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Conversion Ability of Immunotherapy in Hepatocellular Carcinoma: Insights from the International Converse Study

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Keywords
Hepatocellular carcinoma · Conversion · Immunotherapy · Surgery

Abstract
Introduction: The potential for curative conversion with immunotherapy-based systemic treatment used with noncurative intent in patients with hepatocellular carcinoma (HCC) remains debated. This study aimed to provide a reliable epidemiological snapshot of response patterns to atezolizumab plus bevacizumab (AB) therapy, with a focus on curative conversion rates. ***Methods:*** Patients with HCC undergoing first-line noncurative AB or lenvatinib (LENV, used as reference) from 2019 to 2023 were included, using centre-level aggregate data from a broad international consortium. The primary endpoint was the curative conversion rate, differentiating potential conversion (PC) – when objective response (OR) resulted in a consistent decrease in tumour burden and alpha-fetoprotein levels – from actual conversion (AC), when OR led to curative treatment. Secondary endpoints included OR, under-conversion (UC; [PC – AC]/OR) rates, and crude survival rates of AC patients. A meta-analytic approach was employed to analyse aggregate data. ***Results:*** Forty-eight international centres treating 2,379 patients with HCC with a noncurative intent (1,401 with AB and 978 with LENV) were included. A significant discrepancy was observed between PC (16% and 13% for AB and LENV, $p = 0.03$) and AC rates (3% for both AB and LENV, $p = 0.14$). UC rates remained similarly high (40% and 36% for AB and LENV, $p = 0.93$), despite differing OR rates (29% and 24% for AB and LENV, $p = 0.01$). Subgroup and meta-regression analyses did not identify any clear treatment, centre, or patient patterns that explained the high UC rate. The 3-year survival rate for the 72 patients who underwent a curative conversion after AB was 93%. ***Conclusions:*** Although patients treated with AB achieved higher OR and PC rates than those treated with LENV, AC remained similarly low, highlighting a potentially worrisome UC phenomenon in real life, also with novel immunotherapy-based combinations.

Introduction

Hepatocellular carcinoma (HCC) is a major global health issue, ranking as the sixth most common cancer diagnosed and the third leading cause of cancer-related deaths worldwide [1]. This disease shows significant variability in its clinical behaviour, biological features, and outcomes [2–4]. Patients with HCC have access to several treatment options, including liver transplantation (LT), liver resection (LR), thermal ablation (TA), intra-arterial therapies, such as trans-arterial chemoembolisation (TACE) or radioembolisation (TARE), external radiotherapy, and systemic therapies (STs) [5–7]. Recently, immune checkpoint inhibitors (ICIs) have transformed the treatment landscape of advanced HCC, offering improved overall survival [8–10] and higher objective response (OR) rates [11–13]. From this perspective, immunotherapy combinations can potentially enhance the stage migration of patients with HCC from advanced stages only suitable for noncurative options to less extensive disease stages amenable to curative treatments (LT, LR, or TA). Kudo et al. [14] introduced the term "curative conversion" to describe this specific sequential treatment strategy. The term implies that patients with HCC who achieve an exceptional response to noncurative ST may receive sequential therapies with curative intent. The initial noncurative aim of ST is key to differentiating curative conversion from downstaging, where systemic or loco-regional therapy initially aims for "potentially curative" outcomes. Potentially curative means that although a patient is initially unsuitable for curative options, downstaging intentionally seeks to decrease tumour size to make curative treatments feasible [15, 16]. The recent European Association for the Study of the Liver (EASL) guidelines emphasise that patients who achieve downstaging after loco-regional treatment and ST should be considered for LR or LT [17]. High-quality evidence indicates that patients undergoing surgery after downstaging tend to have better outcomes than other treatment modalities [18]. Furthermore, initial studies suggest that patients achieving downstaging with ICIs can safely undergo LR or LT with favourable early results [14, 19]. Unlike downstaging, however, evidence regarding "curative conversion" following noncurative ST for HCC remains limited [20]. More importantly, there may be an underestimation in clinical practice of the potential for ST to enable curative treatment in HCC patients; many patients who show a clinically relevant OR (partial or complete response) post-ST are likely not converted to curative treatments despite being potentially suitable [20], thus missing an opportunity to potentially improve their prognosis. This multicentre international study aimed to assess the capacity for novel systemic immunotherapy-based combinations to achieve curative conversion in HCC patients in real-world settings.

Methods

Study Design

This multicentre retrospective study used aggregate data from each participating centre. The patient's inclusion criteria were age ≥18 years, Child-Pugh Class A or B, first-line ST with atezolizumab plus bevacizumab (AB) or lenvatinib (LENV, taken as the reference group), unsuitability for curative options (LT, LR, or TA) or loco-regional therapies (TACE or TARE) according to local policies, no previous LT, and enrolment for treatment between January 1, 2019, and December 31, 2023. Importantly, as part of the study design, all participating centres were explicitly instructed to include only patients initiated on ST with noncurative intent. This criterion was fundamental to ensure a consistent population across centres and aligns with the conceptual framework proposed by Vitale et al. [21], which defines conversion as the achievement of eligibility for curative strategies following a treatment initiated with palliative intent. BCLC stage C or advanced B stage with contraindications to loco-regional therapy were typical indicators of noncurative treatment intention. The centre's inclusion criterion was providing separate datasets of aggregate data for patients undergoing AB or LENV as first-line ST during the study period.

The primary endpoint of this study was to assess the "real-life" conversion rate of ST used with an initial noncurative intent. Conversions were defined as "potential" when HCC reached "acceptable" (for curative intent treatment) tumour burden (without extra-hepatic disease) and alpha-fetoprotein (AFP) levels at the maximum OR (partial or complete) to therapy according to response evaluation criteria in solid tumours (RECIST) 1.1 independently from subsequent treatment decisions, while as "actual" when resulting in a subsequent curative treatment (LT, LR, or TA). Based on recent literature, we defined tumour burden score (TBS) <8 and AFP levels <1,000 ng/mL as "acceptable" to identify a potential conversion (PC) [22–25]. Secondary endpoints were as follows:

- to assess OR rates (i.e., partial and complete response rates);
- to calculate the under-conversion (UC) rate, defined as (PC – actual conversion [AC])/OR. This parameter describes the proportion of OR patients who obtain a PC that does not translate into an AC;
- to identify covariates explaining the heterogeneity of OR, PC, AC, and UC rates among centres; and
- to estimate 1-, 2-, and 3-year crude patient survival rates after AC.

Each centre had to prepare two independent databases for patients treated with AB and those treated with LENV as a reference group, and had the opportunity to participate with one or two databases. For each database, the enrolled centre provided aggregate data for all patients treated with noncurative first-line ST and subgroups of patients obtaining a curative conversion. The aggregate data concerned the following variables: centre's characteristics (centre primary speciality, number of patients discussed at a multidisciplinary tumour board, presence of a transplant program, presence of an expert hepatobiliary surgeon or radiologist); patients' characteristics (number of females, number of patients older than 70 years, number of patients with diabetes, number of patients with ECOG performance status [PS] > 0); liver disease aetiology (number of patients with history of alcohol abuse, hepatitis C virus positive, hepatitis B virus [HBV] positive, or metabolic-associated steatotic liver disease [MASLD] diagnosis); liver function (number of patients with clinically relevant portal hypertension, albumin bilirubin [ALBI] grade >1, Child-Pugh class B); tumour characteristics (TBS > 8, intrahepatic vascular invasion, extra-hepatic vascular invasion, metastases, and AFP ≥1,000 ng/mL); previous treatments (number of patients undergoing previous LR, TA, TACE, or TARE); and response to treatment (number of patients obtaining stable disease, partial response, complete response, AC, or PC at maximum radiological response according to RECIST 1.1).

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and complied with good clinical practices and applicable laws and regulations. Since this study was based on the retrospective survey method and involved only aggregate data, submitting the protocol to Ethical Review Boards was deemed optional.

Statistical Analysis

Centre-related values are expressed as frequencies (%) and compared using the two-tailed Pearson's chi-squared or Fisher exact test. Conversely, a meta-analytic approach was used to analyse the patient-related aggregate data recorded in each dataset. This means that overall event frequency or effect size was computed for each covariate as a weighted average of centre-specific frequencies or effect sizes, with larger centres having larger weights. A random forest model was preferred to limit the impact of larger centres and better account for centre heterogeneity. For meta-analysis estimating a single proportion (prevalence), the Freeman-Tukey-transformed proportions were used.

To compare the covariates of different treatment groups (e.g., AB vs. LENV), the risk ratio (and its standard error) for binary outcomes was calculated. The heterogeneity between centres for each covariate was assessed using the I^2 test. Meta-regression methods and subgroup analyses were used to identify covariates (i.e., moderators) explaining the inter-centre heterogeneity of OR, PC, AC, and UC rates. Given the small number of AC cases per centre, the baseline characteristics of these patients were described using crude rates. Based on the number of converted patients dead and alive at different time intervals, 1-, 2-, and 3-year crude survival rates were also calculated. All statistical calculations were performed using STATA Stata/SE 18.0 (1985–2023).

