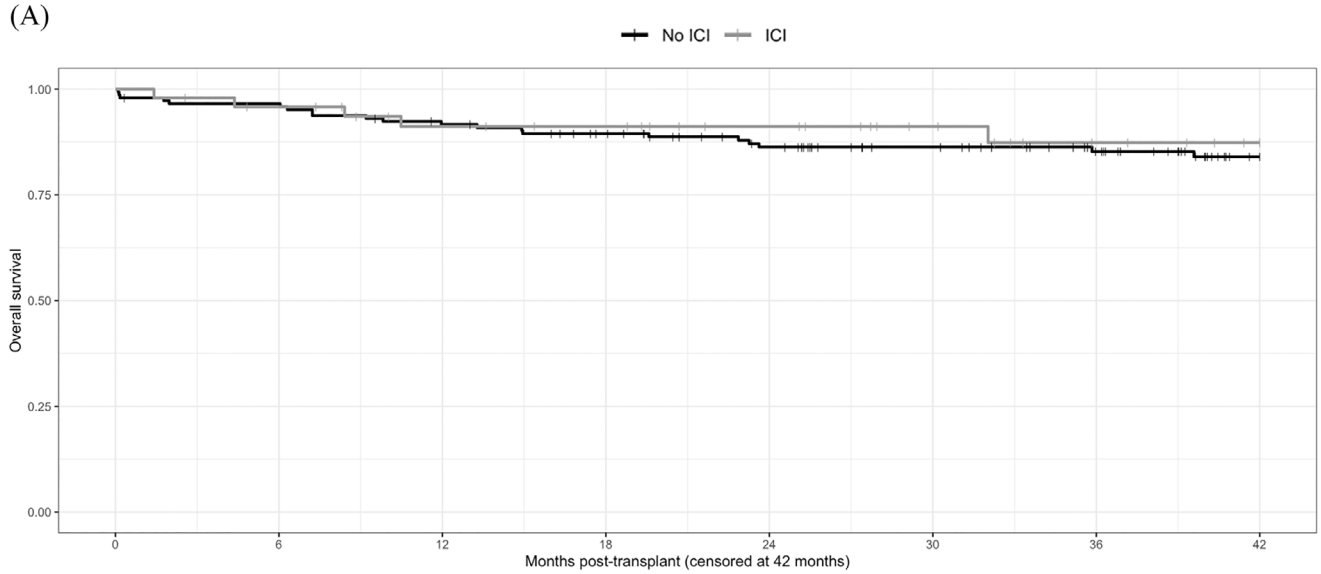
Note: Continuous variables are expressed as median (P_{25}–P_{75}).
[a]Comparisons between cohorts for continuous variables were performed using student's *t*-test and for categorical variables using chi-square test or Fisher's test, when appropriate (if expected frequencies in any cell were <5).

One of the key considerations when using ICI pre-LT is the washout period. Based on our findings, we validate previous results and confirm to be safe a washout period of at least 50 days for patients receiving ICI [12]. Although the ILCA-ILTS consensus [7] suggests a shorter period of at least four weeks to allow a washout of 2 to 3 half-lives, our study supports a 50-day washout as optimal. In this setting, other factors can be relevant as the half-life of the therapeutic molecule is not the only relevant factor for clearance, the occupancy of the receptor is longer than the half-life, and it could be affected by many factors related to the receptor or the drug [20–22]. Age has been described as a risk factor with younger patients developing more rejection [23], however, we did not identify this association. Factors not explored in our study, such as blood loss and transfusion during transplant surgery or post-transplant immunosuppression protocols need to be explored in the future [24].

Our data confirm that overall survival is similar in both cohorts. When comparing patients with and without post-transplant rejection, the Kaplan–Meier curves show a visual separation that does not reach statistical significance. Although our results do not demonstrate a significant difference, this observation raises an interesting hypothesis that should be evaluated in larger studies to determine whether a true survival difference exists.

