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Breaking Barriers for Intensive Care Admission in Patients With Advanced HCC on Immunotherapy

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Keywords: adverse events | hepatocellular carcinoma | immunotherapy | intensive care

ABSTRACT

Background and Aims: Intensive Care Unit (ICU) admission is usually denied to patients with advanced hepatocellular carcinoma (HCC) due to the perceived poor prognosis associated with both cirrhosis and liver cancer. However, immunotherapy based on immune checkpoint inhibitors (ICI) has transformed the treatment landscape, and the role of critical care is becoming more relevant in managing adverse events. We aim to assess the outcome of patients with advanced HCC treated with ICI admitted to the ICU.

Methods: We evaluated patients treated with ICI combinations across 20 medical centres globally between November 2012 and April 2024. Demographic data, ICI types, causes of admission, organ support, and mortality in the short and medium term were recorded.

Results: Of 1065 patients, 47 (4.4%) were admitted to the ICU. Most were male (76.6%) with cirrhosis (93.6%), and 59.7% received ICI as first-line therapy. The primary reasons for ICU admission were immune-related adverse events (irAE) in 46.8% and variceal bleeding in 29.8%. The median time to ICU admission was 115 days [IQR 38–202] after the initiation of ICI treatment. Among patients admitted due to irAEs, the median time was 51 days [IQR 31–137]. ICU mortality was 25.5%. Two-thirds were alive 28 days post-ICU discharge, with 3- and 6-month survival rates of 83% and 69%. Of the 61.3% of survivors, they were rechallenged with ICI or started new HCC therapy.

Conclusions: irAEs are the main cause of ICU admission in patients with advanced HCC receiving ICI. Despite the severity, 66% were discharged, and nearly half resumed treatment. These findings highlight the vital role of ICU care in managing HCC patients, challenging the notion of denying them intensive care.

Abbreviations: AUC, area under the curve; CT, clinical trials; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitors; ICU, intensive care units; IQR, interquartile range; irAE, immune-related adverse events; PS, performance status; ROC, receiver operating characteristic.

For affiliations refer to page 8.

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Summary

- Our study followed a group of HCC patients who were receiving immunotherapy and became sick enough to need ICU support.
- The reassuring news are that most of them survived the critical episode, recovered well, and could restart anti-cancer treatment afterwards.
- These results show that high-level intensive care can make a real difference and should not be ruled out simply because a patient has advanced liver cancer.
- Decisions about ICU admission should be individualised, not automatic exclusions.

1 | Background

The emergence of immune checkpoint inhibitors (ICI) has revolutionised the therapeutic landscape of hepatocellular carcinoma (HCC) over the last years. These novel agents have substantially enhanced the overall response rate and notably improved the overall survival of patients with advanced HCC compared to tyrosine kinase inhibitors. ICI-based combinations such as Atezolizumab-Bevacizumab [1], Tremelimumab-Durvalumab [2], Camrelizumab-Rivoceranib [3], and Ipilimumab-Nivolumab [4] have been demonstrated to be superior to their respective control arm in clinical trials (CT) in terms of survival.

Despite the adequate safety profile of these ICI combinations reported in CT and real-world data [1–8], these drugs are not devoid of serious adverse effects, which, although infrequent, may be potentially life-threatening. Moreover, it should be considered that in most patients, HCC develops in the context of cirrhosis. Even in the absence of HCC, these patients are at high risk of complications and mortality due to potential decompensations [9–11].

The mortality of cirrhotic patients is higher than that of non-cirrhotic patients in the Intensive Care Units (ICU), reflecting the lethality of liver decompensation. On the other hand, this profile differs from HCC patients receiving immune-based treatments [12].

Some of these severe and treatment-related adverse events may require admission to the ICU, where proper monitoring and management are conducted. There is a significant gap in the literature regarding the outcomes of HCC patients admitted to the ICU, mainly because they were considered, in the past, terminal patients not candidates for critical care. The prognosis of HCC subjects admitted to the ICU due to immune-related adverse events (irAE) is also poorly known [13]. Data from observational studies stemming from other malignancies with more extensive experience in the use of ICI describe the reasons for admission and the outcomes following admission to the ICU in these [14–16] oncological patients, with an ICU mortality rate that ranges between 17.2% and 22.6% [14, 15, 17]. Despite the disparity among the patients included in such studies and the complications that prompt admission to the ICU, all studies concur in the necessity to establish adverse events management networks, particularly those associated with oncological treatments.