Results

Characteristics of Included Centres and Patients

Table 1 depicts the main characteristics of the included centres and patients. We included 35 Italian centres (Italian database) that treated 1,364 patients (702 with AB and 662 with LENV) and 13 non-Italian centres (non-Italian database) that treated 1,015 patients (699 with AB and 316 with LENV) during the study period: 70% of centres contributing to the AB database were Italian and treated 50% of AB patients, while 73% of centres contributing to the LENV database were Italian and treated 67% of LENV patients. Of the 48 participating centres, 45 (94%) contributed to the AB database (1,401 patients) and 40 (83%) to the LENV database (978 patients). Moreover, 39 (81%) contributed to both the AB and LENV databases, while 10 (21%) contributed only to one database (8 to the AB and 2 to the LENV database). Most non-Italian patients treated with AB (628/699, 90%) and LENV (294/316, 93%) were treated in Eastern centres (6 from Japan, 1 from India, and 1 from South Korea). The remaining five Western centres were one from the UK, one from Spain, one from Portugal, and two from the USA. AB and LENV treatments were balanced between oncologic and hepatologic centres. Most of the centres contributing to the AB (73%) and LENV (65%) databases decided on each patient's first-line ST in the context of a multidisciplinary tumour board. Almost all participating centres had an expert hepatobiliary surgeon and interventional radiologist, while 60% of centres prescribing AB and 65% of centres prescribing LENV had an LT program. Patient characteristics in Tables 1 and 2 were described as pooled meta-analytic rates. Patients treated with LENV had more frequent clinically relevant portal hypertension or Child-Pugh class B cirrhosis than patients treated with AB (Table 1). Conversely, patients treated with AB had more frequent intra- and extra-hepatic VI and metastases but less frequent previous treatments (LR, TA, or TACE) than patients treated with LENV (Table 1). Table 2 compares the main characteristics of Italian centres and patients with those of non-Italian centres and patients. The mean number of patients included in each Italian centre was smaller than that of non-Italian centres. As expected, HBV-positive patients were more frequent in non-Italian centres, while hepatitis C virus and MASLD aetiologies were more frequent in Italy. Patients with ALBI grade >1 and Child Class B were more frequent in non-Italian centres, while ECOG PS >0 was more frequent in Italian centres. Among previous treatments, non-Italian centres used TACE more frequently, while Italian centres used TARE more than non-Italian centres. In online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000547792), baseline characteristics of patients achieving AC are described as crude rates. For a descriptive purpose only (a formal statistical comparison with the whole population is not feasible), AC patients, more frequently than the entire population, come from centres with an LT program and a multidisciplinary tumour board discussing each patient, had less than 70 years or ECOG PS 0, and no VI or metastases. Patients treated with AB were converted to LT in 33% of cases, LR in 47%, and TA in 20%.

Primary Endpoint

Seventy-two ACs and 292 PCs were recorded among the 1,401 patients treated with AB, with crude AC and PC rates of 5% and 21%, respectively. Likewise, 43 ACs and 154 PCs were recorded among the 978 patients treated with LENV, for crude AC and PC rates of 4% and 16%, respectively.

The pooled (meta-analytic approach) AC and PC rates are described in Table 1. AC rates were similarly low (Table 1) for both AB and LENV ($p = 0.14$). A notable discrepancy was observed between the AC (3% for both regimens) and PC rates (16% for AB and 13% for LENV, $p = 0.03$, Table 1).

Secondary Endpoints

High OR rates were observed in both the AB (29%) and LENV (24%) groups ($p = 0.01$, Table 1). The proportions of patients with OR obtaining a PC that did not result in an AC (UC rate) were relatively high: 40% (95% CI 28–52) and 36% (95% CI 25–49) with AB and LENV, respectively ($p = 0.93$).

Table 1. Characteristics of the international centres (*n* = 48) and patients (*n* = 2,379)

Variables	AB (45 centres, 1,401 patients)	LENV (40 centres, 978 patients)	*p* value	
Centre's characteristics				
Centre/patients geographical location			0.55	
Italy – centres, *n* (%), patients, *n* (%)	32 (71), 702 (50)	30 (75), 662 (68)		
West – centres, *n* (%), patients, *n* (%)	5 (11), 71 (5)	2 (5), 22 (2)		
East – centres, *n* (%), patients, *n* (%)	8 (18), 628 (45)	8 (20), 294 (30)		
Patients/centre, *n*, mean±SD	31±49	24±18	0.42	
High centre volume[1], *n* (%)	13 (29)	14 (35)	0.64	
Centre speciality, *n* (%)			0.39	
Hepatology	20 (44)	22 (55)		
Oncology	25 (56)	18 (45)		
TB for each patient, *n* (%)	33 (73)	26 (65)	0.36	
LT program, *n* (%)	27 (60)	26 (65)	0.67	
Expert HB surgeon, *n* (%)	41 (91)	38 (95)	0.68	
Expert radiologist, *n* (%)	45 (100)	40 (100)	–	
	Frequence [CI 95%]	Frequence [CI 95%]	*p* value	RR [IC 95%]
Patients' characteristics				
Females	0.19 (0.16–0.22)	0.18 (0.16–0.21)	0.30	1.11 (0.91–1.36)
Age >70 years	0.48 (0.43–0.53)	0.52 (0.46–0–58)	0.40	0.96 (0.87–1.06)
Diabetes	0.30 (0.26–0.34)	0.31 (0.26–0.35)	0.97	1.00 (0.87–1.15)
Alcohol abuse	0.27 (0.22–0.31)	0.26 (0.21–0.32)	0.82	1.02 (0.88–1.17)
HBV positive	0.18 (0.13–0.22)	0.17 (0.13–0.22)	0.51	1.06 (0.89–1.27)
HCV positive	0.40 (0.35–0.46)	0.35 (0.29–0.41)	0.99	1.00 (0.86–1.16)
MASLD	0.22 (0.17–0.27)	0.22 (0.17–0.27)	0.65	1.04 (0.88–1.22)
CRPH	0.28 (0.23–0.33)	0.31 (0.24–0.38)	0.19	0.91 (0.78–1.05)
ALBI grade >1	0.54 (0.45–0.64)	0.51 (0.42–0.61)	0.69	0.98 (0.90–1.07)
Child-Pugh class B	0.07 (0.04–0.10)	0.10 (0.07–0.15)	0.18	0.80 (0.58–1.11)
PST >0	0.35 (0.26–0.44)	0.37 (0.29–0.45)	0.67	1.05 (0.83–1.33)
TBS ≥8	0.58 (0.48–0.67)	0.46 (0.36–0.56)	0.44	1.04 (0.95–1.14)
Intra-hepatic VI	**0.32 (0.27–0.36)**	**0.22 (0.17–0.27)**	**0.01**	**1.27 (1.06–1.51)**
Extra-hepatic VI	**0.14 (0.10–0.19)**	**0.10 (0.07–0.14)**	**0.05**	**1.28 (1.00–1.65)**
Metastases	0.36 (0.30–0.42)	0.32 (0.27–0.37)	0.06	1.13 (0.99–1.28)
AFP ≥1,000 (ng/mL)	0.25 (0.22–0.28)	0.23 (0.19–0.28)	0.64	1.04 (0.89–1.21)
Previous resection	0.24 (0.20–0.29)	0.22 (0.19, 0.27)	0.16	1.16 (0.95–1.42)
Previous ablation	**0.17 (0.13–0.21)**	**0.26 (0.21–0.31)**	**0.02**	**0.82 (0.69–0.96)**
Previous TACE	**0.26 (0.21–0.31)**	**0.38 (0.30–0.45)**	**<0.01**	**0.75 (0.65–0.87)**
Previous TARE	0.04 (0.02–0.08)	0.05 (0.02–0.08)	0.65	1.08 (0.78–1.49)
Response to therapy				
Stable disease	0.42 (0.37–0.46)	0.43 (0.38–0.48)	0.39	0.95 (0.86–1.06)
Partial response	0.23 (0.19–0.27)	0.20 (0.16–0.24)	0.07	1.17 (0.99–1.38)
Complete response	0.03 (0.02–0.05)	0.03 (0.01–0.04)	0.19	1.32 (0.87–2.00)
OR	**0.29 (0.24–0.34)**	**0.24 (0.19–0.28)**	**0.01**	**1.27 (1.06–1.52)**
AC	0.03 (0.01–0.05)	0.03 (0.02–0.04)	0.14	1.33 (0.91–1.95)
PC	**0.16 (0.13–0.20)**	**0.13 (0.10–0.16)**	**0.03**	**1.30 (1.03–1.64)**
UC	0.40 (0.28–0.52)	0.36 (0.25–0.49)	0.93	1.01 (0.84–1.21)

Bolded values are statistically significant values. *n*, number; SD, standard deviation; TB, tumour board; LT, liver transplantation; CI, confidence interval; RR, relative risk; HB, hepatobiliary; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic-associated steatotic liver disease; CRPH, clinically relevant portal hypertension; ALBI, albumin bilirubin; PST, performance status; TBS, tumour burden score; VI, vascular invasion; AFP, alpha-fetoprotein; TACE, trans-arterial chemoembolization; TARE, trans-arterial radioembolization. [1]>30 patients undergoing AB or >24 undergoing LENV in the study period.