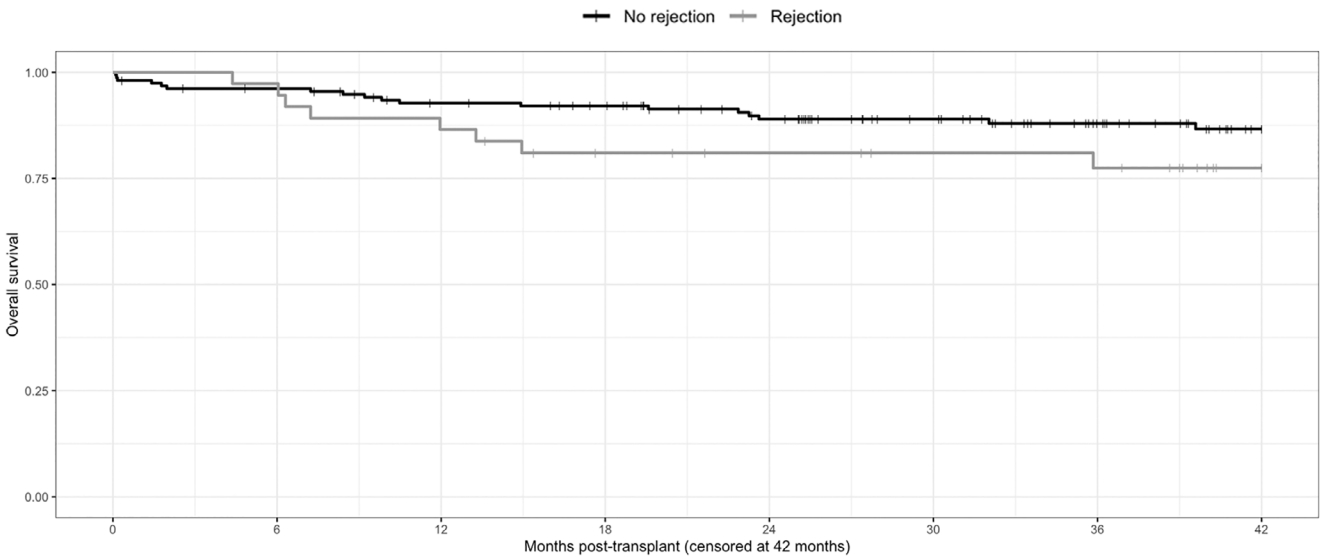
Finally, our results align with those reported by other cohorts [12] although the pathological response observed in our study

(A)



Follow-up (years)	1	2	3	4	5	> 5
Accumulative deaths -ICI cohort	0	1	3	4	6	7
Accumulative deaths -no ICI cohort	0	5	8	10	16	21

(B)



Follow-up (years)	1	2	3	4	5	>5
Rejection cohort deaths	0	3	3	4	7	8
None rejection cohort deaths	0	3	8	10	15	20

FIGURE 2 | (A) Kaplan–Meier showing survival at 5 years divided into ICI vs. non ICI. (B) Kaplan–Meier showing survival at 5 years divided into rejection vs. non-rejection.

was lower than that described by Tabrizian et al. [11]. In addition, even though our cohort was small, patients with no response had a shorter treatment exposure and almost half of the patients who recurred had a short exposure to the ICI (less than 90 days), suggesting overall that longer treatments are needed to achieve a better cancer response. We therefore suggest considering ICI

treatment prior to LT should be at least longer than 3 months but shorter than 12 months.

Although our cohort is small and we were unable to gather enough data to draw definitive conclusions, there is a trend suggesting fewer HCC-driven deaths in the ICI cohort (2 in the ICI cohort vs. 8 in the non-ICI cohort). This could suggest a possible long-term prognostic advantage for patients treated with ICI, potentially reflecting improved disease control compared to other strategies. This must be further explored and confirmed in prospective studies which should also account for other potential confounding factors such as the use of machine perfusion, the number of transfused products, the IS protocols, and others.

