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Multidisciplinary Clinic Approach Improves Immunotherapy Treatment Outcomes in Unresectable Hepatocellular Carcinoma: A Multicentre Retrospective Study

Andrea Dalbeni[a, b] Alessandra Auriemma[c] Marco Vicardi[b] Filippo Cattazzo[b] Maria Elena Bellucco[b, c] Chiara Mazzarelli[d] Federica Villa[e] Giulia Dispinzieri[d] Leonardo Antonio Natola[b] Caterina Soldà[f] Sara Lonardi[f] Luisa Foltran[g] Sara Torresan[g] Simone Rota[g] Tiziana Pressiani[h] Lorenza Rimassa[h, i] David Sacerdoti[b] Michele Milella[c]

[a]Unit of General Medicine C, Medicine Department, University of Verona and University and Hospital Trust (AOUI) of Verona, Verona, Italy; [b]Liver Unit, Medicine Department, University of Verona and University and Hospital Trust (AOUI) of Verona, Verona, Italy; [c]Section of Innovation Biomedicine-Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona and Verona University and Hospital Trust (AOUI), Verona, Italy; [d]Hepatology and Gastroenterology, ASST GOM Niguarda, Milan, Italy; [e]Oncology Department, ASST GOM Niguarda, Milan, Italy; [f]Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [g]Medical Oncology and Cancer Prevention Unit, Department of Medical Oncology IRCCS, Aviano, Italy; [h]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Italy; [i]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitors · Cirrhosis · Prognosis · Multidisciplinary clinic approach

Abstract
Introduction: Given the complexity of managing unresectable hepatocellular carcinoma (HCC), few Italian centres have implemented integrated multidisciplinary clinics (MDTc), where hepatologists and oncologists jointly assess patients. This study aimed to evaluate whether this model improves survival outcomes in patients treated with atezolizumab and bevacizumab (A+B). ***Methods:*** In this multicentre retrospective study, 146 patients with cirrhosis and unresectable HCC treated with A+B were included. Based on the outpatient care model, centres were categorized into two groups: those with MDTc and those with standard oncology clinics, where hepatologists were consulted on demand. Primary outcomes were overall survival (OS) and progression-free survival (PFS); secondary outcomes included disease control rate (DCR) and objective response rate (ORR). An inverse probability weighting (IPW) analysis was performed to adjust for baseline imbalances between groups. ***Results:*** Seventy-seven (53%) patients were managed in MDTc settings, and 69 (47%) in oncology clinics. Median treatment

karger@karger.com
www.karger.com/lic

Correspondence to:
Filippo Cattazzo, filippo.cattazzo@univr.it

duration was 6.0 months (IQR 2.0–11.0). Median OS did not significantly differ between groups [19.7 months (95% confidence intervals [CI]: 16.6–23.1) vs. 13.4 months (95% CI: 10.7–19.5); p = 0.07], whereas median PFS was significantly longer in the MDTc group (13.6 months [95% CI: 8.9–NA] vs. 7.7 months [95% CI: 4.9–13.0]; p = 0.02). While ORR was similar, DCR was higher in the MDTc group (70.1% vs. 60.3%; p = 0.05). Patients followed in MDTc remained on first-line therapy significantly longer (8 months [IQR 3–12] vs. 4 months [IQR 1–8]; p = 0.009). Although the overall treatment discontinuation rate did not differ between the two groups, liver-related events were more frequent and accounted for a greater proportion of discontinuations in oncology clinics (40.6% vs. 10.4%; p = 0.04). Furthermore, treatment duration was shorter in patients discontinuing A+B due to liver-related events than other causes (2.5 months [IQR 1.8–6.3] vs. 7.1 months [IQR 3.9–11.2]; p < 0.001). However, in the IPW analysis, the association between MDTc management and clinical outcomes was no longer significant. ***Conclusions:*** In patients with unresectable HCC treated with A+B, MDTc management did not significantly improved OS but was associated with better PFS and DCR. These benefits were likely driven by longer treatment duration and lower rates of liver-related decompensation, underscoring the value of integrated hepatologic-oncologic management in this complex population.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver tumour and a leading cause of morbidity and mortality worldwide [1, 2]. HCC typically arises in the context of underlying chronic liver disease, most often cirrhosis. Therefore, its management requires a comprehensive, multidisciplinary approach that addresses the complex pathophysiology of both the cancer itself and the underlying liver dysfunction [3, 4].

Until recently, systemic treatment for HCC was limited to the anti-angiogenic agent sorafenib, primarily used in advanced or metastatic cases [5]. However, the introduction of novel targeted therapies and immunotherapies, particularly immune checkpoint inhibitors (ICIs), has significantly expanded the therapeutic landscape. While these advancements have opened new treatment opportunities for patients with unresectable HCC, they also have introduced challenges related to treatment selection and sequencing, and the management of adverse events [6, 7]. This rapidly evolving systemic treatment scenario has contributed to a paradigm shift in HCC therapeutic decision-making emphasizing the importance of individualized patient management through a multiparametric therapeutic hierarchy [8]. This concept aims to maximize outcomes for patients with HCC through multidisciplinary team (MDT)-guided therapeutic planning and management [9–11], requiring a comprehensive understanding of each patient's medical history, overall health status and disease characteristics, including tumour biology, staging, and liver function [3, 4, 12, 13]. As a result, the role of MDTs in HCC management has gained increasing recognition across all disease stages [14]. These teams comprise a diverse range of specialists, including oncologists, hepatologists, internists, liver and transplant surgeons, radiologists, pathologists, radiation oncologists, nurses, and mental health professionals [4, 12, 15, 16]. The combined expertise within MDTs facilitates a holistic and personalized approach to patient care, ensuring coordinated decision-making that optimally addresses both oncological and hepatological complexities [17, 18]. International guidelines, such as those of the European Society for Medical Oncology (ESMO), consistently underscore the importance of MDTs in HCC management [19]. Moreover, the Barcelona Clinic Liver Cancer (BCLC) staging and the American Association for the Study of Liver Diseases (AASLD) guidelines emphasize the need for multidisciplinary evaluation of liver lesions and comprehensive clinical assessment [9, 20]. Similarly, the European Association for the Study of the Liver (EASL) advocates for multidisciplinary discussions, particularly in managing early-stage lesions and surgical strategies [14]. Collectively, these guidelines underscore the necessity of MDTs in developing individualized treatment plans, ensuring that care is both personalized and evidence based. Despite the support from international guidelines, the implementation of MDT-based management remains heterogeneous across healthcare systems. In Italy, HCC care has traditionally been fragmented, further complicated by the interaction between hub centres and peripheral (spoke) hospitals, where patients are referred for specialized management. In tertiary centres, MDTs are usually established to discuss complex cases and define treatment strategies in accordance with guidelines [14]. In recent years, in response to the increasing complexity of systemic therapies, some Italian institutions have introduced integrated multidisciplinary patient management clinics (MDTc). These clinics extend beyond conventional MDT meetings by enabling direct, longitudinal care of HCC

patients by a core team – comprising at minimum a hepatologist and a medical oncologist – present at each outpatient visit, with the support of additional specialists (e.g., gastroenterologists, surgeons, radiologists) as needed. Theoretically, this integrated MDTc model enables optimized management of liver disease and comorbidities, more informed systemic therapy planning, and more effective mitigation of adverse events, particularly liver-related complications.