Table 2. Subgroup analysis of the included centres (n = 48) and patients (n = 2,379)

Variables	Italy		Non-Italian centres	
	AB (32 centres, 702 patients)	LENV (30 centres, 662 patients)	AB (13 centres, 699 patients)	LENV (10 centres, 316 patients)
Centre's characteristics				
Patients/centre, *n* mean±SD	22±17***	22±14***	54±82	32±24
High centre volume[1], *n* (%)	8 (25)***	9 (30)***	5 (38)	5 (50)
Oncologic centre	18 (56)	14 (47)	7 (54)	4 (40)
TB for each patient, *n* (%)	23 (72)	18 (60)	10 (77)	8 (80)
LT program, *n* (%)	19 (59)	20 (67)	8 (62)	6 (60)
Expert HB surgeon, *n* (%)	28 (88)	28 (93)	13 (100)	10 (100)
Expert radiologists, *n* (%)	32 (100)	30 (100)	13 (100)	10 (100)
	Frequence [CI 95%]	Frequence [CI 95%]	Frequence [CI 95%]	Frequence [CI 95%]
Patients' characteristics				
Females	0.19 (0.16–0.22)	0.19 (0.16–0.22)	0.20 (0.13–0.27)	0.17 (0.13–0.22)
Age >70 years	0.47 (0.43–0.51)**	0.53 (0.46–0–60)	0.48 (0.36–0.59)	0.50 (0.39–0.61)
Diabetes	0.28 (0.25–0.32)	0.29 (0.25–0.33)	0.33 (0.24–0.43)	0.35 (0.24–0.47)
Alcohol abuse	0.26 (0.21–0.31)	0.23 (0.18–0.28)***	0.29 (0.19–0.39)	0.35 (0.23–0.48)
HBV positive	0.15 (0.12–0.18)***	0.14 (0.10–0.18)***	0.23 (0.13–0.35)	0.25 (0.13–0.40)
HCV positive	0.46 (0.41–0.51)**,***	0.37 (0.30–0.45)***	0.29 (0.20–0.39)	0.29 (0.21–0.38)
MASLD	0.23 (0.17–0.29)	0.25 (0.19–0.31)***	0.19 (0.13–0.26)	0.15 (0.06–0.26)
CRPH	0.26 (0.20–0.33)	0.29 (0.21–0.38)	0.31 (0.23–0.40)	0.37 (0.23–0.52)
ALBI grade >1	0.48 (0.36–0.61)***	0.46 (0.34–0.59)****	0.66 (0.52–0.79)	0.65 (0.54–0.75)
Child-Pugh class B	0.06 (0.03–0.11)	0.08 (0.04–0.13)***	0.08 (0.03–0.15)*	0.17 (0.09–0.26)
PS >0	0.40 (0.29–0.52)*,****	0.38 (0.28–0.47)	0.23 (0.12–0.37)	0.35 (0.19–0.52)
TBS ≥8	0.53 (0.41–0.65)	0.41 (0.30–0.53)***	0.64 (0.50–0.76)	0.57 (0.39–0.75)
Intra-hepatic VI	0.32 (0.27–0.38)**	0.23 (0.17–0.30)	0.31 (0.22–0.40)**	0.18 (0.10–0.28)
Extra-hepatic VI	0.14 (0.08–0.21)**	0.11 (0.07–0.16)	0.15 (0.09–0.21)*	0.09 (0.03–0.15)
Metastases	0.38 (0.31–0.46)*	0.33 (0.28–0.39)	0.32 (0.23–0.41)	0.28 (0.19–0.38)
AFP ≥1,000 (ng/mL)	0.24 (0.20–0.27)	0.23 (0.18–0.29)	0.26 (0.21–0.31)	0.23 (0.14–0.32)
Previous resection	0.26 (0.22–0.30)	0.23 (0.18,0.29)	0.22 (0.13–0.31)	0.20 (0.13–0.27)
Previous ablation	0.18 (0.13–0.24)**	0.27 (0.22–0.33)	0.14 (0.07–0.22)	0.22 (0.09–0.38)
Previous TACE	0.23 (0.19–0.27)**,***	0.32 (0.26–0.37)	0.33 (0.20–0.46)**	0.54 (0.35–0.73)
Previous TARE	0.07 (0.03–0.11)****	0.08 (0.04–0.12)****	0.01 (0.00–0.04)	0.00 (0.00–0.01)
Treatment response				
Stable disease	0.45 (0.39–0.51)***	0.43 (0.37–0.49)	0.37 (0.31–0.43)*	0.44 (0.36–0.53)
Partial response	0.22 (0.17–0.27)	0.18 (0.13–0.24)***	0.26 (0.22–0.29)	0.23 (0.19–0.28)
Complete response	0.03 (0.01–0.05)	0.03 (0.01–0.05)	0.04 (0.02–0.06)	0.03 (0.01–0.05)
OR	0.28 (0.22–0.36)*	0.22 (0.16–0.28)***	0.31 (0.27–0.36)	0.27 (0.22–0.32)
AC	0.02 (0.01–0.04)	0.02 (0.01–0.04)***	0.05 (0.01–0.9)	0.04 (0.02–0.06)
PC	0.15 (0.10–0.20)	0.12 (0.09–0.16)	0.19 (0.14–0.26)	0.16 (0.11–0.21)
UC	0.41 (0.29–0.54)	0.37 (0.22–0.52)	0.37 (0.15–0.61)	0.38 (0.21–0.57)

n, number; SD, standard deviation; TB, tumour board; LT, liver transplantation; CI, confidence interval; RR, relative risk; HB, hepatobiliary; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic associated steatotic liver disease; CRPH, clinically relevant portal hypertension; ALBI, albumin bilirubin; PS, performance status; TBS, tumour burden score; VI, vascular invasion; AFP, alpha-fetoprotein; TACE, trans-arterial chemoembolisation; TARE, trans-arterial radioembolisation. **$p < 0.05$ or *$p < 0.20$ in comparing AB and LENV in Italy or international centres. ****$p < 0.05$ or ***$p < 0.20$ in comparing Italy and International centres in the same treatment group (AB or LENV). [1]>30 patients undergoing AB or >24 undergoing LENV in the study period.

Subgroup analyses also confirmed these gaps between OR, AC, and PC rates (Table 2). The frequency of partial responses, complete responses, and ACs were higher ($p < 0.2$) in patients treated with AB than those treated with LENV (Table 1).

The OR and PC rates were significantly higher ($p = 0.01$ and $p = 0.03$, respectively) in patients treated with AB than those treated with LENV (Table 1). Conversely, the UC rate was similar in the AB and LENV groups ($p = 0.93$, Table 1).

These differences between patients treated with AB and LENV were confirmed within the Italian and non-Italian subgroups, although with more uncertainty ($p < 0.2$ only for the difference in ORs in Italian patients, Table 2). We also observed higher rates in PRs, ORs, ACs, and PCs in non-Italian than in Italian centres, particularly in the LENV group (Table 2).

Forest plots showed a high heterogeneity between different centres in AB and LENV OR, AC, PC, and UC rates (shown in Fig. 1, 2). This heterogeneity was also confirmed when Italian and non-Italian centres were considered separately (shown in online suppl. Fig. 1, 2). We, therefore, performed univariable (online suppl. Table 2) and multivariable meta-regressions (online suppl. Table 3) to identify variables explaining the heterogeneity in OR, AC, and PC rates among different centres. The presence of an LT program and the proportion of patients >70 years old or with metastases were significantly related to AC rates after AB treatment (online suppl. Table 3). In contrast, the proportion of patients with previous TA and metastases significantly influenced the heterogeneity in ACs after LENV treatment among different centres (online suppl. Table 3).

The proportion of patients with Child-Pugh B class cirrhosis or a TBS ≥8 was significantly related to PC heterogeneity after AB treatment. In contrast, the proportion of patients with extra-hepatic VI or AFP ≥1,000 ng/mL significantly influenced PC heterogeneity after LENV treatment among different centres.

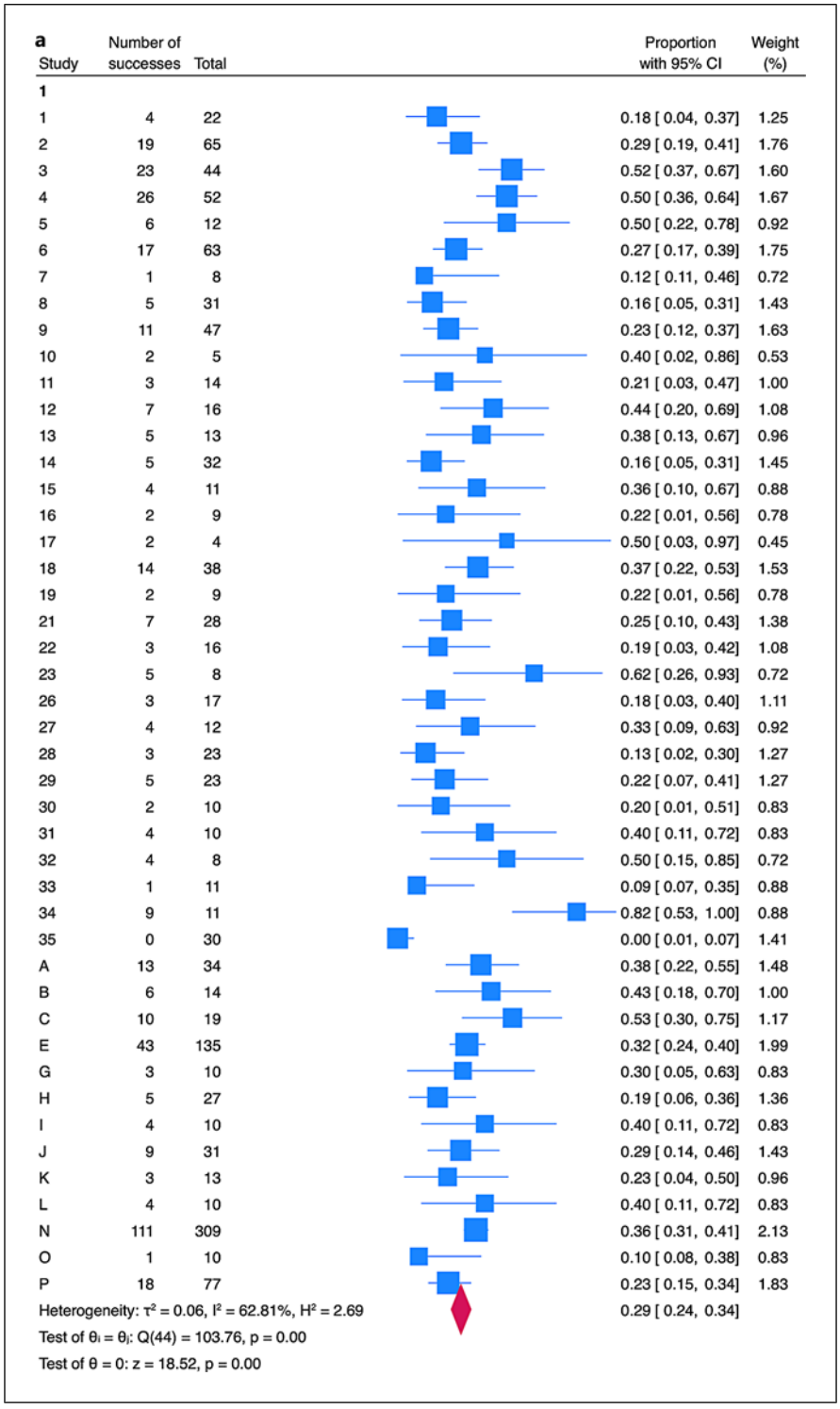
The presence of an LT program was a potential centre-related characteristic that decreased the risk of UC in both the AB and LENV groups (Table 3). The risk of UC was also influenced by the frequency of diabetes and ALBI >1 in patients treated with AB and by the centre volume, the frequency of HBV positivity, and previous ablation in patients treated with LENV (Table 3). Interestingly, 18% of patients treated with AB and 16% treated with LENV were converted to curative therapy after a stable disease to first-line ST (online suppl. Table 1). One-, 2-, and 3-year crude survival rates after AC were 100%, 93%, and 93% for patients treated with AB and 95%, 88%, and 88% for patients treated with LENV (online suppl. Table 1).

