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Initial Systemic Therapy and Clinical Outcomes in Hepatocellular Carcinoma without Prior Locoregional Treatment: A Nationwide Korean Claims-Based Cohort Study

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Abstract

Systemic therapy for hepatocellular carcinoma (HCC) has evolved rapidly, but population-level outcomes after treatment initiation without prior locoregional therapy remain incompletely characterized. We used the Korean National Health Insurance Service database to identify patients with incident HCC during 2020–2023 who initiated systemic therapy within 30 days of diagnosis and were followed through December 31, 2024. Propensity score matching compared atezolizumab plus bevacizumab (atezo/bev) with lenvatinib. A secondary weighted analysis included sorafenib. Among 2,097 eligible patients (atezo/bev, n = 613; lenvatinib, n = 489; sorafenib, n = 995), 918 were matched 1:1. Lenvatinib initiation was associated with higher mortality (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.29–1.72) and earlier treatment discontinuation (HR, 1.41; 95% CI, 1.24–1.61) than atezo/bev initiation, whereas ICU admission did not differ significantly between the atezo/bev and lenvatinib groups (HR, 0.82; 95% CI, 0.57–1.16). These findings describe real-world treatment-associated outcomes in a nationwide cohort and should not be interpreted as causal comparative efficacy because liver function, tumor burden, treatment eligibility, and calendar-time effects were not fully captured.

1. Introduction

Systemic therapy for advanced hepatocellular carcinoma (HCC) has evolved substantially since the introduction of immune-based combinations. The phase III IMbrave150 trial demonstrated that atezolizumab plus bevacizumab (atezo/bev) significantly improved overall survival (OS) and progression-free survival compared with sorafenib in patients with unresectable HCC, establishing atezo/bev as a standard first-line treatment option [1, 2]. Lenvatinib, validated in the REFLECT trial, remains a widely used multikinase inhibitor and a clinically important first-line option, particularly when contraindications to bevacizumab (such as untreated varices or recent bleeding) preclude the use of atezo/bev [3]. In Korea, reimbursement for atezo/bev under the National Health Insurance Service (NHIS) began in May 2022, whereas lenvatinib has been reimbursed since 2018 and sorafenib has long been available [4]. These staggered reimbursement timelines have created a rapidly changing real-world treatment landscape for HCC in Korea.

Although several real-world studies have compared atezo/bev with lenvatinib or lenvatinib-based regimens in unresectable HCC, important methodological gaps remain. First, most studies are based on single-center or multicenter clinical cohorts (typically n = 120–810), limiting external validity and statistical power for subgroup analyses [5–9]. Second, many cohorts include heterogeneous populations in which some patients receive first-line systemic therapy, whereas others transition from locoregional therapy after disease progression. This heterogeneity introduces selection bias that is difficult to address even with propensity-based methods because prior locoregional therapy reflects prognosis, liver reserve, tumor burden, vascular invasion, extrahepatic spread, clinical trajectory, and physician preference. Third, comparative real-world endpoints beyond OS, such as treatment persistence and exploratory health care utilization, remain rarely reported despite their growing importance in claims-based pharmacoepidemiology [10]. However, claims-based analyses of HCC treatment outcomes have

an important limitation: they cannot directly measure Child–Pugh class, albumin-bilirubin (ALBI) grade, Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) stage, alpha-fetoprotein level, tumor burden, vascular invasion, extrahepatic metastasis, or endoscopic and clinical eligibility for bevacizumab. These variables are central to treatment selection and survival. Therefore, nationwide claims data are most informative when the research question is framed as a population-level description and an adjusted association within a clearly defined clinical subgroup, rather than definitive causal comparison of drug efficacy.

To address these gaps, we used Korea's nationwide NHIS claims database to identify patients with incident HCC who initiated systemic therapy within 30 days of diagnosis without prior locoregional treatment. We characterized initial systemic drug therapy and estimated adjusted associations after atezo/bev or lenvatinib initiation using propensity score matching (PSM). Sorafenib was included in a secondary three-arm analysis using stabilized inverse probability of treatment weighting (IPTW) to provide historical treatment context. The analysis was intended to characterize treatment-associated outcomes in routine practice rather than estimate causal comparative efficacy.