It is essential, therefore, to expand our knowledge on patient complications and to delve deeper into the management and prognosis of these serious adverse events. This would facilitate the process of shared decision-making between doctors, including intensivists, patients, and caregivers [16, 18].

Our study aims to characterise patients with advanced HCC treated with ICI schemes who are admitted to the ICU, as well as their outcomes and subsequent therapies.

2 | Patients and Methods

We retrospectively evaluated all patients with HCC receiving ICI-based schemes in 20 medical centres worldwide between November 2012 and April 2024. Inclusion criteria were HCC patients older than 17 years who started treatments with ICI combinations and were admitted to the ICU. We registered demographic characteristics, type of ICI combination, line of treatment, reason for ICU admission, and treatments received at ICU, including organ support. For each patient, admission to the ICU was recorded along with the date of admission, date of death, cause of death, or date of discharge. Additionally, from those patients who were discharged alive, the second-line therapy received was documented, as well as the survival status at 28 days, 3, and 6 months from the date of ICU discharge.

2.1 | Study Definitions

Immuno-related adverse events (irAE) include those adverse events in which immune hyperactivation has occurred and other potential causes have been reasonably excluded.

The type of adverse event was classified based on the affected organ or system according to the Common Terminology Criteria for Adverse Events (CTCAE) classification v5.0.

Intercurrent event was defined as problems not related to ICI that happened during ICI; for instance, spontaneous bacterial peritonitis or variceal bleeding are considered cirrhosis complications but not intercurrence.

Organ support was defined as receiving either vasopressors, mechanical ventilation, renal replacement therapy, or plasma exchange.

2.2 | Statistical Analysis

Quantitative variables are expressed as median and interquartile range [IQR (25th–75th percentiles)]. Categorical variables are described using absolute frequencies and percentages (%). Differences between qualitative variables were assessed using the chi-square test or Fisher's exact test. To identify baseline predictors of mortality in the ICU and at 30 days post-UCI discharge, we utilised Cox proportional hazards regression models. This approach allowed us to estimate hazard ratios (HR) for mortality based on patient characteristics, severity at admission, and treatments received. The HRs were presented with 95% confidence intervals (CI). We utilised Receiver Operating

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Characteristic (ROC) curves and the Area Under the Curve (AUC) to determine the optimal cut-off point for predicting mortality in our cohort. The significance level was set at 0.05 (two-sided). Times to event data were estimated by Kaplan–Meier with plots and median (95% confidence interval [95% CI]). The analysis was conducted using Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.

3 | Results

Between November 2012 and June 2024, 1.065 patients received at least one dose of systemic therapy with ICI-based regimens across 20 medical centres worldwide. A total of 47 patients (4.4%) met the inclusion criteria for the study (life-threatening event requiring critical care).

The median follow-up at the database lock in June 2024 was 9.5 months (IQR: 4–20.4) since treatment initiation and 3.1 months (IQR: 0.7–12.5) since ICU admission. During this period, 32 patients (68.1%) died, while 15 (31.9%) remained alive.

3.1 | Baseline Characteristics Regarding HCC

Table 1 summarises the baseline characteristics of the 47 patients included in the final analysis, the majority of whom were male (76.6%) and had a median age of 67 years (IQR 62–75). Among the total, 44 (93.6%) had cirrhosis and 34 (77.8%) were Child Pugh A with a median MELD score of 8 (IQR 7–11). The Eastern Cooperative Oncology Group (ECOG)-Performance Status (PS) was 0, 1, and 2 in 21 (44.7%), 23 (49%), and 3 (6.4%) patients, respectively, before ICU admission. Two-thirds of the patients ($n = 31$; 66%) were BCLC-C, 21 patients (44.7%) had macrovascular invasion, and 15 (31.9%) had metastasis. Most of them received ICI as a first line of systemic therapy (59.7%). The most common ICI-based regimen was the combination of Atezolizumab-Bevacizumab (66%). Nivolumab in monotherapy, administered in 6 patients (12.8), was the most frequent in the following lines of treatment. Twenty-one patients (44.7%) had not received any other treatment before systemic therapy.

3.2 | Data at ICU Admission and Clinical Outcome During Hospitalisation

Most of the patients were admitted due to irAE (46.8%; $n = 22$), followed by variceal bleeding (29.8%; $n = 14$). Concomitant myositis with myocarditis ($n = 2$), myocarditis ($n = 2$), nephritis ($n = 2$), pneumonitis, and hepatitis ($n = 2$) were the most frequent irAEs requiring ICU admission (Table S1).