In this study, we explored the impact of an integrated MDTc approach on survival outcomes in patients with HCC receiving first-line systemic treatment with atezolizumab plus bevacizumab (A+B) [21, 22]. Additionally, we compared the incidence of treatment-related adverse events, focussing on liver-related complications, between patients managed within an MDTc model versus those followed in standard oncology clinics.

Methods

A total of 146 patients with cirrhosis and HCC who received first-line therapy (A+B) at secondary and tertiary care centres across Italy were retrospectively enrolled between May 2022 and December 2024. The inclusion criteria were a diagnosis of liver cirrhosis (histologically confirmed or supported by compatible clinical, laboratory, and radiological findings) and a radiological and/or histological diagnosis of unresectable HCC, defined as stage B or C according to the BCLC classification, with indication for first-line systemic treatment [9].

Demographic, clinical, and biochemical characteristics were recorded at the time of treatment initiation. These included age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), BCLC stage, aetiology of liver disease, baseline Child-Pugh score, Model for End-Stage Liver Disease (MELD), and alpha-fetoprotein (AFP) levels. Information on prior treatments for underlying etiological factors contributing to chronic liver disease was also recorded. Regarding the aetiology of liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD) was defined according to Delphi consensus as the presence of hepatic steatosis associated with a cardiovascular risk factor and no more than two alcohol units per day, in the absence of other causes of liver disease [23]. Metabolic-alcoholic liver disease, according to the Delphi consensus, was defined as the presence of hepatic steatosis associated with a cardiovascular risk factor and a daily alcohol intake of 20–50 g (140–350 g per week) for females and 30–60 g for males (or 210–420 g per week) [23].

The study involved five centres in northern Italy (Lombardy, 2 centres; Veneto, 2 centres; Friuli-Venezia Giulia, 1 centre). Two centres evaluated and followed up patients with HCC receiving A+B within a MDTc (ASST Grande Ospedale Metropolitano Niguarda, Milan; Azienda Ospedaliera Universitaria Integrata, Verona) and 3 within a specialized oncology clinic, operating in Comprehensive Cancer Centres (IRCCS Humanitas Research Hospital, Milan; Istituto Oncologico Veneto-IOV-and Azienda Ospedaliera Universitaria, Padova; CRO Aviano, Pordenone).

All five centres discussed cases within an MDT to determine the best therapeutic approach for each patient. In centres with a MDTc-based care pathway, patient evaluations during both the first and each follow-up visit were conducted jointly by a senior internist/hepatologist and a senior medical oncologist, with the participation of residents from both specialities. Other healthcare professionals, including pharmacists, dietitians, and nursing staff, are part of the overall care team but are not exclusive to the MDTc for the management of unresectable HCC. In centres with an oncology clinic-based care pathways, patients were evaluated by a senior medical oncologist, with the participation of oncology residents, while internists/hepatologists were consulted as needed, programming the consultation. The senior internist/hepatologist evaluation before starting therapy permits optimisation of cardiovascular and hepatological therapy necessary in this contest.

All patients received first-line A+B following multidisciplinary assessment, according to each institution's local practice. Adverse events were classified and their severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) and managed according to current guidelines [24]. Treatment was continued until disease progression, patient refusal, occurrence of unmanageable toxicities, deterioration of liver function or achievement of conversion surgery indications or liver transplantation.

Radiological assessments were performed at baseline and subsequently every 9–12 weeks, according to individual centre policies. Radiological progression was defined independently by each centre according to RECIST criteria v1.1, based on multiphasic CT or MRI scans conducted as part of periodic restaging. Tumour burden was calculated measuring maximum tumour diameter and the number of nodules [25].

The primary outcomes were overall survival (OS), defined as the time from treatment start until death from

any cause or the last clinical follow-up, and progression-free survival (PFS), defined as the time from treatment start to radiological progression or death, whichever occurred first, or the last clinical follow-up.

Secondary outcomes included oncological treatment discontinuation due to hepatic decompensating events, including gastrointestinal bleeding, new-onset or recurrent grade 2–3 ascites and new-onset or recurrent encephalopathy, in patients who previously exhibited normal levels of consciousness, whichever occurred first and objective response, evaluated according to RECIST v1.1 [25]. Disease control rate (DCR) was defined as the percentage of patients who achieved either complete response (CR), partial response or stable disease, and objective response rate (ORR) was defined as the percentage of patients who achieved either CR or partial response as their best response. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation for normally distributed data or as median with interquartile range for non-normally distributed data, as determined by the Shapiro-Wilk test. Categorical variables were expressed as percentages. Comparisons of continuous variables were conducted using either the Student's *t* test or the Mann-Whitney U test, depending on the data distribution (normal or non-normal). Categorical variables were compared using the Chi-square test, while the Fisher's exact test was used when appropriate.

The cumulative probabilities for OS and PFS between the two groups (MDTc vs. oncology clinics) were estimated using the Kaplan-Meier analysis and compared with the log-rank test. To account for potential confounders, univariate and multivariate Cox regression models were used to identify independent predictors of OS and PFS. Covariates with p value <0.1 in univariate analysis were included in the multivariate models, and the results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Logistic regression analysis was performed to assess the impact of MTDc vs. oncologic clinics on DCR and ORR, adjusting for clinically relevant covariates. Results are expressed as odds ratios (ORs) with 95% CI.

A subgroup analysis was performed including only patients meeting the IMbrave150 trial inclusion criteria, in particular excluding those with Child-Pugh B and with platelet counts below 75,000/mm^3 [21]. To avoid collinearity among variables, MELD, BCLC, and Child-Pugh scores were not included in the same multivariate models.

To adjust for baseline imbalances between MDTc and oncology clinic groups, propensity scores were estimated using logistic regression including only the variables that differed significantly between the two groups at baseline, namely the individual markers of portal hypertension (oesophageal and/or gastric varices and ascites), chosen for their substantial clinical relevance. Stabilized weights were derived from these scores to create a pseudo-population with balanced baseline characteristics, assessed using standardized mean differences (SMD <0.1 indicating adequate balance, online supplementary Table S5; for all online suppl. material, see https://doi.org/10.1159/000549738). Weighted Cox proportional hazards models and weighted logistic regression models were then applied to evaluate the effect of MDTc versus oncology clinics on OS, PFS, DCR, and ORR. Both average treatment effect (ATE) and average treatment effect on the treated were calculated to provide complementary estimates of the treatment effect.

For all analyses, p values <0.05 were considered statistically significant. All p values were two-tailed, and all confidence intervals (CIs) were set at 95%. Analyses were performed using the Jamovi software (The Jamovi project, 2022, v 2.3.18).