2. Methods

2.1 *Data source and ethics*

We conducted a retrospective nationwide cohort study using data from the Korean NHIS claims database, which captures diagnoses (ICD-10), prescriptions, procedures (Electronic Data Interchange [EDI] codes), and demographic information for virtually the entire South Korean population [11]. Dates and causes of death were obtained through routine linkage with Statistics Korea's cause-of-death registry, included by default in NHIS research releases. The study was performed in accordance with the Declaration of Helsinki and its later amendments and was approved by the Institutional Review Board of CHA University Bundang Medical Center, Seongnam, Korea (IRB No.: CHAMC 2024-05-051). The requirement for informed consent was waived by the Institutional Review Board of CHA University Bundang Medical Center because anonymized administrative data were used. Reporting followed the STROBE and RECORD-PE guidelines for studies using routinely collected health data [12, 13].

2.2 *Cohort definition*

We identified adults (age ≥ 19 years) with incident HCC, defined by both ICD-10 code C22.0 and concurrent registration in the rare intractable disease program (V193), between January 1, 2020 and December 31, 2023. The index date for cohort entry was the earliest date on which both criteria were met. Incident HCC required no previous record meeting the HCC definition from the beginning of the available database period in 2007 through the day before the index date.

To assemble the cohort of patients receiving systemic therapy without prior locoregional treatment, the following criteria were applied: First, patients with any locoregional therapy before the first systemic therapy dose, assessed throughout the entire available look-back period, were excluded. Locoregional

therapies evaluated (full EDI code lists in Supplementary Table S1) included: (i) hepatic resection and liver transplantation; (ii) local ablation, including radiofrequency ablation, microwave ablation, cryoablation, and percutaneous ethanol injection; (iii) transarterial therapies, including conventional or drug-eluting-bead transarterial chemoembolization, transarterial radioembolization, and hepatic arterial infusion chemotherapy; and (iv) external-beam, stereotactic-body, or proton-beam radiotherapy. Second, only patients who initiated atezo/bev, lenvatinib, or sorafenib within 30 days of the index date and had no systemic anticancer therapy before diagnosis were included. Twenty-two patients who initiated other regimens were excluded because of insufficient numbers.

2.3 *Index date, exposure, and follow-up*

Time zero for all analyses was defined as the date of the first systemic therapy dose because treatment exposure was assigned at treatment initiation. Using the diagnosis date as time zero would include a pre-treatment interval during which patients had to remain alive to initiate therapy and could introduce immortal-time bias if diagnosis-to-treatment intervals differed across groups [14]. Exposure was defined by the first systemic regimen initiated on the index date. Atezo/bev initiation required claims for the first administrations of atezolizumab and bevacizumab on the same date or within ± 3 days; a subsequent treatment cycle was not required for exposure classification. The primary two-group analysis compared atezo/bev with lenvatinib. A three-arm cohort that included sorafenib was analyzed as a secondary contextual comparison. Patients were followed from the index date until the outcome of interest, loss to follow-up, or the administrative end of follow-up on 31 December 2024, whichever occurred first.

2.4 *Outcomes*

The primary outcome was OS, defined as the interval from the index date to all-cause death. Secondary outcomes were time to treatment discontinuation (TTD) and exploratory time to intensive care unit (ICU) admission. TTD was defined as the interval from the index date to the earliest of the following: (i) a gap of ≥ 30 days after the end of the expected treatment-coverage period for the index regimen; (ii) switching to or adding any non-index systemic anticancer agent; or (iii) all-cause death. Dose adjustments without a regimen change were considered treatment continuation. The 30-day threshold reflects the standard outpatient prescription cycle in Korea (28–30 days) and was selected to sensitively capture real-world treatment persistence. Time to ICU admission was defined as the interval from the index date to the first ICU room billing claim and was evaluated as an exploratory health care use endpoint that may reflect severe clinical deterioration but is also influenced by institutional practice and end-of-life care. Patients without the event were censored at death, the end of follow-up, or the administrative cutoff, whichever occurred first. For the ICU outcome, patients with an ICU admission during the 30 days before the index date were excluded so that the analysis captured incident ICU admission after systemic therapy initiation.

2.5 *Covariates*

Baseline covariates were ascertained at the index date using prespecified look-back windows. Demographic variables (age, sex, and income quintile based on insurance premiums) were measured at

the index date. Liver disease etiologies were assessed during the preceding 5 years and treated as non-mutually exclusive categories: chronic hepatitis B, chronic hepatitis C, alcoholic liver disease, non-alcoholic fatty liver disease, and other etiology. Hypertension, diabetes mellitus, chronic kidney disease, end-stage renal disease, and the Charlson Comorbidity Index were assessed during the same 5-year window [15]. Claims-based baseline proxies for hepatic decompensation and treatment eligibility—ascites, variceal or gastrointestinal bleeding, portal vein thrombosis, and hepatic encephalopathy—were identified within 30 days before the index date. These variables were not considered substitutes for Child–Pugh class, ALBI grade, ECOG performance status, BCLC stage, tumor burden, or direct assessment of bevacizumab eligibility.