The median time from the first dose of immunotherapy to ICU admission was 115 days [IQR 38–202], being similar for patients admitted due to variceal bleeding (106 days [IQR 38–196]) or for other reasons (155 days [IQR 70–202]; $p = 0.74$). Notably, this time was significantly shorter for those admitted due to irAE, at 51 days [IQR 31–137]; $p = 0.02$.

Half of the patients (51.5%) required organ support at admission or during ICU stay: 16 (34%) required vasopressor support (all with norepinephrine): 6 (27.3%) were admitted due to irAE, 5 (35.7%) due to variceal bleeding and 5 (45.5%) due to intercurrences ($p = 0.6$). Nine required invasive mechanical ventilation,

TABLE 1 | Clinical characteristics at ICU admission.

Total cohort ($n = 47$)	*n* (%)
Age (IQR)	67 (62–75)
Male (*n*/%)	36 (76.6)
BCLC stage A[a]/B/C	2 (4.3)/14 (29.7)/31 (66)
Macrovascular invasion	21 (44.7)
Extrahepatic disease	15 (31.9)
Cirrhosis	44 (93.6)
Child Pugh A/B/C	34 (77.3)/10 (22.7)/0 (0)
MELD score	8 (7–11)
ECOG PS (0/1/2)	21 (44.7)/23 (49)/3 (6.4)
History of arterial hypertension	23 (48.9)
History of type II diabetes mellitus	31 (66)
History of dyslipidemia	36 (76.6)
SOFA score	4 (2–8)
ACLF	14 (29.8)
CLIF-C ACLF score (in patients with ACLF)	46 (45–48)
Line of treatment	
First line	28 (59.7)
Second line	11 (23.4)
Third or further line	8 (17)
Organ support during admission	
Vasopressors	16 (34)
Mechanical ventilation[b]	9 (19.1)
Renal replacement therapy	2 (4.3)
Plasma exchange	1 (2.1)
Scheme of treatment	
Atezolizumab-Bevacizumab[c]	32 (68.1)
Nivolumab	6 (12.8)
Tremelimumab-Durvalumab[d]	5 (10.6)
Pembrolizumab	2 (4.3)
Others[e]	2 (4.3)

Abbreviations: ACLF, acute on chronic liver failure; BCLC, barcelona clinic liver cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartilic range; PS, performance status; SOFA, sepsis related organ failure assessment.
[a]BCLC-A patients received immunotherapy-based combinations in the context of treatment stage migration.
[b]Three patients required nasal high flow therapy & 1 patient non-invasive mechanical ventilation.
[c]One patient monotherapy Atezolizumab.
[d]One patient monotherapy Tremelimumab and 1 patient monotherapy Durvalumab.
[e]Relatinib-Nivolumab and anti-TLR7.

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8 of them with irAE (36%). Finally, 2 (4.6%) patients required renal replacement therapy, both admitted for irAE (9%).

The median SOFA score for the whole cohort at ICU admission was 4 (IQR 2–8), 4 (IQR 2–8) for patients with irAE, 4 (IQR 2–8) for those admitted due to variceal bleeding, and 8 (IQR 2–11) for other intercurrences. Table S2 summarises the SOFA score at ICU admission.

One third of the patients (29.8%) developed a bacterial infection at admission or during admission ($n = 14$), with pneumonia (5 patients; 35.7%) and spontaneous bacterial peritonitis (4 patients; 28.5%) the most common infections. Infections were more prevalent in subjects admitted due to intercurrences (6 patients; 54.5%), followed by patients with irAE (5 patients; 22.7%), and those with variceal bleeding (3 patients; 21.4%) ($p = 0.1$).

Fourteen patients (29.8%) developed acute on chronic liver failure (ACLF) at admission or during ICU stay (2 patients ACLF 1, 6 patients ACLF 2 and 6 ACLF 3). ACLF developed in 4 of 22 patients (18.2%) admitted for irAE, in 4 of 14 (28.6%) with variceal bleeding, and in 5 of 8 (62.5%) of those admitted for other reasons.

3.3 | Treatment of irAE

Despite specific treatment varying among types of irAE and centres, the majority of patients received corticosteroids (72.7%) and 22.7% other immunosuppressive drugs (including Infliximab, Rituximab, Tofacitinib and Abatacept). Plasma exchange was performed in 1 (4.5%) patient, and 2 (9.1%) received immunoglobulins. Table 2 summarises the immunosuppressive treatment by irAE.

3.4 | ICU Discharge

As a whole, 12 (25.5%) patients died during ICU admission. Of these, 6 patients were admitted due to an irAE (2 instances of hepatitis, and one case each of pneumonitis, encephalitis, myositis-myocarditis, and a thrombocytopenia), 3 due to

TABLE 2 | Summary of immunosuppressive therapy at the ICU in patients admitted due to irAE.