Results

A total of 146 consecutive patients (mean age 69.9 ± 9.7 years, 82.2% male) with HCC (BCLC stage B or C) were enrolled. Median follow-up and treatment duration were 11.0 months (IQR 5.0–16.0) and 6 months (IQR 2–11), respectively. Patients' characteristics, according to the treatment group, are summarized in Table 1. Seventy-seven (53%) patients were managed by MDTc, whereas 69 (47%) were managed in oncology clinics. The two groups were comparable in terms of demographic characteristics, cirrhosis aetiologies, prevalence of comorbidities, baseline Child-Pugh score, ALBI grade, and tumour burden score. Clinically significant portal hypertension – defined as the presence of one or more of the following: oesophageal or gastric varices, platelet count <150,000/mmc, or radiological ascites – was more prevalent among patients managed by MDTc compared to those managed in oncology clinics (67% vs. 36%, p < 0.001). In particular, oesophageal varices were more frequently observed at baseline esophagogastroduodenoscopy (38.7% vs. 18.6%, p = 0.012), and

Table 1. Baseline characteristics of entire cohort and divided according to the outpatient care model (MDT clinics vs. oncology clinics)

	Entire cohort (*n* = 146)	MDTc (*n* = 77)	Oncology clinic (*n* = 69)	*p* value
Age, years	69.6 (9.7)	68.4 (10.2)	70.9 (9.0)	0.131
Male, *n* (%)	120 (82.2)	64.0 (83.1)	56.0 (81.2)	0.758
Cirrhosis aetiology, *n* (%)				
HBV	27 (18.5)	16 (20.8)	11 (15.9)	0.452
HCV	76 (52.1)	39 (50.6)	37 (53.6)	0.720
ALD	41 (28.1)	22 (28.6)	19 (27.5)	0.889
MASLD	25 (17.1)	11 (14.3)	14 (20.3)	0.336
MetALD	7 (4.8)	5 (6.5)	2 (2.9)	0.310
SVR, *n* (%)[1]	46 (60.5)	20 (66.7)	26 (70.3)	0.812
Comorbidities, *n* (%)				
Arterial hypertension	71 (48.6)	34 (44.2)	37 (53.6)	0.253
T2DM	53 (36.6)	26 (34.2)	27 (39.1)	0.539
Hypercholesterolemia	16 (11.0)	5 (6.5)	11 (16.2)	0.063
Hypertriglyceridemia	4 (2.8)	1 (1.3)	3 (4.5)	0.247
Heart failure	2 (1.4)	2 (2.6)	0 (0.0)	0.178
Atrial fibrillation	8 (5.6)	5 (6.7)	3 (4.4)	0.558
Chronic kidney disease	2 (1.4)	0 (0.0)	2 (3.0)	0.129
Baseline home therapies, *n* (%)				
NSBB	33 (22.6)	25 (32.5)	8 (11.6)	0.003
SBBs	30 (20.6)	15 (19.5)	15 (21.7)	0.797
ACE-inhibitors/ARBs	57 (39.0)	23 (29.9)	34 (49.3)	0.018
Diuretics	51 (34.9)	29 (37.7)	22 (31.9)	0.465
PPIs	59 (40.4)	26 (33.8)	33 (47.8)	0.106
Statins	29 (19.8)	13 (16.8)	16 (23.2)	0.308
Insulin	18 (12.3)	11 (14.3)	7 (10.1)	0.431
Metformin	25 (17.1)	12 (15.6)	13 (18.8)	0.653
Aspirin	19 (13.0)	6 (7.8)	13 (18.8)	0.043
DOACs	8 (5.5)	5 (6.5)	3 (4.4)	0.545
Lactulose	14 (9.6)	10 (12.9)	4 (5.8)	0.127
Rifaximin	6 (4.1)	3 (3.9)	3 (4.3)	0.891
Previous treatment, *n* (%)	107 (73.3)	59 (76.6)	48 (69.6)	0.336
Resection	43 (29.5)	18 (23.4)	25 (36.2)	0.072
MWA/RFA/PEI	47 (32.2)	34 (44.2)	13 (18.8)	0.039
TACE/TARE	48 (32.9)	34 (44.2)	14 (20.3)	0.250
SIR	19 (13.0)	10 (13.0)	9 (13.0)	0.500
SBRT	3 (2.1)	2 (2.6)	1 (1.5)	0.768
Child-Pugh, *n* (%)				0.247
A	137 (93.8)	69 (89.6)	68 (98.6)	
B	9 (6.2)	8 (10.4)	1 (1.4)	
Pre-treatment EGDS, *n* (%)	145 (99.3)	76 (98.7)	69 (100)	0.342
Oesophageal varices, *n* (%)	40 (27.4)	29 (37.7)	11 (15.9)	0.012
Gastric varices, *n* (%)	2 (1.4)	2 (2.6)	0 (0.0)	0.203
Congestive gastropathy, *n* (%)	33 (22.6)	21 (27.3)	12 (17.4)	0.355
Previous band ligation, *n* (%)	14 (9.6)	11 (14.3)	3 (4.4)	0.081
Clinically portal hypertension, *n* (%)	77 (51)	52 (67)	25 (36)	0.001
Ascites, *n* (%)	15 (10.3)	12 (15.6)	3 (4.3)	0.024
Hepatic encephalopathy, *n* (%)	2 (1.4)	1 (1.3)	1 (1.4)	0.945

Table 1 (continued)

	Entire cohort (n = 146)	MDTc (n = 77)	Oncology clinic (n = 69)	p value
WBC, mmc	6,045.9 (2,520.1)	5,630.0 (2,030.3)	6,498.0 (2,910.5)	0.039
Neutrophils, %	61.1 (11.0)	61.2 (9.7)	60.9 (12.7)	0.879
Lymphocytes, %	25.2 (10.7)	24.4 (9.0)	26.2 (12.8)	0.363
NLR	2.6 (1.8–3.5)	2.5 (1.8–3.4)	2.7 (1.8–3.5)	0.565
Hb, g/dL	13.3 (1.8)	13.2 (1.8)	13.4 (1.9)	0.391
PLTs, $\times 10^3$/mmc	163.9 (98.5)	150.9 (85.5)	178.1 (110.0)	0.098
Bilirubin, mg/dL	1.0 (0.7)	1.1 (0.8)	0.9 (0.5)	0.129
Albumin, g/dL	4.0 (0.5)	4.0 (0.5)	3.9 (0.4)	0.527
ALBI grade, n (%)				0.965
1	67 (45.9)	37 (48.1)	30 (43.5)	
2	62 (42.5)	34 (44.2)	28 (40.6)	
TBS	7.3 (5.3–9.9)	7.1 (4.4–9.9)	7.6 (5.3–10.5)	0.198
TBS risk, n (%)				0.249
1	16 (11.0)	10 (13.0)	6 (8.7)	
2	88 (60.3)	40 (52.0)	48 (69.6)	
3	10 (6.9)	3 (3.9)	7 (10.2)	
Number of nodules	5.0 (2.0–7.0)	5.0 (2.0–7.0)	6.5 (2.0–7.0)	0.793
Metastases, n (%)	40 (48.8)	17 (39.5)	23 (59.0)	0.124
Macroscopic vascular invasion, n (%)	22 (15.1)	11 (14.3)	11 (15.9)	1,000
BCLC stage, n (%)				0.760
B	38 (26.0)	21 (27.3)	17 (24.6)	
C	108 (73.9)	56 (72.7)	52 (75.4)	
Follow-up time, months	11.0 (5.0–16.0)	13.0 (7.0–17.3)	10.7 (8.6–15.4)	0.019