2.6 *Statistical analysis*

To balance measured baseline differences between atezo/bev and lenvatinib, we estimated a propensity score (PS) using multivariable logistic regression including age, sex, income quintile, liver disease etiologies, hypertension, diabetes, chronic kidney disease, end-stage renal disease, and the Charlson Comorbidity Index. The four baseline hepatic-decompensation and treatment-eligibility proxies were not included in the prespecified primary PS model; their post-matching distributions were reported to characterize balance in available severity proxies. Matching used greedy 1:1 nearest-neighbor matching without replacement and a caliper width of 0.2 times the pooled standard deviation of the logit of the PS [16]. Balance was assessed using standardized mean differences (SMDs), with $|SMD| < 0.10$ considered adequate.

OS, TTD, and time to ICU admission in the matched cohort were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with robust standard errors clustered by matched pairs. Because major HCC prognostic factors were unmeasured, the HRs were interpreted as adjusted associations conditional on available claims-based covariates rather than as unbiased causal treatment effects. The proportional hazards assumption was assessed graphically and statistically using scaled Schoenfeld residuals [17]. When the proportional hazards assumption was not satisfied, HRs were interpreted as average associations over follow-up rather than as constant relative effects.

For the three-arm comparison, stabilized IPTW was derived from a multinomial logistic regression model of treatment assignment using the same covariates as the PS model, with atezo/bev as the reference group. Weight distributions were inspected and truncated at the 1st and 99th percentiles to mitigate the influence of extreme weights. Weighted Kaplan–Meier curves and weighted Cox regression with robust standard errors were used to estimate pairwise HRs (lenvatinib vs. atezo/bev and sorafenib vs. atezo/bev). This analysis was prespecified as secondary and contextual because sorafenib use was affected by treatment-era and reimbursement changes.

Subgroup analyses were prespecified by age (< 65 vs. ≥65 years), consistent with definitions of older adults in Korean and Japanese HCC guidelines. Stratum-specific hazard ratios were obtained by fitting separate Cox models within each age group, and treatment-by-age interactions were tested using cross-

product terms in the matched (or weighted) cohort. Additional covariate adjustment was planned for any covariate with a post-matching SMD ≥ 0.10. In the final matched cohort, no measured baseline covariate exceeded this threshold; therefore, additional Cox models adjusting for age and other etiology indicators were treated as robustness analyses rather than corrections for residual imbalance.

Because key prognostic variables (Child–Pugh class, ECOG performance status, BCLC stage, alpha-fetoprotein level, tumor size and number, vascular invasion, extrahepatic metastasis, and bevacizumab eligibility factors such as varices or bleeding risk) are not captured in the claims data, we computed E-values for the primary OS estimates and, as supplementary sensitivity analyses, for the other reported HR estimates. These quantify the minimum strength of association (on the HR scale) that an unmeasured confounder would need to have with both treatment and outcome to fully explain the observed association, but they do not exclude clinically plausible residual confounding [18]. The E-value analysis was used as a transparency tool rather than as evidence that residual confounding was absent. Two-sided p values < 0.05 were considered statistically significant. Given the prespecified outcome hierarchy, no formal multiplicity adjustment was applied. All analyses were performed using SAS Enterprise 7.1 (SAS Institute, Cary, NC, USA).

2.7 Code availability

The SAS code used for data management and statistical analysis is available from the corresponding author on reasonable request, subject to Korean National Health Insurance Service data-access restrictions and applicable institutional requirements.

2.8 Use of generative AI

ChatGPT (OpenAI) was used solely to assist with language editing and organization during manuscript preparation. All substantive scientific content, data analyses, interpretation, and final decisions were performed and verified by the authors, who take full responsibility for the final manuscript.