Cause of admission ($n = 22$)	ICI-based treatment	Immunosuppressive therapy in the ICU
Myositis + Myocarditis	Relatinib-Nivolumab	Corticosteroids, Tofacitinib, Abatacept and Infliximab
	Treme-Durva	Corticosteroids, Rituximab, Plasma Exchange, Ig and Tocilizumab
Myocarditis	Atezolizumab-Bevacizumab	Corticosteroids and Ig
	Atezolizumab-Bevacizumab	Corticosteroids
Myositis	Durvalumab	Corticosteroids + Ig
Pneumonitis	Pembrolizumab	Infliximab
	Nivolumab	Corticosteroids + Infliximab
Hepatitis	Atezolizumab-Bevacizumab	Corticosteroids
Acute myocardial infarction[a]	Atezolizumab-Bevacizumab	No immunosuppressive therapy
Nephritis	Atezolizumab-Bevacizumab	Corticosteroids
	Pembrolizumab	
Renal failure	Nivolumab	No immunosuppressive therapy
Colitis	Tremelimumab-Durvalumab	Corticosteroids
Diabetes mellitus	Atezolizumab-Bevacizumab	No immunosuppressive therapy
Guillain-Barré syndrome	Atezolizumab-Bevacizumab	Corticosteroids
Encephalitis	Atezolizumab-Bevacizumab	No immunosuppressive therapy
Atrial fibrillation due to hypothyroidism	Atezolizumab-Bevacizumab	Corticosteroids
Thrombopenia	Atezolizumab-Bevacizumab	Corticosteroids
Anaphylaxis	Nivolumab	No immunosuppressive therapy
Cytokine release syndrome	Anti-TLR7	Corticosteroids
Infusion-related syndrome	Atezolizumab-Bevacizumab	Corticosteroids

Abbreviation: Ig, immunoglobulins.
[a]Potentially irAE after other causes were ruled out.

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variceal bleeding, and 3 due to other intercurrences (a cranial traumatism, a hemorrhagic stroke, and an opioid intoxication). The majority of patients who died during admission required organ support (91.6% vs. 37.1%; $p = 0.002$). ACLF (6 at admission and 1 during their admission) was frequently observed in patients who died (58.3% vs. 20% in ICU survivors; $p = 0.03$).

Thirty-five patients (74.5%) were discharged from the ICU. Among them, 16 were admitted due to irAE (45.7%), 11 (31.4%) due to variceal bleeding, and 8 (15.8%) due to other intercurrences. Time to discharge was shorter in patients admitted due to variceal bleeding (4 [3–5] days) compared to patients admitted for other reasons (6 days [3–10]). Table S3 summarises the causes of ICU admission and associated ICU mortality.

3.5 | Outcomes After ICU Discharge

Two out of the 35 patients discharged from the ICU (5.7%) were readmitted within the next 28 days after discharge. Additionally, 4 patients (11.4%) died in the month following discharge. Mortality during ICU admission or after 28 days was 34% (57.1% in patients with ACLF and 24.2% in those without ACLF; $p = 0.045$) (Figure 1). Six-month mortality based on the cause of admission was 63.6%, 57.1%, and 54.5% in patients admitted for irAE, variceal bleeding, or other intercurrences, respectively (Figure S1).

Thirty-one (65.9%) patients were alive one month after discharge; of them, 24 patients were alive after three months (82.8%), and 2 patients did not reach the follow-up period. After 6 months from discharge, 18 patients (69.2%) remained alive, and 3 additional patients did not reach the follow-up period (Figure 2). The cause of death in those patients who died before 3 months was not related to tumour progression in the majority of the patients (Table 3).

3.6 | ICI Rechallenge or Subsequent HCC Treatment

Among patients who were alive 28 days after discharge, 15 (48.4%) patients resumed at least one of the drugs from their previous ICI-based regimen scheme −35.7% of those admitted for variceal bleeding and 36.4% in those admitted for irAEs. Additionally, 4 (12.9%) patients initiated a second-line treatment (2 patients tyrosine kinase inhibitors, 1 patient stereotactic body radiation therapy, and 1 patient transarterial chemoembolization). The median time from discharge to the reintroduction of the ICI-based scheme was 17 (IQR 13–34) days (Figure 3).