Discussion

This study represents one of the most extensive investigations conducted on noncurative first-line immunotherapy-based ST [26] and, to our knowledge, the most comprehensive epidemiological study on curative conversion [20]. The first result of this study is to provide epidemiological evidence about the actual curative conversion rate in patients with HCC undergoing first-line AB (or LENV as reference) with noncurative intent. The available evidence about the conversion rate is, in fact, unclear and largely heterogeneous. In a recent study by Zhang et al. [27], only 1 out of 224 patients undergoing noncurative ST had a curative conversion to LR. Conversely, in a study by Zhu et al. [28], the curative conversion rate after tyrosine kinase inhibitors (TKI) plus anti-PD-1 antibodies was 24%. In a recent meta-analysis by Xu et al. [20], the pooled curative conversion rates (to LR only) were 8% in the TKI group, 28% in the TKI + PD-1 group, and 5% in the AB group, respectively. In the study by Tomonari et al. [29], of the 244 enrolled patients undergoing first-line ST, 12 (4.9%) underwent conversion therapy, 6 out of 131 (4.6%) were treated with LEN, and 6 out of 113 (5.3%) were treated with AB. However, these studies are biased by small sample sizes and low-quality study designs. The AC rate observed in our study was 3%, lower than the smaller studies mentioned above. However, the AC rate became 5% for AB and 4% for LENV in non-Italian (almost exclusively Eastern) centres (shown in Table 2 and online suppl. Fig. 1, 2). These AC rates were based on meta-analytic pooled results. Therefore, the considerable heterogeneity in AC rates among our participating centres (shown in Fig. 1, 2b) could partially explain the heterogeneity in AC rates found in the abovementioned literature.

A further noteworthy aspect of this study is integrating the PC endpoint, which was conceptualised as an objective surrogate marker for curative conversion, to mitigate inter-centre heterogeneity. Surprisingly, we found a considerable discrepancy between PC and AC rates (16% vs. 3% for AB and 13% vs. 3% for LENV, respectively).

This discrepancy may indicate that several patients who achieved significant OR after noncurative ST and became potentially eligible for surgery or TA were not offered curative treatments, possibly due to several factors not captured by the present analysis or possibly



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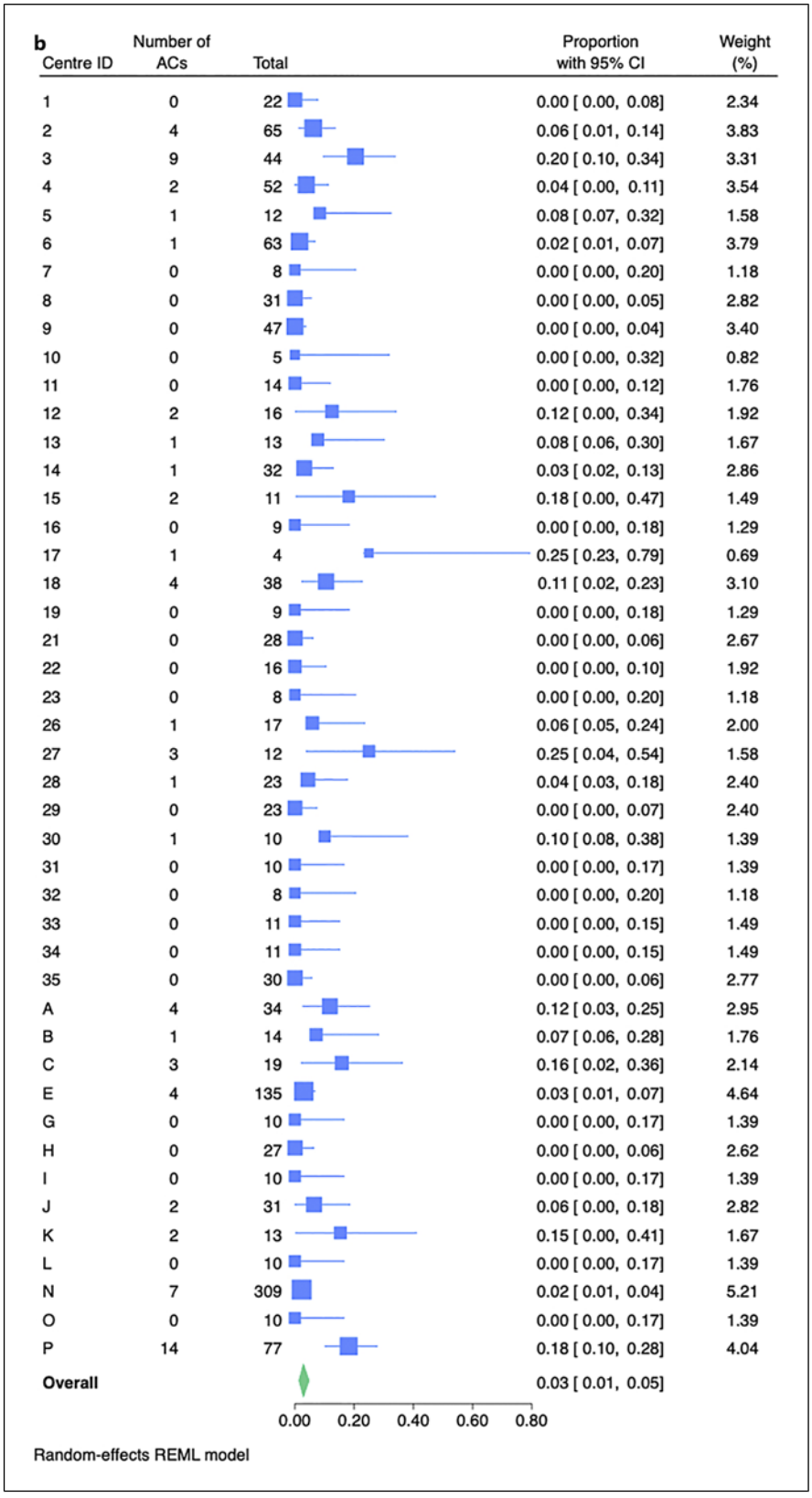