3. Results

3.1 *Cohort and baseline characteristics*

During the 2007–2023 diagnosis surveillance period, 132,734 patients met the HCC definition (ICD-10 C22.0 with concurrent V193 registration). Restriction to incident HCC diagnosed during 2020–2023, with no previous HCC record across the entire available database history, yielded 51,234 patients. Another 39,048 patients were excluded because they had at least one record of locoregional therapy before the first systemic dose, leaving 12,186 patients without prior locoregional treatment who were assessed for systemic therapy initiation. Of these, 10,067 were excluded because systemic therapy was not initiated within 30 days after diagnosis or systemic anticancer treatment occurred before diagnosis. Among the remaining 2,119 patients, 22 initiated other regimens and were excluded, yielding 2,097 patients treated with atezo/bev (n = 613), lenvatinib (n = 489), or sorafenib (n = 995) (Fig. 1; Supplementary Fig. S1).

Baseline characteristics of the full three-arm cohort are summarized in Table 1. The mean age was 64.2 years, and 84.3% of patients were men. Hepatitis B was the main etiology (51.5%), followed by ALC (19.6%) and NAFLD (13.2%), reflecting the epidemiology of HCC in Korea. Before PSM, the atezo/bev and lenvatinib groups differed in several characteristics, including the prevalence of other etiologies, age, and CCI (Supplementary Table S2). After 1:1 PSM using a caliper width of 0.2 × the pooled SD of the logit PS, 459 patients per group were matched (n = 918). All measured covariates were balanced after matching (all |SMD| <0.10), and hepatic decompensation indicators (ascites, variceal bleeding, PVT, and HE), which were not included in the PS model, also showed acceptable post-matching balance (Table 2). This balance applies only to measured claims-based variables and does not imply balance in unmeasured liver function, tumor stage, performance status, or bevacizumab eligibility. Additional Cox models adjusting for age and the other-etiology indicator were reported as robustness analyses (Supplementary Table S3).

Table 1
Baseline characteristics of the study cohort by first-line systemic therapy.

Variable	Atezo/bev (n = 613)	Lenvatinib (n = 489)	Sorafenib (n = 995)
Age, years, mean (SD)	65.2 (12.1)	63.9 (11.2)	63.7 (11.7)
Male sex, n (%)	512 (83.5)	401 (82.0)	855 (85.9)
Income quintile (Q1 lowest), n (%)			
Q1	154 (25.1)	121 (24.7)	240 (24.1)
Q2	104 (17.0)	74 (15.1)	184 (18.5)
Q3	124 (20.2)	106 (21.7)	227 (22.8)
Q4	114 (18.6)	99 (20.3)	183 (18.4)
Q5	117 (19.1)	89 (18.2)	161 (16.2)
Etiology (non-mutually exclusive)			
Hepatitis B	323 (52.7)	230 (47.0)	526 (52.9)
Hepatitis C	55 (9.0)	36 (7.4)	87 (8.7)
Alcoholic liver disease	109 (17.8)	66 (13.5)	235 (23.6)
NAFLD	87 (14.2)	79 (16.2)	111 (11.2)
Other	162 (26.4)	160 (32.7)	257 (25.8)
Comorbidities			
Hypertension	348 (56.8)	272 (55.6)	530 (53.3)
Diabetes mellitus	286 (46.7)	220 (45.0)	445 (44.7)
Chronic kidney disease	13 (2.1)	13 (2.7)	26 (2.6)
ESRD	1 (0.2)	1 (0.2)	2 (0.2)
Charlson Comorbidity Index, mean (SD)	5.5 (2.6)	5.8 (3.0)	5.9 (2.9)
Hepatic decompensation indicators (30-day look-back)			
Ascites (R18)	39 (6.4)	27 (5.5)	132 (13.3)
Variceal/GI bleeding	28 (4.6)	22 (4.5)	64 (6.4)
Portal vein thrombosis	22 (3.6)	15 (3.1)	52 (5.2)

Data are presented as n (%) unless otherwise indicated. Atezo/bev: atezolizumab plus bevacizumab; ESRD: end-stage renal disease; NAFLD: non-alcoholic fatty liver disease; GI: gastrointestinal.

Variable	Atezo/bev (n = 613)	Lenvatinib (n = 489)	Sorafenib (n = 995)
Hepatic encephalopathy	4 (0.7)	4 (0.8)	20 (2.0)

Data are presented as n (%) unless otherwise indicated. Atezo/bev: atezolizumab plus bevacizumab; ESRD: end-stage renal disease; NAFLD: non-alcoholic fatty liver disease; GI: gastrointestinal.

Table 2
Covariate balance before and after 1:1 propensity score matching (atezo/bev vs. lenvatinib).