This study has various strengths and shows novelty in the field as it is the first which uses an optimal propensity score matching (1:3) on variables most plausibly linked to rejection to reduce confounding and ensure comparable follow-up eras. Furthermore it represents one of the larger reported cohorts from the Western world, including patients from both Europe and North America with more than 50% of nonreported previously patients. Third, the study provides granular timing data, validating a $\geq$ 50-day washout as a pragmatic threshold, and increases the knowledge not only of the rejection but also about the tumour characteristics.

However, our study has several limitations, inherent to its retrospective design, including a potential confounding factor. Despite this cohort being predominantly male and viral hepatitis related liver disease, with no information on race or ethnicity, the results may be applicable to other populations. We acknowledge the potential bias building the non-ICI cohort for center-specific differences in baseline immunosuppression and rejection treatment protocols from a single institution (Toronto General Hospital). To address this, we accounted for these factors in our statistical analysis to control for any potential confounding effects arising from institutional practices. The relatively small sample size, particularly in the ICI cohort, may limit the power to detect statistically significant differences in rejection rates and other outcomes. Given the low overall rejection rate in our study, it is challenging to draw definitive conclusions. The low number of events (9 rejection episodes in the ICI cohort) makes it challenging to identify potential risk factors for rejection in this context. Furthermore, since the study was not designed as an intention-to-treat analysis and the primary endpoint was post-transplant rejection, we did not systematically capture patients who received ICI but were not ultimately transplanted. As a result, the efficacy of ICI as a downstaging or bridging strategy could not be assessed. Future research is on its way to determine this.

The comparison between ICI's is impacted by the era effect, as Nivolumab (PD-1) use potentially constitutes earlier more conservative experience compared to more recent Atezolizumab (PD-L1) era as demonstrated by the higher risk explants seen in this experience. Additionally, the heterogeneity in ICI treatment protocols, including the type of ICI used, duration of treatment, and washout periods, introduces variability that may impact the interpretation of the findings. In addition, the heterogeneity of immunosuppression protocols between centers cannot be accounted for. The study also lacks long-term follow-up data, which is crucial for assessing the durability of graft function and survival outcomes over time. Furthermore, as a retrospective study, the accuracy of the data relies on the quality of medical records, which may vary across centers.

In conclusion, rejection rates in the ICI cohort were comparable to those in the non-ICI group, and most rejection episodes were successfully managed. These findings support the safety of ICI prior to LT when there is appropriate washout time; however, optimal duration of therapy and post-transplant protocols to reduce rejection.

Author Contributions

L. Aceituno: substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. **C. Magyar:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **P. Tabrizian:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **R. Marino:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **K. Watt:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **D. Chascsa:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **G. Schnickel:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **V. Banz:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **F. Alconchel:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **Celia Martagon:** substantial contributions to acquisition of data. **C. Moctezuma:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **T. Baker:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **C. Nwaduru:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **F.J. Krendl:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **R. Oberhuber:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **L. Ruiz-Ortega:** substantial contributions to acquisition of data. **C. Demers:** substantial contributions to acquisition of data and final approval of the version to be published. **R. Bucur:** substantial contributions to acquisition of data and final approval of the version to be published. **G. O'Kane:** revising the article critically for important intellectual content; and final approval of the version to be published. Supervised the project and provided assistance with writing the manuscript. **A. Vogel:** revising the article critically for important intellectual content; and final approval of the version to be published. Supervised the project and provided assistance with writing the manuscript. **B. Mínguez:** substantial contributions to acquisition of data; revising the article critically for important intellectual content; and final approval of the version to be published. **G. Sapisochin:** substantial contributions to conception and design, and analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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Ethics Statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the institutional review boards of all participating centers.

Consent

Given the retrospective nature of the study, the requirement for informed consent was waived by each institution's ethics committee.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to institutional privacy regulations but are available from the corresponding author on reasonable request and following data-sharing agreements.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apt70528-sup-0001-Supinfo.docx.