ARBs, angiotensin receptor blockers; ACE, angiotensin converting enzyme; AFP, alpha fetoprotein; ALBI score/grade, albumin-bilirubin; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; DOACs, direct oral anticoagulants; EGD, esophagogastroduodenoscopy; Hb, haemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic-dysfunction and alcohol-related liver disease; T2DM, type 2 diabetes mellitus; MWA, microwave ablation; NSSBs, non-selective β-blockers; PEI, percutaneous ethanol injection; PLTs, platelets; PPIs, proton pump inhibitors; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; SSBs, selective β-blockers; SVR, sustained virological response after HCV eradication; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TBS, tumour burden score; WBC, white blood count. [1]Missing data: 13 (33.3%) in the MDTc group, 2 (5.4%) in the oncology clinic group.

radiologically documented mild-to-moderate ascites was also more common in the MDTc group (15.8% vs. 4.3%, p = 0.024). Regarding chronic therapies prescribed prior to initiation of A+B, patients in the MDTc group had a higher baseline use of non-selective beta-blockers (NSBBs) (32.5% vs. 11.6%, p = 0.003), whereas those managed in oncology clinics more frequently received ACE inhibitors or angiotensin receptor blockers (50% vs. 30.7%, p = 0.018). Among locoregional treatments, a higher number of ablative procedures (microwave or radiofrequency ablation and percutaneous ethanol injection) were reported in patients managed by MDTc, compared to those managed in oncology clinics (44.2% vs. 18.8%, p = 0.039) before starting A+B.

A non-significant trend towards longer median OS was observed in the MDTc group (19.7 months [95% CI: 16.6–23.1] vs. 13.4 months [95% CI: 10.7–19.5], log-rank p = 0.076; Fig. 1). The estimated OS rates at 12 and 24 months were 74% (95% CI: 64%–85%) and 26% (95% CI: 14%–46%), respectively, for patients managed by MDTc, and 54% (95% CI: 42%–69%) and 27% (95% CI: 15%–45%), respectively, for patients managed in oncology clinics. Table 2 reports variables significantly associated with OS in univariate and multivariate Cox

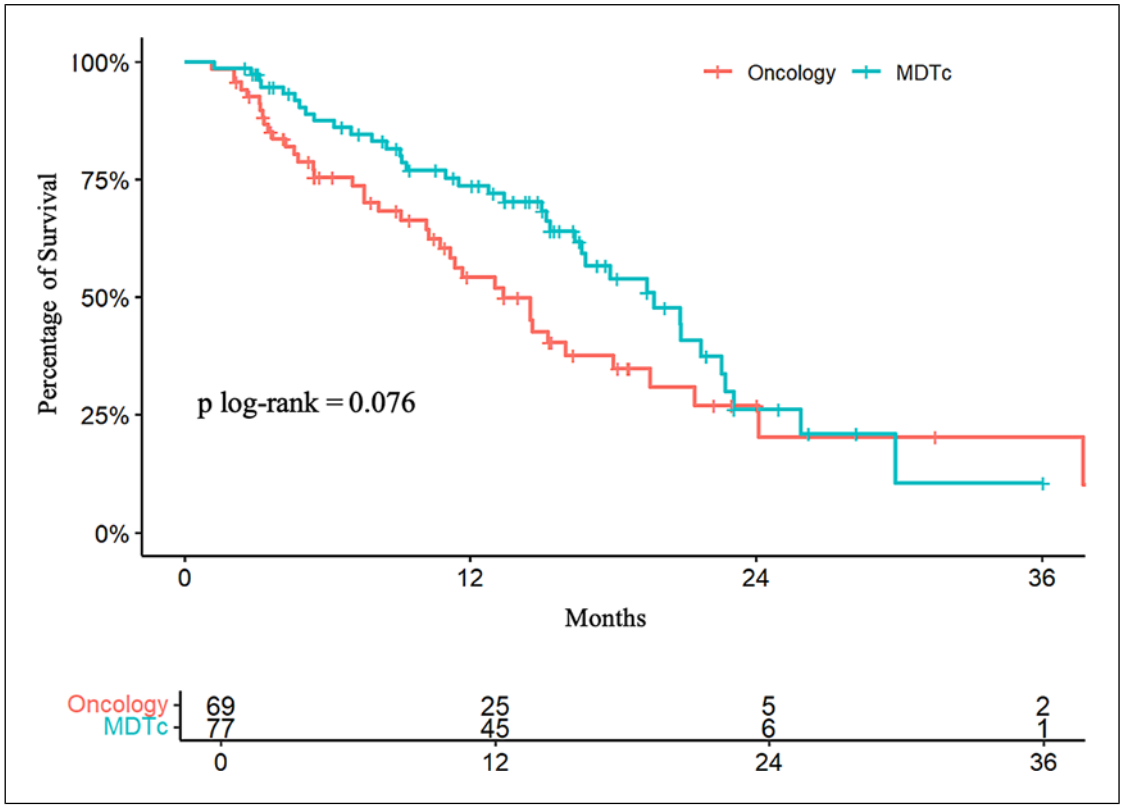

Fig. 1. OS according to the outpatient care model (MDT clinics vs. oncology clinics).

regression analysis: being managed in an MDTc, previous locoregional therapies, ALBI grade, hepatitis C virus (HCV) aetiology, and serum AFP levels >400 ng/mL were significantly associated with OS at univariate analysis, but only MDTc-based management (HR 0.57, 95% CI: 0.33–0.99) and AFP >400 ng/mL (HR 2.92, 95% CI: 1.64–5.22) remained independent predictors of longer and shorter OS, respectively, in multivariate analysis.

A significant difference in PFS was observed between patients managed by MDTc and those managed in oncology clinics (13.6 months [95% CI: 8.9–NA] vs. 7.7 months [95% CI: 4.9–13.0], log-rank p = 0.024; Figure 2). The estimated PFS rates at 12 and 24 months were 54% (95% CI: 43%–68%) and 29% (95% CI: 16%–51%) for MDTc patients, and 38% (95% CI: 28%–53%) and 18% (95% CI: 8%–40%) for patients managed in oncology clinics. MDTc-based care pathway, HCV-related aetiology, and Child-Pugh score ≤7 remained independent predictors of longer PFS in multivariate analysis (Table 3).

ORR did not significantly differ between the two groups, while more patients managed by MDTc achieved disease control (DCR 70.1% vs. 60.3%, p = 0.05) (Table 4). Multivariate analysis identified disease aetiology (HCV), diabetes, and liver function (CP ≤7) as independent predictors of ORR (online suppl. Table S1), whereas management by MDTc was the only variable significantly impacting DCR (OR 2.31, 95% CI: 1.01–4.58, p = 0.048; online suppl. Table S2).