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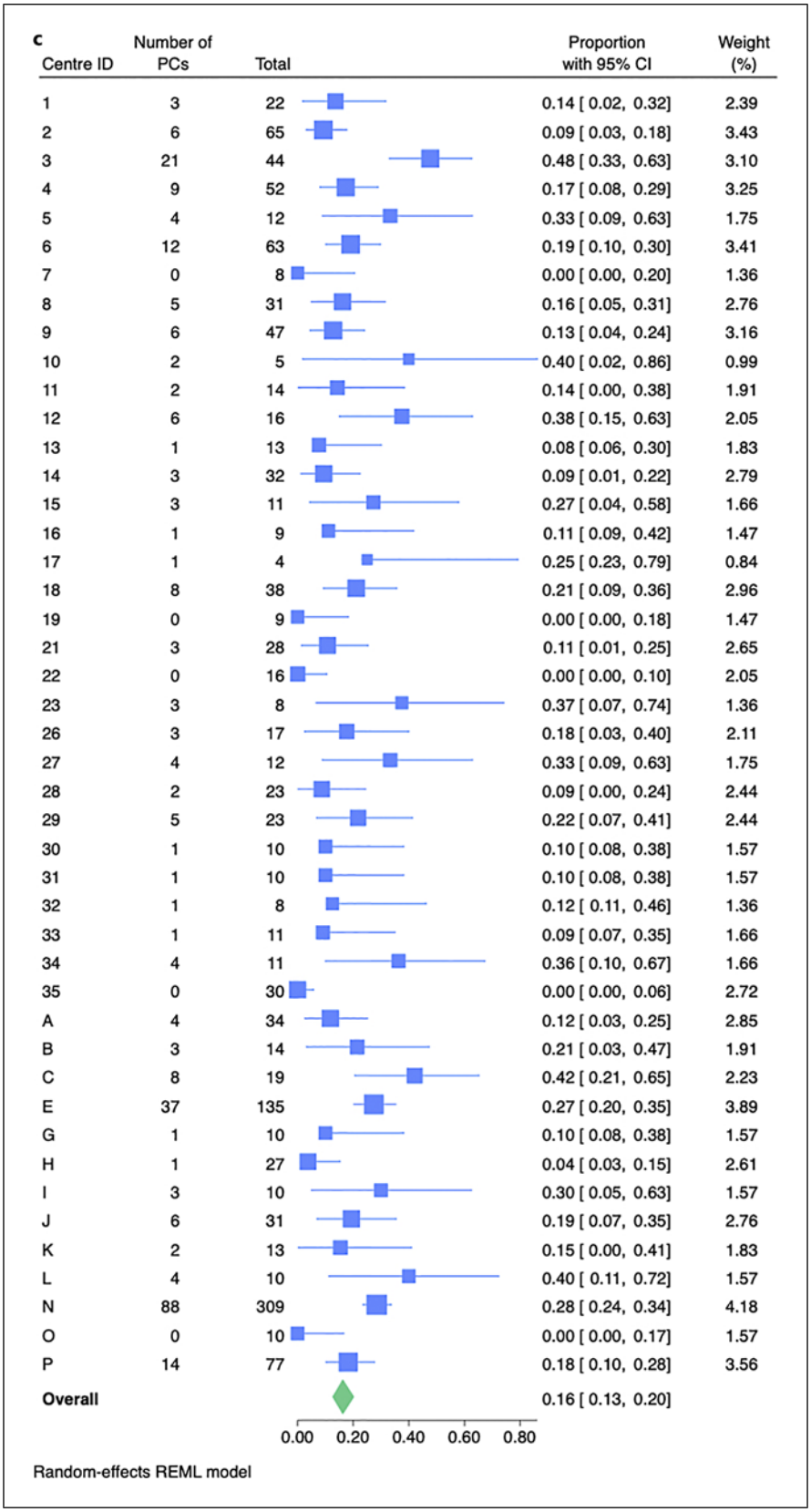

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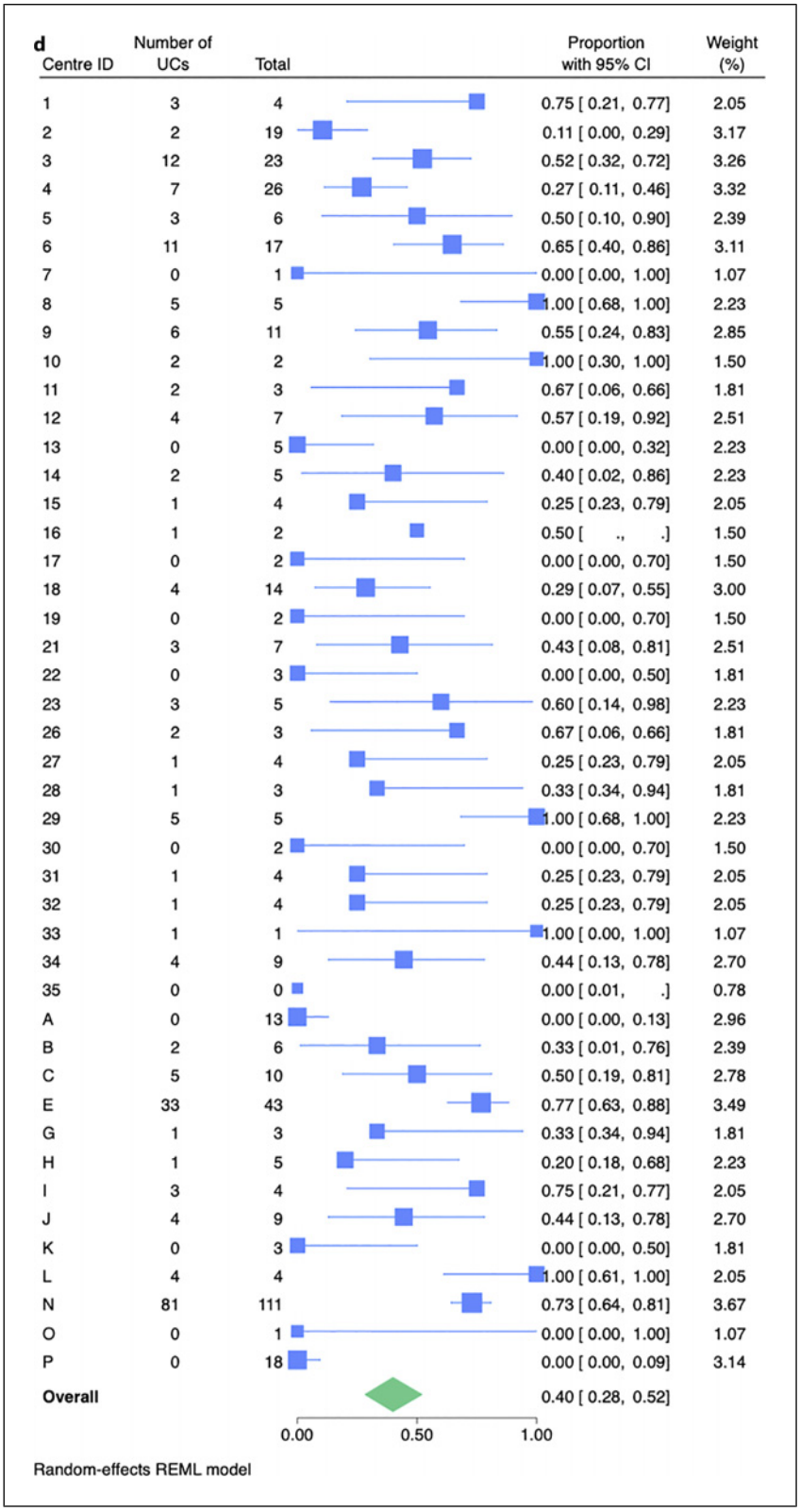
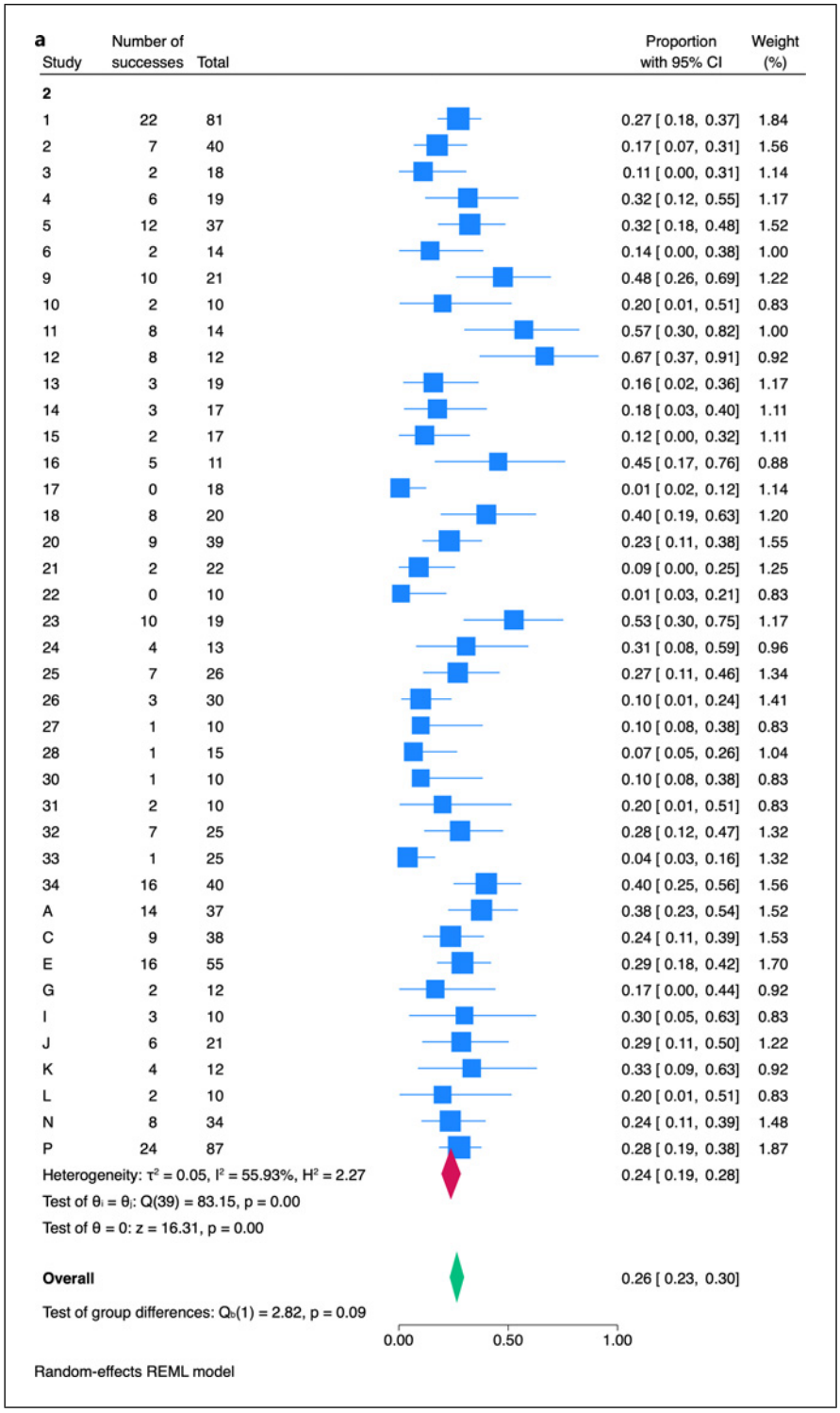


Fig. 1. Forest plots of the proportions of ORs (**a**), ACs (**b**), PCs (**c**), and UCs (**d**) in AB-treated patients (n = 1,401) of the included international centres (n = 45). OR, objective response; AC, actual conversion; PC, potential conversion; UC, under-conversion.