3.7 | Predictors of Mortality

The SOFA score at admission was the only independent variable associated with ICU mortality (HR 1.34 [1.11–1.62]; $p = 0.002$), 28-day mortality (HR 1.27 [1.10–1.48]; $p = 0.001$) and 6-month mortality (HR 1.19 [1.06–1.34]; $p = 0.004$) after adjusting for treatment-line, ALBI score and BCLC stage before admission. The area under the curve (AUC) for the Receiver Operating Characteristic (ROC) curve for SOFA score to correctly classify ICU mortality, 28-day

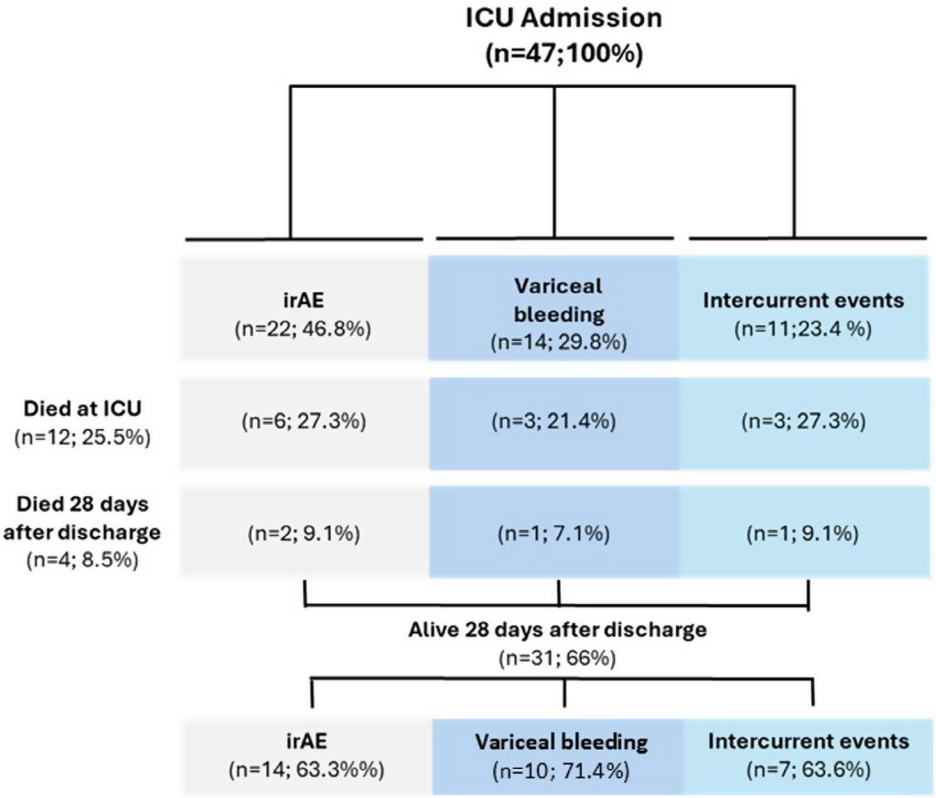

FIGURE 1 | Flowchart of patients admitted to the ICU based on the cause of admission and outcome at discharge. ICU, intensive care unit, irAE, immune-related adverse event.

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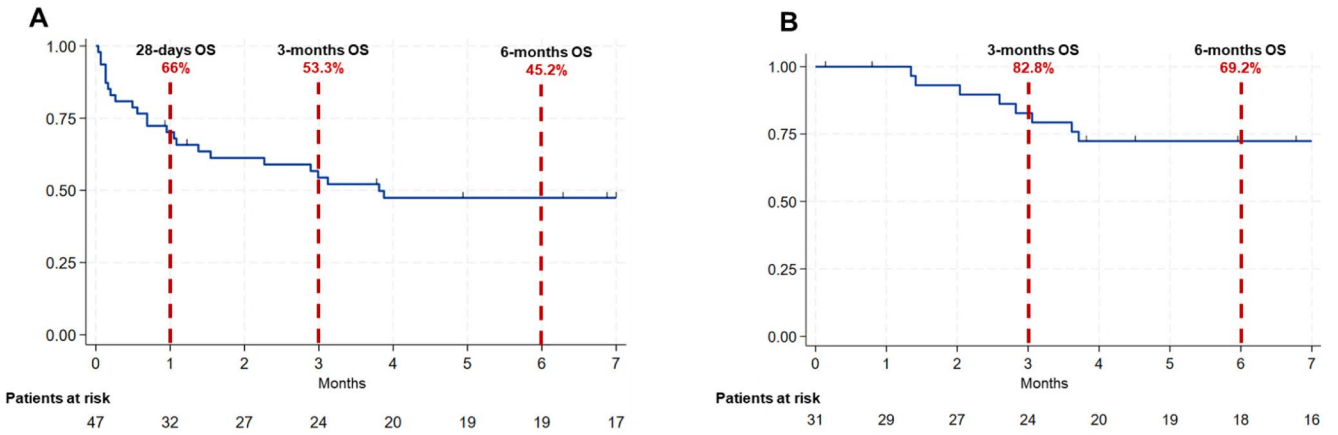