Overall, patients managed by MDTc remained on first-line treatment for a significantly longer period than those managed in oncology clinics (median treatment duration: 8 months (IQR 3–12) vs. 4 months (IQR 1–8), p = 0.009; Table 4). Although the overall number of treatment discontinuations did not significantly differ between groups (62 patients [80.6%] vs. 53 [76.8%], respectively), liver-related events were more frequent and accounted for a higher proportion of discontinuations in patients followed in oncology clinics (40.6% vs. 10.4%, p = 0.046). Moreover, when comparing patients who discontinued A+B due to liver-related events versus other causes, treatment duration was significantly shorter in the former group (2.5 months [IQR 1.8–6.3] vs. 7.1 months [IQR 3.9–11.2], p < 0.001). No significant differences were observed in the proportion of patients

Table 2. Univariate and multivariate step regression analysis for OS

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
MDTc vs. oncology clinics	0.66	0.42–1.05	0.08	0.55	0.31–0.97	0.04
Age ≥70 (yes vs. no)	1.12	0.71–1.78	0.62	–	–	–
Male sex (yes vs. no)	1.30	0.73–2.30	0.37	–	–	–
BMI ≥30 (yes vs. no)	1.12	0.51–2.46	0.77	–	–	–
HBV (yes vs. no)	0.79	0.43–1.47	0.46	–	–	–
HCV (yes vs. no)	0.67	0.42–1.07	0.09	0.84	0.47–1.51	0.5
ALD (yes vs. no)	0.91	0.55–1.51	0.70	–	–	–
MASLD (yes vs. no)	1.38	0.76–2.52	0.29	–	–	–
MetALD (yes vs. no)	0.62	0.19–1.99	0.42	–	–	–
T2DM (yes vs. no)	1.09	0.68–1.76	0.71	–	–	–
Previous locoregional therapies (yes vs. no)	0.60	0.36–0.98	0.04	0.64	0.34–1.20	0.16
Ascites (yes vs. no)	1.77	0.90–3.48	0.08	1.98	0.77–5.05	0.15
Oesophageal or gastric varices (yes vs. no)	0.70	0.42–1.20	0.20	–	–	–
Child ≤7 (yes vs. no)	0.90	0.33–2.46	0.83	–	–	–
ALBI ≥2 (yes vs. no)	1.85	1.11–3.10	0.02	1.51	0.84–2.71	0.16
AFP ≥400 ng/mL (yes vs. no)	2.28	1.37–3.79	<0.01	2.92	1.64–5.22	< 0.01
TB risk ≥2 vs. <2	0.94	0.55–1.61	0.82	–	–	–
Number of nodules >3 (yes vs. no)	1.03	0.93–1.13	0.57	–	–	–
Metastases (yes vs. no)	0.91	0.52–1.60	0.74	–	–	–
Macroscopic vascular invasion (yes vs. no)	1.64	0.93–2.96	0.10	–	–	–

AFP, alpha fetoprotein; ALBI, albumin-bilirubin; ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic-dysfunction and alcohol-related liver disease; TB, tumour burden; T2DM, type 2 diabetes mellitus; ALBI, albumin/bilirubin ratio.

who received second-line therapy (29.9% vs. 30.3%, p = 0.492).

The use of locoregional treatments during systemic therapy did not differ between the two groups (Table 4). Notably, 3 patients managed by MDTc (vs. none in the oncology group) underwent liver transplantation after successful downstaging during systemic treatment.

Regarding AEs of any grade, ALT elevation (15.8% vs. 4.0%, p = 0.035), increased blood pressure (34.8% vs. 15.8%, p = 0.008), and thrombocytopenia (22.1% vs. 10.4%, p = 0.05) were more frequently observed in patients managed in oncology clinics (Table 5). However, no significant differences were observed in the incidence of severe (grade 3–4) AEs between groups (Table 5).

A subgroup analysis of patients meeting the IMbrave150 inclusion criteria (IMbrave150 "in"; n = 125) showed consistent results with the main analysis. Patients managed by MDTc exhibited better OS (19.4 months [95% CI: 16.4–NA] vs. 13.4 months [95% CI: 10.2–19.5]) and PFS (10.5 months [95% CI: 8.7–NA] vs. 7.7 months [95% CI: 4.9–13.0]) (online suppl. Fig. S1–S2). In this subgroup, multivariate Cox regression confirmed MDTc-based care pathway as an independent predictor of both longer OS and PFS. Additionally, high AFP levels and HCV-related aetiology confirmed their roles as independent predictors of shorter OS and longer PFS, respectively, in the IMbrave150 "in" population (online suppl. Tables S3, S4).

After applying inverse probability weighting (IPW), the effect of the treatment group (MDTc vs. oncology clinics) was no longer statistically significant across all outcomes, including OS, PFS, DCR, and ORR. This

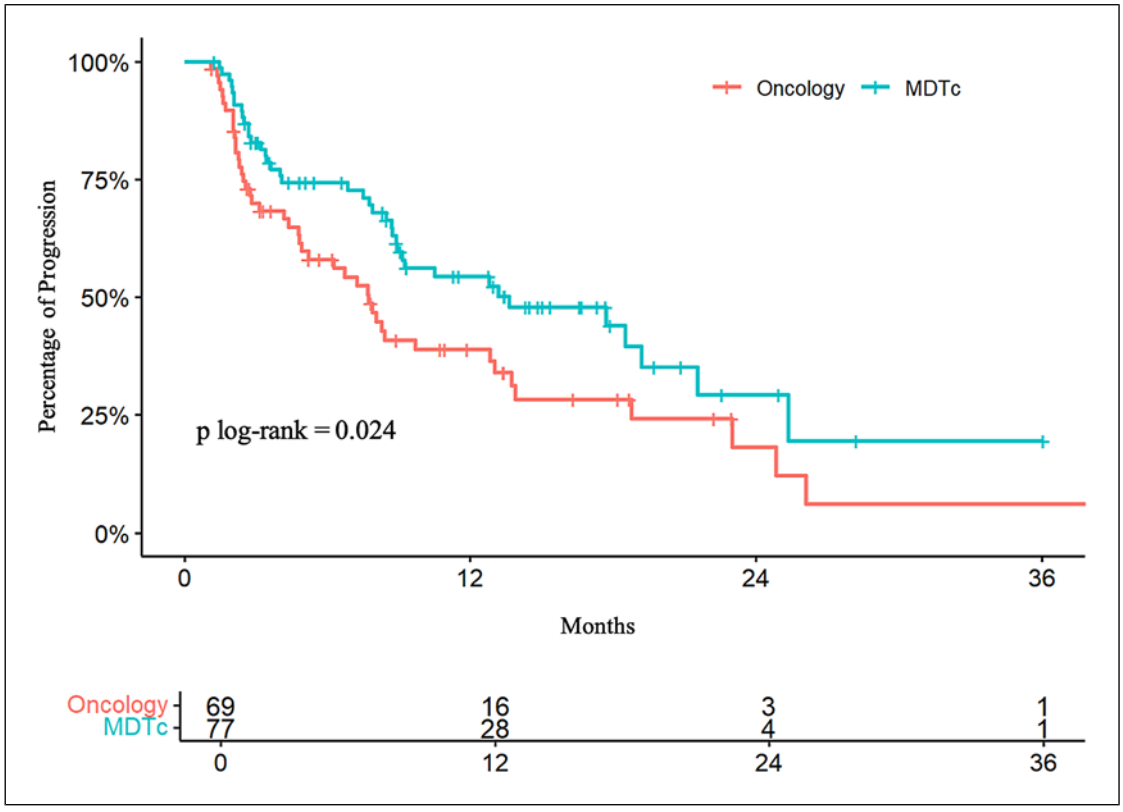

Fig. 2. PFS according to the outpatient care model (MDT clinics vs. oncology clinics).