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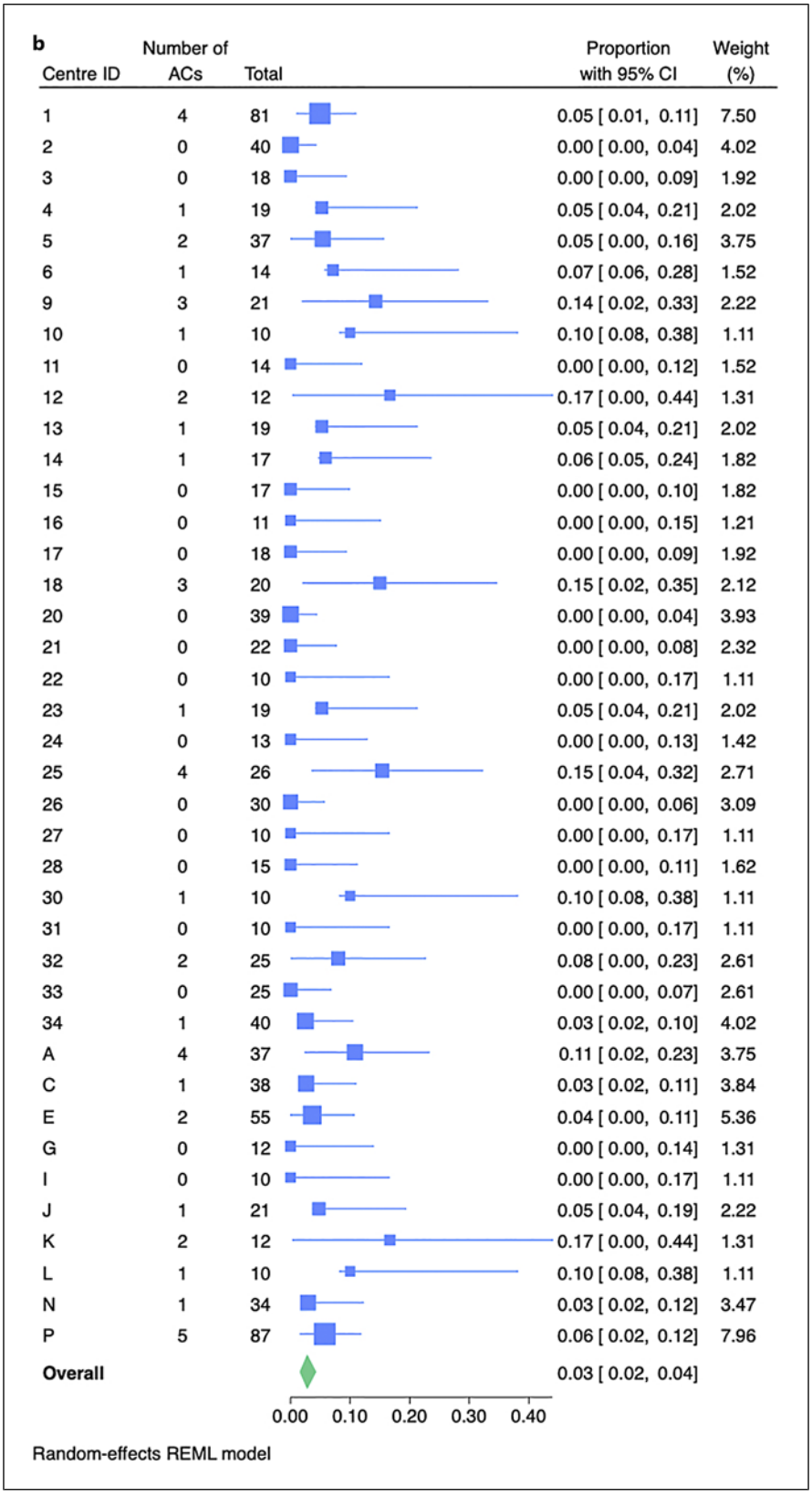

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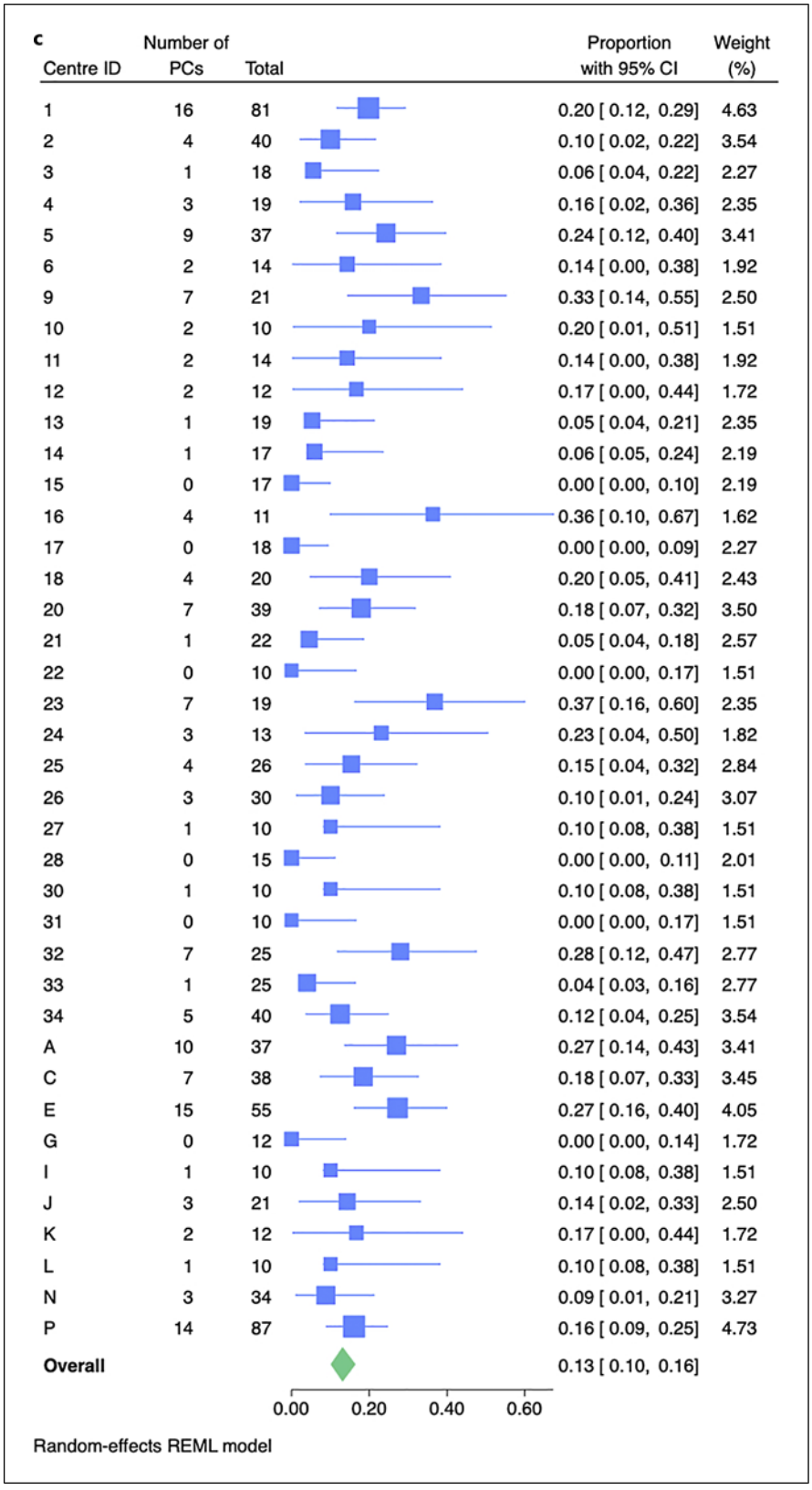