FIGURE 2 | (A) Kaplan–Meier survival curve at 28 days, 3, and 6 months after ICU admission in the whole cohort. (B) Kaplan–Meier survival curve at 3, and 6 months among patients alive 28 days after ICU discharge. ICU, intensive care unit; irAE, immune-related adverse event.

TABLE 3 | Causes of death based on 3-month mortality in patients alive at 28 days from discharge.

	Cause of death ($n=16$)	
Time from discharge	**Tumour progression**	**Non-related to tumour progression**
≤3 months ($n=5$)	2 (40%)	3 (60%)
>3 months ($n=11$)	9 (81.8%)	2 (18.2%)

mortality, and 6-month mortality was (0.842 [0.726–0.959]), (0.768 [0.624–0.912]), and (0.680 [0.522–0.838]), respectively. The cut-off ≥12 exhibits a 100% specificity in the three analyses with a sensitivity of 33.3%, 25% and 16.7%, respectively.

4 | Discussion

This study represents the first and largest international cohort of patients with advanced HCC treated with ICI and admitted to the ICU. Sixty-five percent of patients were alive after 28 days of ICU discharge, and 48.4% of those discharged were eligible for immunotherapy rechallenge. At six months, 69.2% of the patients who survived the first 28 days remained alive. These findings challenge the traditional paradigm of denying ICU admission to HCC patients, demonstrating that many can survive and continue effective treatments like immunotherapy. ICU mortality in this cohort was 25.5%, aligning with rates reported for cirrhotic patients in other series, though slightly higher than in other cancer types without cirrhosis [13, 14, 17].

In the realm of critical care, decisions are often made based on immediate prognoses and survival odds. Patients with HCC, due to their complex clinical status, are frequently viewed as having limited chances of recovery. However, this study suggests that the survival outcomes of these patients can be more favourable than previously believed, particularly when intensive care is provided.

While the clinical challenges are undeniable, the data show that with proper support, many of these patients survive long after their critical illness.

Thus, this study is a reflection that the advent of immunotherapy [1, 2] is reshaping the profile of cirrhotic patients managed in the ICU [13]. It is well established that ICU outcomes differ significantly between cirrhotic and non-cirrhotic patients, with the former experiencing worse outcomes [12]. The rate of mortality has been observed to vary significantly across studies (34.3%–71.9%) [19–21], and it is defined by the type of irAE, being neurological and cardiological, one of the most short-term lethal complications [22]. In the present study, the 25.5% of ICU mortality is aligned with the ICU mortality reported in a Taiwanese study, with 19.5% for patients with cirrhosis and liver cancer [13]. Likewise, in our cohort and despite the number of patients included, cardiac disorders (including those with associated myasthenia) and neurological disorders exhibit ICU and 28-day mortality of 33.3%–50%.

While ICU mortality in our cohort aligns with rates observed in other cirrhotic patients who were not candidates for liver transplantation, it is slightly higher than the rates reported by Joseph et al. [14], (17% for irAE and 23% for other intercurrent events) and Toffart et al. [17] (22% for irAE and 20% for other intercurrent events) in other cancer types. However, it should be noted that, according to the reports from these studies, the patients included did not have underlying cirrhosis.

Currently, corticosteroids remain the mainstay for managing immune-related events, and despite concerns about their use in cirrhotic patients, their efficacy in managing irAEs was consistent in our cohort. Additionally, the heterogeneity in the immunosuppressive treatments administered to patients in our cohort (including immunoglobulins, plasma exchange, rituximab or infliximab among others), even for the same complication, highlights the lack of data and consensus among physicians and underscores the need for the development of prospective studies and standardised protocols to effectively manage immune-related complications in patients with cirrhosis.