finding was consistent in both weighted Cox proportional hazards models and in the estimation of average treatment effect and average treatment effect, indicating that the apparent advantage observed in the unadjusted analyses was largely driven by differences in baseline patient characteristics (online suppl. Tables S6, S7).

Discussion

In this retrospective, multicentre study, patients with HCC receiving A+B systemic therapy and managed within a MDTc experienced significantly better disease control (longer PFS and a higher DCR) compared to those managed by standard oncology clinics, translating into a non-significant trend towards improved OS. These differences remained significant after adjusting for potential confounders through multivariable Cox regression models and were confirmed in a predefined subgroup analysis restricted to patients meeting the inclusion criteria of the IMbrave150 trial. However, after adjustment using IPW, the effect of MDTc management on OS, PFS, DCR, and ORR was no longer statistically significant.

Expert multidisciplinary tumour board evaluation is widely acknowledged as a cornerstone in the management of HCC [26–29]. Multiple real-world studies have underscored the advantages of managing complex diseases such as HCC within a MDT, consistently reporting improvements in patient outcomes, including reductions in morbidity and adverse events [30–33]. This multidisciplinary approach has therefore been endorsed by international guidelines, including those from ESMO [14, 19].

In contrast to many other malignancies, HCC typically develops in the context of underlying chronic liver disease, most often cirrhosis. This makes the management of hepatic comorbidities a key determinant of treatment success. For this reason, both hepatologists and oncologists should be involved from the outset of systemic treatment. Based on this rationale, certain Italian centres have established dedicated MDT outpatient clinics, in which hepatologists and oncologists jointly evaluate patients, allowing for longitudinal,

Table 3. Univariate and multivariate step regression analysis for PFS

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
MDTc vs. oncologic clinics (yes vs. no)	0.61	0.40–0.95	0.03	0.58	0.38–0.90	0.02
Age ≥70 (yes vs. no)	0.75	0.48–1.15	0.18	–	–	–
Male sex (yes vs. no)	1.67	0.92–3.03	0.09	1.67	0.92–3.06	0.09
BMI ≥30 (yes vs. no)	0.97	0.47–2.01	0.93	–	–	–
HBV (yes vs. no)	1.13	0.65–1.95	0.67	–	–	–
HCV (yes vs. no)	0.61	0.39–0.94	0.03	0.52	0.33–0.82	<0.001
ALD (yes vs. no)	1.14	0.72–1.82	0.57	–	–	–
MASLD (yes vs. no)	1.54	0.89–2.67	0.12	–	–	–
MetALD (yes vs. no)	0.76	0.28–2.07	0.58	–	–	–
T2DM (yes vs. no)	0.88	0.56–1.38	0.58	–	–	–
Previous locoregional therapies (yes vs. no)	0.88	0.54–1.43	0.61	–	–	–
Child ≤7 (yes vs. no)	0.15	0.02–1.11	0.06	0.13	0.02–0.92	0.04
Ascites (yes vs. not)	1.43	0.80–2.56	0.23	–	–	–
Oesophageal or gastric varices (yes vs. not)	0.97	0.24–3.95	0.97	–	–	–
ALBI ≥2 (yes vs. no)	0.90	0.56–1.46	0.68	–	–	–
AFP ≥400 ng/mL	1.48	0.90–2.42	0.11	–	–	–
TB risk ≥2 vs. <2	0.98	0.59–1.62	0.92	–	–	–
Number of nodules >3 (yes vs. no)	1.01	0.99–1.01	0.74	–	–	–
Metastases (yes vs. no)	0.85	0.55–1.32	0.48	–	–	–
Macroscopic vascular invasion (yes vs. no)	0.89	0.54–1.48	0.66	–	–	–

AFP, alpha fetoprotein; ALBI, albumin-bilirubin; ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic-dysfunction-associated steatotic liver disease; MetALD, metabolic-dysfunction and alcohol-related liver disease; TB, tumour burden; T2DM, type 2 diabetes mellitus; ALBI, albumin/bilirubin ratio.

comprehensive, and coordinated management of both the cancer and the underlying liver dysfunction.

Understanding the reasons why MDTc management could be better in terms of PFS in patients with HCC is particularly intriguing given the comparable time to radiological progression, rates of immunotherapy discontinuation, second-line therapies initiation and use of logo-regional treatments between the two study groups. A key finding is that patients managed by MDTc remained on first-line treatment significantly longer, despite similar overall discontinuation rates. This difference appears to be driven primarily by a reduced incidence of early liver-related events – including ascites, encephalopathy, or gastrointestinal bleeding – in the MDTc group. Since patients experiencing decompensation were more likely to discontinue A+B early, as demonstrated by the significantly shorter treatment duration among those who stopped immunotherapy due to other reasons, the lower incidence of such events in the MDTc group may have indirectly prolonged treatment duration and improved clinical outcomes suggesting that hepatology co-management played a crucial preventive role. This may reflect earlier detection of subclinical portal hypertension, more proactive therapeutic adjustment, and timely management of hepatic comorbidities. Of note, patients managed by MDTc were more frequently prescribed NSBBs, a drug class that has demonstrated efficacy in reducing liver-related events even in patients with compensated cirrhosis. This is consistent with evidence from randomized controlled trials and meta-analyses, which collectively support

Table 4. Treatment response, duration, discontinuation, and other treatments during A+B of entire cohort and divided according to the outpatient care model (MDT clinics vs. oncology clinics)