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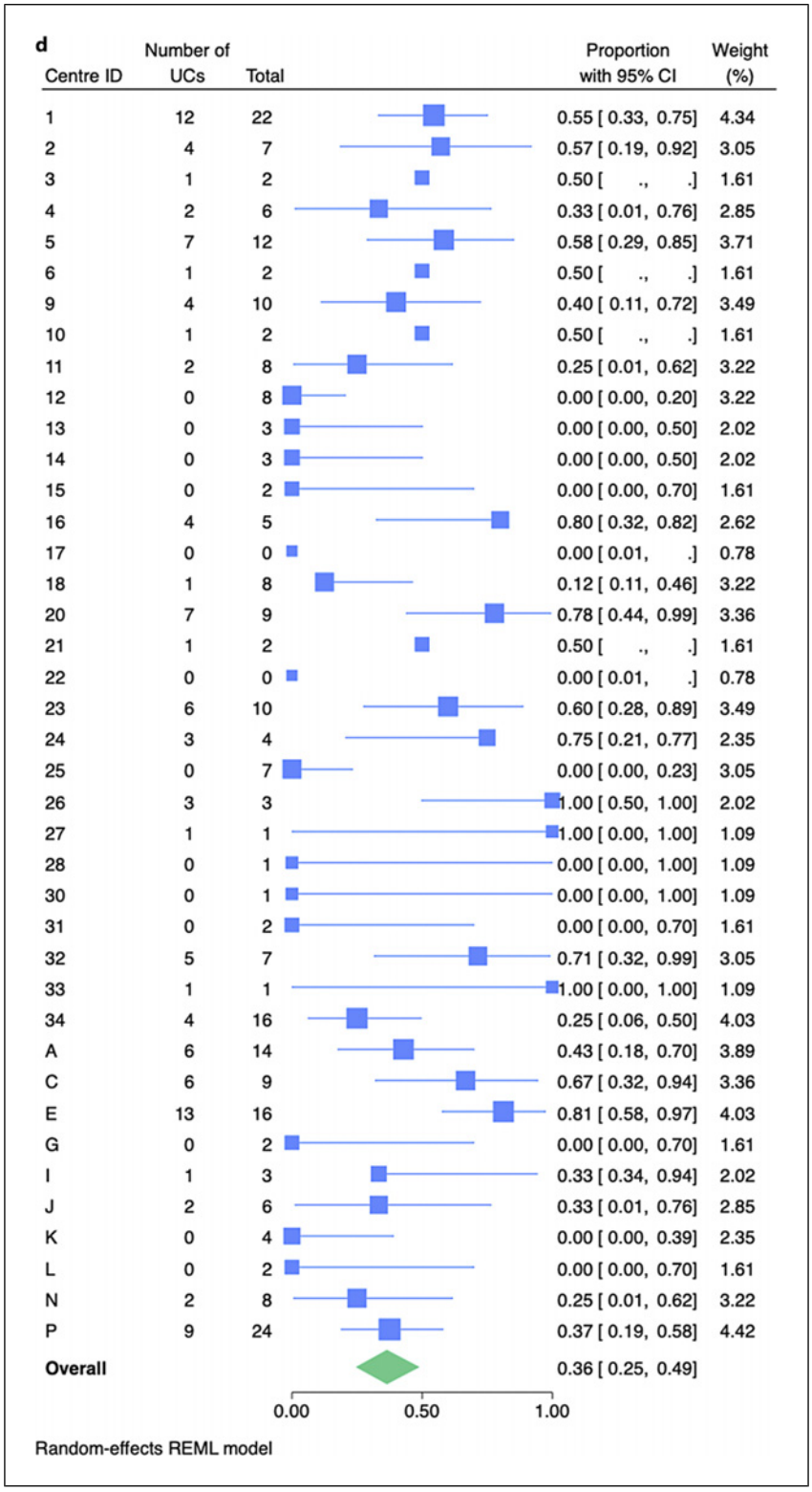

Fig. 2. Forest plots of the proportions of ORs (**a**), ACs (**b**), PCs (**c**), and UCs (**d**) in LENV-treated patients (n = 978) of the included international centres (n = 40). OR, objective response; AC, actual conversion; PC, potential conversion; UC, under-conversion.

Table 3. Meta-regression of the included international centres ($n = 48$) and patients ($n = 2,379$): impact of centre- and patient-related variables on UC rates

Variables	AB coefficient, p value	LENV coefficient, p value
Centre's characteristics		
Italian centre	0.073, 0.73	0.012, 0.95
High centre volume[1]	−0.016, 0.94	0.440, 0.01
Oncologic centre	0.214, 0.27	−0.152, 0.43
Discussion of each patient at TB	−0.158, 0.45	0.122, 0.53
Presence of a LT program	−0.334, 0.09	−0.304, 0.10
Presence of an expert HB surgeon	0.022, 0.96	−0.288, 0.59
Patients' frequencies		
Females	0.503, 0.54	−1.544, 0.19
Age >70 years	−0.608, 0.32	0.797, 0.14
Diabetes	1.299, 0.06	0.361, 0.60
Alcohol abuse	−0.461, 0.45	−0.311, 0.59
HBV positive	−0.530, 0.45	−1.314, 0.04
HCV positive	−0.066, 0.91	−0.248, 0.65
MASLD	−0.166, 0.79	0.644, 0.26
CRPH	0.303, 0.61	−0.368, 0.43
ALBI grade >1	0.549, 0.16	−0.133, 0.74
Child-Pugh class B	−0.149, 0.84	−0.054, 0.94
PS >0	0.439, 0.23	−0.651, 0.12
TBS ≥8	−0.578, 0.15	−0.169, 0.63
Intra-hepatic VI	−0.774, 0.21	−0.794, 0.22
Extra-hepatic VI	0.454, 0.42	−0.855, 0.33
Metastases	0.257, 0.66	0.750, 0.25
AFP ≥1,000, ng/mL	0.120, 0.87	0.115, 0.87
Previous resection	−0.225, 0.76	0.618, 0.36
Previous ablation	−0.651, 0.35	−0.922, 0.09
Previous TACE	0.199, 0.74	0.485, 0.28
Previous TARE	0.246, 0.77	1.089, 0.28

HCV, hepatitis B virus; HBV, hepatitis B virus; MASLD, metabolic associated steatotic liver disease; PS, performance status; VI, vascular invasion; AFP, alpha-fetoprotein; TACE, trans-arterial chemoembolization; TARE, trans-arterial radio-embolization; CRPH, clinically relevant portal hypertension. [1]>30 patients undergoing AB or >24 undergoing LENV in the study period.

due to a preference for continuing ST. We introduced the composite endpoint UC to analyse this phenomenon better, suggesting that there is a potential risk of UC: although potentially eligible, about 40% of patients obtaining an OR after AB treatment were not offered a treatment with curative intent. The only two relevant moderators of UC in the meta-regression analysis (Table 3) after AB therapy were the presence of an LT program and the proportion of patients with diabetes. Interestingly, the presence of an LT program was also crucial in influencing the heterogeneity of AC response in patients treated with AB (online suppl. Table 3). Although none of the patients were managed primarily by surgeons, we hypothesise that the involvement of HPB or transplant surgeons in multidisciplinary tumour boards might have promoted a re-evaluation of treatment options. These findings support the clinical importance of the multiparametric discussion (including patient comorbidities) of each patient with HCC by an expert multidisciplinary tumour board (including all the specialities involved in HCC management) [30]. This result is also significant because a non-negligible proportion of centres prescribing AB (28%) did not discuss all patients at a multidisciplinary tumour board. In comparison, 41% did not have an LT program (Table 1).

Unfortunately, this study cannot provide any insight into the prognostic impact of these high UC rates. On one side, recent evidence described optimal long-term clinical outcomes for patients with durable partial [31] or complete response [32] after immunotherapy combinations, thus supporting a continuation of ST. In the recent study by Scheiner et al. [32], only 13 out of 174

patients (7%) who obtained complete responses after immunotherapy combinations underwent curative conversion. Despite this low AC rate, these patients had very high long-term survival. Similar evidence derives from the long-term survival analysis of patients enrolled in the HIMALAYA phase 3 study, showing high 5-year OS figures for patients treated with STRIDE (durvalumab plus tremelimumab), up to 63.4% for patients reaching CR or PR >50%, and 28.7% for patients with disease control [33].

On the other side, the high-quality evidence supporting the concept of downstaging now endorsed by the EASL guidelines [17, 18] suggests that this UC phenomenon (i.e., the high discrepancy between PC and AC rates) could have a negative prognostic impact on patients' outcomes. Although only with a descriptive and preliminary value, patients converted to curative therapies after AB in this study reached a considerable 93% 3-year survival (online suppl. Table 1). This result is similar to a recent study in which patients obtaining clinical or pathological complete responses after curative conversion had a 100% survival rate after a median follow-up of 21 months [14]. Moreover, curative conversion has the intrinsic advantage of potentially reaching a tumour-free and drug-free status [14]. However, more solid studies are needed to understand the potential prognostic improvement related to a curative conversion strategy. Ideally, to demonstrate the advantage of a change of plan (i.e., intent to cure therapy) after a response to ST, we should design a randomised controlled trial (RCT) in which patients who obtain a response are randomised to the experimental arm to change therapeutic strategy, with more radical intent, or to the control arm to continue ST. The design of this type of RCT raises unavoidable ethical considerations that are not easily resolved. While waiting for data from similar RCTs, a clinical practice study controlled with historical cohorts and matched with appropriate propensity analyses could partially address these shortcomings [34, 35], following the "emulated trials" design.

Another relevant result of this study is that it confirmed in a real-life setting almost the same OR rates (29% and 24%, respectively) obtained from AB and LENV first-line ST in the setting of pivotal clinical RCTs [7–9]. Interestingly, it also suggested a potential superiority of AB over LENV treatment in terms of OR rates (29% versus 24%, $p = 0.01$, Table 1). This difference was observed, although patients treated with AB had more aggressive features in terms of intra- and extra-hepatic VI and metastasis frequencies (Table 1). Moreover, it was particularly evident in Italian centres but less critical in non-Italian ones (Table 2).

Furthermore, bridging the discrepancy between PC and AC while accounting for the observed UC rate necessitates a comprehensive assessment of clinical decompensation risk during longitudinal follow-up. This critical factor may significantly impact treatment continuation, whether systemic or curative, and survival outcomes [36, 37]. This understanding is crucial for developing precise patient selection criteria and improving long-term therapeutic strategies.

The marked inter-centre heterogeneity observed following OR achievement represents a distinctive feature of this study. Identifying and explaining this heterogeneity poses significant challenges due to multiple potential contributing factors: (1) variations in post-response management protocols across participating centres, (2) differences in local clinical expertise and available resources, and (3) centre-specific patient populations with distinct demographic and clinical characteristics. Notably, only in recent years have we observed such clinically significant response rates to ST; this relatively new phenomenon may partially explain the behavioural differences among centres without prospective evidence (shown in Fig. 1). Understanding these variations is crucial as they may influence long-term outcomes and inform future standardisation efforts in multicentre prospective trials.