One of the key findings from our study is that nearly one-third of all ICU admissions and almost half of those discharged were

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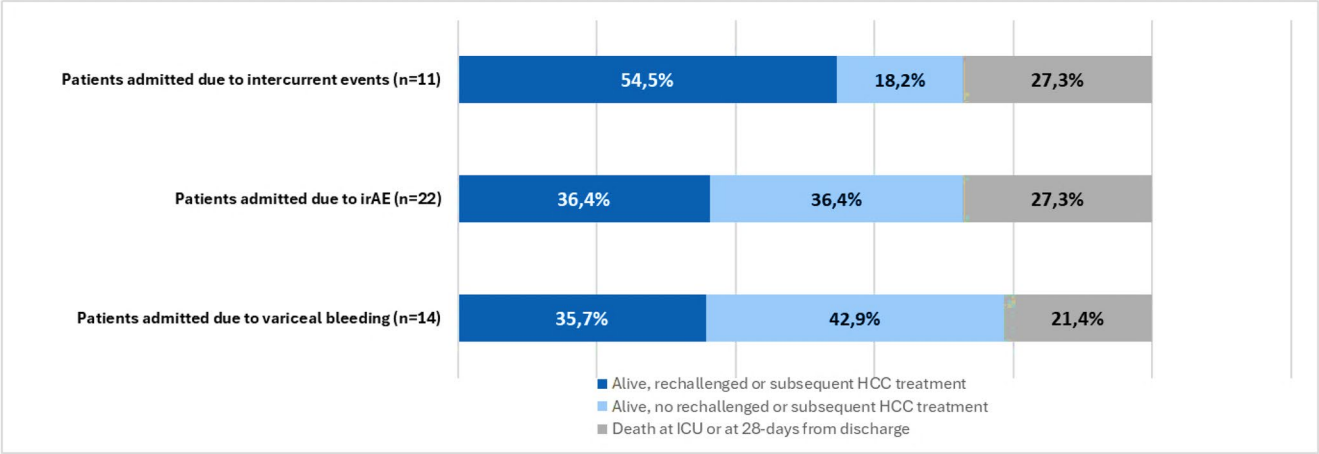

FIGURE 3 | Proportion of patients rechallenged/subsequent HCC treatment, no rechallenged, and death within admission or at 28 days, based on the cause of admission. HCC, hepatocellular carcinoma; irAE, immune-related adverse event.

eligible for immunotherapy rechallenge. Notably, the rate of rechallenge in HCC patients admitted due to irAEs in our cohort is comparable to the 37.9% reported by Joseph et al. [14]. However, the likelihood of rechallenge or new treatment for HCC varied significantly based on the reason for ICU admission, with rates of 35.7%, 36.4%, and 54.5% for HCC patients admitted due to variceal bleeding, irAEs, and other intercurrent events, respectively. This marked disparity, particularly among patients admitted for other intercurrent events (54.5% rechallenge rate in our cohort compared to 36.4% in the cohort reported by Joseph et al. [14], which included various cancer types except HCC), underscores potential differences in clinical characteristics or management strategies. These findings suggest a need for further investigation to better understand the factors driving these outcomes.

The SOFA score at admission showed a promising AUC (0.842) in defining the best cut-off for predicting mortality during admission. In our cohort, SOFA score >12 exhibited a 100% specificity for short-term mortality. Despite it being informative, the small sample size and sensitivity limit their robustness and need further validation. Moreover, despite it being well known that prognosis in critical care is better established after some days of unrestricted therapy for example, SOFA score 48–72 h after ICU admission in the context of liver cancer, the crucial point is the decision to admit or not the patients, and this is the reason why we focus on the baseline parameters instead of evolutionary events. Additionally, in other tumour types treated with immunotherapy-based regimens, ECOG-PS was associated with worse outcomes, whereas a history of immune toxicity was associated with better outcomes in multivariate analysis [17]. However, in this cohort, this proposed score was not validated. It could be related to the low number of patients with ECOG-PS >1.

Our study has several limitations, notably the selection bias inherent to its retrospective design: ICU admission was determined by individual physician judgement and bed availability at each centre. In addition, the relatively small number of outcome events in our cohort raises the risk of model overfitting, underscoring the need for external validation. Nevertheless, this represents the first multicentre analysis to show that a subset of patients with advanced hepatocellular carcinoma continue immunotherapy under intensive-care support. A critical unmet need remains the development of predictive tools—whether clinical scores or biomarker panels—to identify those most likely to benefit from ICU admission.

5 | Conclusion

In this cohort, ICU admissions occurred in 4.4% of patients undergoing ICI-based therapy, with irAEs being the leading cause, followed by variceal bleeding. Despite the severity of these conditions, 66% of the patients were successfully discharged, and nearly half resumed oncology treatment, demonstrating eligibility for immunotherapy rechallenge. These findings highlight the critical importance of not denying ICU admission to patients with advanced HCC receiving ICI-based regimens. Defining the factors that contribute to better outcomes and identifying the most effective therapeutic strategies for managing irAEs in these patients should be prioritised in future research.