	Entire cohort (n = 146)	MDTc (n = 77)	Oncology clinic (n = 69)	p value
Treatment duration, months	6 (2–11)	8 (3–12)	4 (1–8)	0.009
Best response, n (%)	42 (28.8)	17 (22.1)	25 (36.2)	0.224
Complete response (CR)	6 (4.1)	4 (5.2)	2 (2.9)	
Partial response (PR)	27 (18.5)	17 (22.1)	10 (14.5)	
Stable disease (SD)	59 (40.4)	33 (42.9)	26 (37.7)	
Progressive disease (PD)	42 (28.8)	17 (22.1)	25 (36.2)	
ORR (CR+PR), n (%)	34 (23.3)	21 (27.3)	13 (18.8)	0.235
DCR (CR+PR+SD), n (%)	92 (63.0)	54 (70.1)	38 (60.3)	0.050
Radiological progression, n (%)	84 (57.5)	39 (50.7)	45 (65.2)	0.059
Time to progression, months	4 (2–8)	6 (2–9)	4 (2–8)	0.270
Treatment discontinuation, n (%)	115 (78.8)	62 (80.6)	53 (76.8)	0.591
Cause of treatment discontinuation, n (%)				0.046
Progression	64 (44)	32 (52)	18 (34.8)	
Clinician's decision	18 (12)	11 (18)	3 (5.8)	
Death	13 (9)	7 (10.4)	4 (7.2)	
Adverse events	15 (10)	5 (9.2)	7 (11.6)	
Liver-related event	36 (25)	7 (10.4)	21 (40.6)	
Further treatment line, n (%)	46 (31.5)	23 (29.9)	23 (33.3)	0.492
Other treatments during A+B, n (%)	22 (15.1)	11 (14.3)	11 (15.9)	0.579
MWA/PEI/RFA	3 (2.1)	1 (1.3)	2 (2.9)	0.347
TACE	4 (2.7)	2 (2.9)	2 (2.9)	0.853
TARE	4 (2.7)	1 (1.3)	3 (4.4)	0.310
Liver transplant	3 (2.1)	3 (3.9)	0 (0.0)	0.047
Death, n (%)	76 (52.1)	37 (48.1)	39 (56.5)	0.306

MWA, microwave ablation; A+B, Atezolizumba/Bevacizumab; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

the role of NSBBs in reducing decompensation and mortality in cirrhosis [34–36].

With respect to OS, although a favourable trend was observed in the MDTc group, statistical significance was not reached in the overall population. This may be partially explained by differences in baseline liver function: the MDTc group had a higher prevalence of clinically significant portal hypertension and a larger proportion of patients with Child-Pugh B cirrhosis. These factors may have attenuated the survival benefit attributable to MDTc management. Such imbalances likely reflect intrinsic centre-specific referral patterns or patient populations rather than selection bias. To address these differences, a subgroup analysis was performed including only patients who met the inclusion criteria of the IMbrave150 trial, excluding those with Child-Pugh scores >7 or platelet counts <75,000/mm^3. Within this more homogeneous population, MDTc management remained significantly associated with longer PFS and OS, strengthening the hypothesis that coordinated hepatologic-oncologic care enhances outcomes even in well-compensated patients. Overall, the clinical performance of A+B in our study cohort was consistent with that observed in the IMbrave150 trial and in other recent real-world studies (online suppl. Table S8) [22, 37, 38].

In the multivariable Cox regression analyses, MDTc management was independently associated with improved OS, and AFP levels above 400 ng/mL were significantly associated with worse OS, a finding consistent with previously reported data identifying elevated AFP as a marker of tumour aggressiveness and poor prognosis in HCC [39]. As for PFS, independent predictors of better outcomes included management in the MDTc setting, HCV-related aetiology, and Child-Pugh A liver

Table 5. Adverse events of any grade and grade 3–4 according to the outpatient care model (MDT clinics vs. oncology clinics)

	MTDc clinic (*n* = 77)		Oncology clinic (*n* = 69)	
	any grade	grade 3 or 4	any grade	grade 3 or 4
Fatigue, *n* (%)	43 (55.8)	3 (3.9)	27 (39.1)	3 (4.4)
Anorexia, *n* (%)	12 (15.6)	0 (0.0)	13 (18.8)	0 (0.0)
Weight loss, *n* (%)	17 (22.1)	1 (1.3)	11 (15.9)	0 (0.0)
Fever, *n* (%)	12 (15.6)	2 (2.6)	9 (13.0)	2 (2.9)
Dysphonia, *n* (%)	1 (1.3)	0 (0.0)	4 (5.8)	0 (0.0)
Anaemia, *n* (%)	2 (2.6)	1 (1.3)	7 (10.1)	0 (0.0)
Thrombocytopenia, *n* (%)	8 (10.4)	1 (1.3)	15 (21.7)	0 (0.0)
Leukopenia, *n* (%)	2 (2.6)	0 (0.0)	3 (4.3)	0 (0.0)
Hand-foot syndrome, *n* (%)	4 (5.2)	1 (0.0)	0 (0.0)	0 (0.0)
Skin rash, *n* (%)	6 (7.8)	0 (0.0)	3 (4.3)	0 (0.0)
Prurito, *n* (%)	8 (10.4)	0 (0.0)	5 (7.2)	0 (0.0)
Vascular ulcers, *n* (%)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea/vomiting, *n* (%)	14 (18.2)	0 (0.0)	3 (4.3)	0 (0.0)
Mucositis, *n* (%)	3 (3.9)	2 (2.6)	4 (5.8)	0 (0.0)
Dysgeusia, *n* (%)	1 (1.3)	0 (0.0)	1 (1.4)	0 (0.0)
Diarrhoea, *n* (%)	14 (18.4)	1 (1.3)	14 (20.3)	1 (1.4)
Abdominal pain, *n* (%)	15 (19.5)	0 (0.0)	6 (8.7)	0 (0.0)
AST elevation, *n* (%)	7 (9.1)	1 (1.3)	10 (14.5)	2 (2.9)
ALT elevation, *n* (%)	4 (5.2)	1 (1.3)	11 (15.9)	1 (1.4)
Bilirubin elevation (>1 mg/dL), *n* (%)	6 (7.8)	3 (4.0)	2 (2.9)	0 (0.0)
Arterial hypertension, *n* (%)	12 (15.6)	1 (1.3)	24 (34.8)	5 (7.2)
Arterial thrombosis, *n* (%)	2 (2.6)	0 (0.0)	2 (2.9)	0 (0.0)
Venous thrombosis, *n* (%)	1 (1.3)	0 (0.0)	2 (2.9)	1 (1.4)
Epistaxis, *n* (%)	6 (7.8)	0 (0.0)	5 (7.2)	0 (0.0)
Haemorrhoidal bleeding, *n* (%)	3 (3.9)	0 (0.0)	1 (1.4)	0 (0.0)
Variceal bleeding, *n* (%)	4 (5.2)	3 (3.9)	1 (1.4)	1 (1.4)
Other GI bleeding, *n* (%)	4 (5.2)	1 (1.3)	2 (2.9)	1 (1.4)
Hypothyroidism, *n* (%)	5 (6.5)	0 (0.0)	3 (4.3)	0 (0.0)
Hyperthyroidism, *n* (%)	0 (0.0)	0 (0.0)	3 (4.3)	1 (1.4)
Proteinuria, *n* (%)	6 (7.8)	2 (2.6)	2 (2.9)	0 (0.0)
Immune-related colitis, *n* (%)	1 (1.3)	1 (1.3)	2 (2.9)	1 (1.4)
Immune-related hepatitis, *n* (%)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Immune-related pneumonia, *n* (%)	1 (1.3)	0 (0.0)	1 (1.4)	0 (0.0)

function. Although with clear advantage, the association between HCV aetiology and improved outcomes aligns with some data suggesting a differential response to immunotherapy in patients with viral-related HCC, potentially linked to distinct tumour microenvironment features and immune activation profiles [40–42].