This study has several significant limitations. Although it enrolled probably the largest cohort of patients undergoing first-line AB treatment, it is a retrospective study based on aggregate data. The absence of individual data dramatically limits our ability to make causal inferences to understand the UC phenomenon. For this reason, this study has mainly epidemiological relevance, giving solid evidence about real-life curative conversion rates. Another limitation of this study was the absence of patient survival endpoints in the whole population. We deliberately choose not to consider survival for the entire cohort of included patients because of the intrinsic limits of prognostic analysis of meta-analytic approaches and the short follow-up of most enrolled patients. Again, the primary endpoint of this study is to obtain a valid epidemiologic snapshot of the curative conversion phenomenon worldwide.

Finally, although the concepts of PC and UC are the most original aspects of this study, they must be carefully considered. The main limitation of our PC definition is that it is solely based on tumour characteristics.

However, treatment decisions in HCC are highly complex and should be made through a multiparametric personalised process involving an expert tumour board [23, 38]. The curative conversion strategy should be regarded as part of a more complex framework recently described as a multiparametric converse therapeutic hierarchy. A recent review on this topic [21] elaborates on this framework and its clinical implications.

From this perspective, PC should not be regarded as a direct proxy for curative eligibility but rather as an upper-bound estimate of patients who might become technically suitable for curative approaches, provided that other critical parameters – such as liver function, comorbidities, PS, patient preferences, and institutional expertise – are also favourable factors. Based on these considerations, the UC rates in this study could be overestimated. It is reasonable that a certain proportion of PCs were not eligible for curative therapies due to the patient's general condition, liver dysfunction, specific tumour characteristics (i.e., metastatic disease, location of nodules), or technical contraindications [34]. While conceptually distinct from OR, PC partly overlaps with it and should be interpreted cautiously.

Nevertheless, we must also consider a potential underestimation of the UC phenomenon in this study. Cut-offs (i.e., TBS <8 or AFP <1,000) inherently carry the risk of excluding patients who were just beyond these limits but achieved a good biological response to ST. For example, Shen et al. [31] have recently shown that the outcomes of patients achieving a partial response or stable disease after AB were not influenced by specific radiological arrival points (i.e., cut-offs). At the same time, they were mainly influenced by the duration of treatment response (durable versus non-durable response). Moreover, recent evidence showed that curative conversion could also be performed after a durable, stable disease [14, 31]. This was confirmed in our study, where 18% of patients treated with AB were converted to curative therapy after a stable disease to first-line ST (online suppl. Table 1).

In conclusion, the results of this study can be considered a valuable benchmark for obtaining indirect comparisons among different uncontrolled studies estimating benefits in the conversion therapy setting. However, they also highlight a significant discrepancy between AC and PC rates in real life. These findings suggest that the conversion potential of novel immunotherapy combinations in HCC might be underestimated, with most patients continuing ST. Further research in the form of well-designed prospective studies is required to confirm this "UC" phenomenon and determine whether it has a negative prognostic impact on these patients.

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Statement of Ethics

This study was conducted according to the ethical principles in the Declaration of Helsinki and was consistent with good clinical practices and applicable laws and regulations. As this study was conducted using a retrospective survey design and involved only aggregate, non-identifiable data, submission to an Ethical Review Board was not required under current regulations. As this study was conducted using a retrospective survey design and involved only aggregate, non-identifiable data, obtaining individual patient consent for participation was not required under current regulations. In all cases, informed consent was routinely obtained for medical procedures as well as for privacy and data handling.

Conflict of Interest Statement

Alessandro Vitale, Massimo Iavarone, Lorenza Rimassa, Masafumi Ikeda, Masatoshi Kudo, and Edoardo G. Giannini were members of the journal's Editorial Board at the time of submission. Hong Jae Chon received consulting or advisory roles with Eisai, Roche, ONO, MSD, BMS, BeiGene, Sanofi, Servier, AstraZeneca, Menarini, and GreenCross Cell, and research grants from Roche, Dong-A ST, and Boryung Pharmaceuticals. Hiroshi Imaoka received research funding from Ono Pharmaceutical. Masafumi Ikeda has received consulting fees from AbbVie, AstraZeneca, Bayer, Chugai, Eisai, Eli Lilly Japan, MSD, and Ono Pharmaceutical; honoraria from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly Japan, Gilead, MSD, Sumitomo Dainippon, and Takeda; and research funding from AstraZeneca, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly Japan, MSD, Ono Pharmaceutical, Merck-Serono, and Novartis. Francesco Tovoli reports being consultant for Eisai, Roche, and AstraZeneca Giuseppe Cabibbo participated in advisory boards and received speaker fees for Bayer, Eisai, Ipsen, AstraZeneca, MSD, Roche, and Gilead. Massimo Iavarone received support from Roche, AstraZeneca, Bayer, Roche Diagnostics, Gilead, MSD, EISAI, and IPSEN. Fabio Marra reports being consultant for Roche, AstraZeneca, MSD/EISAI, and Ipsen. Claudia Campani received speaking fees from Roche, AstraZeneca, Travel fees Roche, and AstraZeneca. Hidenori Toyoda, M.D., Ph.D., received lecturer's fee from Gilead Sciences, AbbVie, Eisai, Fujifilm WAKO, Terumo, Takeda, Chugai, Kowa, and Bayer but do not receive fee or funding regarding this study. Andrea Casadei-Gardini reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, and Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, and Servier; travel expenses from AstraZeneca; and research grants (to Institution) from AstraZeneca and Eisai. Lorenza Rimassa reports consulting/advisory role for AbbVie, AstraZeneca, Basilea, Bayer, BMS, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, and Zymeworks; received honoraria/lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, and Servier; received travel expenses from AstraZeneca; received research funding to their institution from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences, and Zymeworks. Antonio Avallone reports receipt of honoraria or consultation fees for speaker, consultancy, and advisory roles from Amgen, Bayer, Eisai, Merck-Serono, MSD, Bristol-Meyers, and Takeda. Caterina Soldà reports advisory role for AstraZeneca. Filippo Pelizzaro reports advisory role for MSD and received travel and accommodation expenses from MSD. Erika Martinelli reports the following: Merck-Serono – invited speaker; Pierre Fabre – writing engagement, advisory board, invited speaker, and travel grant; Servier – writing engagement, advisory board, and invited speaker; BAYER – invited speaker; Roche – writing engagement, advisory board, and invited speaker; AstraZeneca – writing engagement and travel grant; Merck S.p.A. – invited speaker; ESMO – invited speaker; MSD – writing engagement and advisory board; and Takeda – advisory board and invited speaker. Donatella Marino received advisory board fees from F. Hoffmann-La Roche AG, MSD, Merck & Co, Inc., AstraZeneca, and travel expenses from Pierre Fabre and Amgen Inc. Jorge Adeva Alfonso reports consulting or advisory role for MSD Oncology, Basilea Pharmaceutical, Servier, Incyte, AstraZeneca, and received travel and accommodations expenses

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Alessandro Vitale, Jung Sun Kim, Giuseppe Cabibbo, Andrea Casadei-Gardini, Massimo Iavarone, Lorenza Rimassa, Francesca Romana Ponziani, and Francesco Tovoli contributed equally to the conception, design, and development of the project, as well as to the writing and critical revision of the manuscript. Alessandro Vitale, Hong Jae Chon, and Umberto Cillo contributed equally to the coordination of data collection and the management of interactions with participating centres. They were also actively involved in drafting the manuscript and in its critical revision. Beodeul Kang, Chan Kim, Hiroshi Imaoka, Masafumi Ikeda, Masatoshi Kudo, Tomoko Aoki, Raffaella Tortora, Marco Guarracino, Bernardo Stefanini, Mariarosaria Marseglia, Alba Sparacino, Ciro Celsa, Mariangela Bruccoleri, Eleonora Alimenti, Fabio Marra, Claudia Campani, Sherrie Bhoori, Vincenzo Mazzaferro, Rodolfo Sacco, Antonio Facciorusso, Andrea Martini, Leonardo Stella, Lucia Cerrito, Hidenori Toyoda, Satoshi Yasuda, Federico Rossari, Margherita Rimini, Goki Suda, Takuya Sho, Gianluca Masi, Caterina Vivaldi, Tiziana Pressiani, Satoru Kakizaki, Atsushi Naganuma, Antonio Avallone, Anna Nappi, Gianpaolo Vidili, Caterina Soldà, Francesca Bergamo, David J Pinato, Filippo Pelizzaro, Francesco Giuseppe Foschi, Alice Secomandi, Francesco Verderame, Enrico Bronte, Erika Martinelli, Donatella Marino, Sara Grasselli, Andrea Olivani, Maurizia Brunetto, Francesco Damone, Andrea Mega, Luca Marzi, Emiliano Tamburini, Matteo Ramundo, Piera Federico, Bruno Daniele, Edoardo Giovanni Giannini, Andrea Pasta, Filomena Morisco, Maria Guarino, Celine Hoyek, Sara Boninsegna, Ajay Gupta, David Sacerdoti, Andrea Dalbeni, Irina Calvo Ramos, Jorge Adeva Alfonso, Carlo Saitta, Concetta Pitrone, Maria Luisa Lentini Graziano, Nunzia Farella, Maria Rendina, Teresa Grassi, Maria Grazia Rodriquenz, Evaristo Maiello, José Presa, Inês Pinho, Yoichi Hiasa, Masashi Hirooka, Jocelin Chen, Gianluca Arrichiello, Carlo Aschele, and Alessandro Furlanetto contributed to data collection at their respective centres and participated in the organisation and management of the collected data. All authors contributed to drafting the manuscript and its critical revision.

Data Availability Statement

Individual patient data are not available due to the study design, based on aggregated data provided by each participating centre. Aggregated data that support the findings of this study are not publicly available for privacy reasons but are available from the corresponding author upon reasonable request.

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