Author Contributions

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Ethics Statement

Ethics approval and consent to participate: The project has been conducted in accordance with current regulations. The project was approved by the Ethical Committee of Hospital Clinic in Barcelona (version 3.0, 01/11/2023).

Conflicts of Interest

M.F. Speaker fee: AstraZeneca. L.G.d.F. Research grant: Bayer; Advisory board: AstraZeneca, Bayer, Roche; Speaker fee: Roche, AstraZeneca, Bayer, Sirtex, MSD, BMS. M.A. Roche, AstraZeneca, AbbVie, Gilead. R.S. None. J.-C.N. Research grants from Ipsen and Bayer. M.I. Speaker Bureau and Advisory Board: Roche, Astra Zeneca, Bayer, Roche Diagnostics, Gilead, MSD, EISAI, IPSEN. S.R. None. S.P. Advisory Board: AstraZeneca, Roche; Speaker Fee: Roche, AstraZeneca, Eisai; Travel Grant: AbbVie, Gilead, Roche. R.J. None. M.C. Advisory Board: Roche, Eisai, MSD, AstraZeneca; Travel grant: Roche. R.R. Sponsored Lectures (National): Advanz Farm. Other COI: Conference attendance and educational activities: Gilead, Abbie, Roche, Advanz. M.S.-Z. Speaker fees: Bayer; Travel grants: Bayer, BTG, MSD-Eisai, and Roche. N.J.-E. None. S.M. None. M.I. None. J.A. Speaker: Pfizer, AZ, Roche, Travel grants: Roche, AZ, Research Grants: Roche. T.H. Speaker fee: Eisai, AstraZeneca; Travel Grant: Roche. J.E.L.-B. Medical training (consultant): Roche, BMS, Servier, Pfizer, Sanofi, Janssen, Ipsen, Merck, Amgen, Travel grants for conferences: Roche, Ipsen, BMS, Pfizer, Servier, Sanofi, Merck, Amgen. M.T.F. Speaker fee: Eisai, Roche; Gilead; Travel Grants: Eisai, Roche, Astrazeneca, Boston Scientific, Gilead. S.C. Travel expenses and congress registrations Roche. A.L. Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma and Roche; Speaker honoraria from Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, Astra Zeneca, EISAI, Roche, Advanz Pharma and MSD; Advisory and consultancy honoraria from EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho and MSD; Principal Investigator-associated Institutional Funding form QED, Merck, Boehringer Ingelheim, Servier, Astra Zeneca, GenFit, Panbela Therapeutics, Novocure GmbH, Camurus AB, Albireo Pharma, Taiho, TransThera, Jazz Therapeutics and Roche; Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. J.I.M. Speaker Fee: Roche, Astra Zeneca, Knight, Bayer, Gilead. E.R. none. A.M.L. Speaking fee: Amgen, Astra Zeneca, Bristol-Myers, Eisai, MSD, Roche, Servier. Advisory Board: Amgen, Astra Zeneca, Eisai, Roche. A.L. Speaker in educational activities supported by industries (Eisai, Astellas Pharma S.A., Roche Farma, Advanz Pharma). M.V. Lecture fees, consulting work, travel support, and congress registration: Astrazeneca, Roche, Boston. A.M. Speaker in educational activities, lecture fees, consulting work, travel support, and congress registration: Astrazeneca, Roche, Boston, EISAI, and Sirtex. J.F. None. M.R. Consultant or Advisory Role: AstraZeneca, Bayer, BMS, Eli Lilly, Geneos, Ipsen, Merck, Roche, Universal DX, Boston Scientific, Engitix Therapeutics, Parabilis Medicines Inc.; Speaking: AstraZeneca, Bayer, BMS, Eli Lilly, Gilead, Roche, Biotoscana Farma.; Travel support: Astrazeneca, Roche, Bayer, BMS, Lilly, Ipsen; Principal or sub-Investigator of drug under development: Abbvie, BMS, Adaptimmune, Nerviano, Medivir, Bayer, Ipsen, Astrazeneca, Terumo, Incyte, Roche, Boston Scientific, Medivir; Grant Research Support (to the institution): Bayer, Ipsen; Educational Support (to the institution): Bayer, Astrazeneca, Eisai- Merck MSD, Roche, Ipsen, Lilly, Terumo, BMS, Next, Boston Scientific, Ciscar Medical, Eventy C3 LLC (Egypt).

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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