Similarly, a better-preserved liver function, as indicated by Child-Pugh A status, is a well-established predictor of treatment tolerability and disease control in patients with cirrhosis and HCC. Notably, these associations were confirmed in the sensitivity analysis limited to patients fulfilling the IMbrave150 inclusion criteria, further reinforcing the robustness of these findings and their applicability to a real-world population.

Regarding secondary outcomes, while ORR did not differ significantly between the two groups, DCR, which encompasses not only partial and CRs but also radiological disease stability, was higher in the MDTc cohort and this association remained significant after adjustment for several confounders (online suppl. Tables S1–S2). A potential explanation lies in the observed longer duration of treatment in the MDTc group, which could have favoured the maintenance of stable disease even in the absence of overt tumour regression [43, 44, 45].

Interestingly, HCV aetiology and Child-Pugh A status were positively associated with ORR, findings that are biologically plausible, as outlined above [40, 41]. In contrast, the association between type 2 diabetes mellitus and a higher ORR appears less intuitive and is not supported by current evidence. This unexpected finding may reflect residual confounding, a chance association in a limited sample size, or potentially unmeasured factors influencing tumour response in patients with diabetes and should be interpreted cautiously.

However, data on sustained virological response (SVR) among patients with HCV-related aetiology were incomplete and therefore not included in the regression models. As SVR is known to influence prognosis in HCV-related HCC, the limited availability of this information may have affected the interpretation of the finding that HCV aetiology was associated with better outcomes. This makes it difficult to determine whether the apparent prognostic advantage reflects the supposed biological behaviour of virally induced HCC, which seems to be associated with better treatment responsiveness [41] or rather the beneficial effect of viral eradication itself, which is known to reduce the risk of hepatic decompensation [46].

For DCR, no other variable beyond MDTc management was significantly associated, supporting the hypothesis that proactive co-management of liver disease might improve the overall control of tumour progression in patients receiving systemic therapy.

As discussed in the previous sections, the higher prevalence of ascites and oesophageal varices among patients managed in the MDTc group reflects a population with more advanced liver disease and more severe portal hypertension. Theoretically, this should attenuate rather than enhance the impact of multidisciplinary management on both primary and secondary outcomes. Nevertheless, our analyses consistently demonstrated a clear centre-related advantage, attributable to a lower incidence of hepatic decompensation events and consequently longer duration of therapy in the MDTc group. The IPW analysis should therefore be interpreted with caution, as adjusting for baseline "confounding" factors related to the severity of portal hypertension may partially obscure the protective effect of multidisciplinary care in patients with more advanced disease.

To the best of our knowledge, this is the first study describing a multidisciplinary outpatient clinic where oncologists and hepatologists jointly manage patients with HCC from the initiation of systemic therapy onward. This collaborative model allows real-time, integrated decision-making and close monitoring of both cancer progression and liver-related complications, within a streamlined clinical pathway. The MDTc-based approach was associated with a significantly longer PFS and higher DCR compared to standard oncological care. Importantly, even though the difference in OS did not reach statistical significance in the total population, a clear trend favouring the MDTc group was observed, and statistical significance was achieved in subgroup analyses suggesting a clinically relevant benefit that warrants further investigation.

Despite these strengths, several limitations must be acknowledged. Firstly, the study is based on a relatively small sample size and a retrospective design, which may be affected by residual confounding despite statistical adjustment. Secondly, variability in clinical practice between centres, especially in terms of access to hepatology expertise, may have influenced patient outcomes and limited external validity. In the Italian National Health System, where access to specialist care is universal and organized on a regional basis, referral is primarily driven by clinical complexity rather than socioeconomic status or patient motivation. If a referral bias exists, it is more likely in the direction of sending more advanced patients to tertiary MDT clinics, potentially strengthening rather than weakening the observed benefits of MDTc management. Furthermore, classification and recording of liver-related events could be challenging,

leading to incomplete follow-up. The definition of clinically significant portal hypertension relied on non-invasive surrogate markers, including oesophageal or gastric varices, platelet count <150,000/mmc, and radiological ascites. Data on the presence of collateral circulation on imaging were not systematically available, and the hepatic venous pressure gradient (HVPG), the gold standard for its diagnosis, was not measured, which may have led to some misclassification of disease severity. Furthermore, although treatment duration was reported, the exact number of doses of atezolizumab and bevacizumab administered to each patient was not systematically recorded, limiting the granularity of treatment exposure assessment. Another important limitation is the absence of data on the frequency and nature of hepatology or internal medicine consultations in the standard care group, as well as the lack of information on visits with other specialists. Additionally, although the multidisciplinary model likely impacts patient-reported outcomes such as quality of life, these aspects were not formally evaluated in this study. Finally, the lack of statistically significant differences in OS should be interpreted considering the study design, sample size, and the fact that patients in MDTc centres were, on average, more clinically complex at baseline.

In conclusion, in this multicentre retrospective study, we observed that the MDTc approach significantly improved PFS and DCR in patients with HCC undergoing first-line A+B treatment, compared to standard oncological care. Although the difference in OS did not reach statistical significance, a trend favouring MDTc management was observed. This study suggests the potential benefit of a joint multidisciplinary approach, with the involvement of hepatologists/internists and oncologists in a single clinical setting, allowing for more tailored treatment strategies and better management of liver disease-related complications. If confirmed in prospective trials, this model could pave the way towards a new standard of care for patients with unresectable HCC. However, implementing the MDTc approach may present challenges in smaller centres, where resource limitations, lower availability of specialized professionals, and the need for healthcare system restructuring could hinder its adoption. While the findings of this study suggest that MDTc has the potential to significantly enhance HCC management, its broader implementation will require careful attention to both infrastructural and economic considerations.

Acknowledgments

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Statement of Ethics

This study protocol was reviewed and approved by CE, approval No. [Prog. 2524CESC]. All participants provided written informed consent before enrolment in the study.

Conflict of Interest Statement

A.D. consulting fees from MSD, Roche, AstraZeneca. Lecture fees from Eisai. A.A. consulting fees from MSD, Roche, AstraZeneca. M.C. consulting fees from MSD, Roche, Astrazeneca, Eisai. L.R. reports receiving grant/research funding from AbbVie, AstraZeneca, BeiGene, Exelixis, Fibrogen, Incyte, IPSEN, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences and Zymeworks. Consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, Bristol Myers Squibb, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, IPSEN, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology and Zymeworks. Lecture fees from AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Guerbet, Incyte, IPSEN, Roche and Servier. Travel expenses from AstraZeneca and Servier. The remaining authors have no conflicts of interest to declare.

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Author Contributions

A.D., A.A., M.V., F.C., M.E.B., C.M., F.V., G.D., L.A.N., C.S., S.L., L.F., S.T., S.R., T.P., L.R., D.S., and M.M. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Azienda Ospedaliera Universitaria Integrata di Verona.

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