Variable	Before PSM (atezo/bev vs. lenvatinib)	Absolute SMD before PSM	After 1:1 PSM (atezo/bev vs. lenvatinib)	Absolute SMD after PSM
Age	65.2 vs 63.9	0.112	64.4 vs 64.4	0.003
Male sex	83.5% vs 82.0%	0.098	83.4% vs 82.8%	0.017
Income quintile	-	0.074	-	≤ 0.033
HBV	52.7% vs 47.0%	0.113	49.9% vs 50.8%	0.017
HCV	9.0% vs 7.4%	0.059	7.8% vs 9.4%	0.054
ALC	17.8% vs 13.5%	0.118	14.4% vs 14.8%	0.012
NAFLD	14.2% vs 16.2%	0.055	16.1% vs 15.5%	0.018
Other	26.4% vs 32.7%	0.138	29.6% vs 28.5%	0.024
Hypertension	56.8% vs 55.6%	0.023	56.2% vs 56.2%	0.000
Diabetes mellitus	46.7% vs 45.0%	0.033	45.8% vs 47.1%	0.026
CKD	2.1% vs 2.7%	0.035	2.6% vs 2.6%	0.000
ESRD	0.2% vs 0.2%	0.010	0.2% vs 0.0%	0.066
CCI, mean	5.50 vs 5.78	0.098	5.59 vs 5.70	0.039
Ascites†	6.4% vs 5.5%	0.036	5.7% vs 6.8%	0.045
Variceal bleeding†	4.6% vs 4.5%	0.003	4.8% vs 4.8%	0.000
PVT†	3.6% vs 3.1%	0.029	3.1% vs 3.7%	0.036
HE†	0.7% vs 0.8%	0.019	0.9% vs 0.9%	0.000

†The baseline hepatic-decompensation and treatment-eligibility proxies were not included in the prespecified primary PS model; their post-matching distributions are shown to characterize balance in available claims-based severity proxies. For income quintile, the post-matching value denotes the largest category-specific absolute SMD. Atezo/bev, atezolizumab plus bevacizumab; ALC, alcoholic liver disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; NAFLD, non-alcoholic fatty liver disease; PS, propensity score; PSM, propensity score matching; PVT, portal vein thrombosis; SMD, standardized mean difference.

3.2 *Overall survival*

In the matched cohort, the observed OS differed between treatment groups, with a higher mortality hazard among patients initiating lenvatinib than among those initiating atezo/bev (HR, 1.49; 95% CI, 1.29–1.72; $p < 0.001$). A robustness model additionally adjusting for the other-etiology indicator yielded a

similar estimate (HR, 1.48; 95% CI, 1.29–1.72; p < 0.001). The proportional hazards assumption was not fully satisfied for OS (Schoenfeld test, p = 0.026); therefore, the HR should be interpreted as an average association over follow-up rather than a constant relative effect.

The three-arm IPTW analysis yielded similar estimates (Table 3): HR 1.42 (95% CI 1.26–1.61) for lenvatinib versus atezo/bev and HR 2.00 (95% CI 1.76–2.26) for sorafenib versus atezo/bev, both p < 0.001. The markedly higher HR for sorafenib likely reflects treatment-era effects and physician selection rather than pharmacologic differences; therefore, sorafenib was retained as a secondary historical reference rather than a contemporary comparator.

Table 3
Hazard ratios for overall survival, time to treatment discontinuation, and exploratory time to ICU admission.

Analysis/outcome	Comparison	HR	95% CI	p	PH p
Two-arm PSM (matched n = 918)					
Overall survival	Lenvatinib vs. atezo/bev	1.49	1.29–1.72	< 0.001	0.026
TTD	Lenvatinib vs. atezo/bev	1.41	1.24–1.61	< 0.001	0.018
Time to ICU admission	Lenvatinib vs. atezo/bev	0.82	0.57–1.16	0.26	0.089
Three-arm IPTW (n = 2,097)					
Overall survival	Lenvatinib vs. atezo/bev	1.42	1.26–1.61	< 0.001	—
	Sorafenib vs. atezo/bev	2.00	1.76–2.26	< 0.001	—
TTD	Lenvatinib vs. atezo/bev	1.39	1.23–1.56	< 0.001	—
	Sorafenib vs. atezo/bev	2.27	2.00–2.57	< 0.001	—
Time to ICU admission	Lenvatinib vs. atezo/bev	0.93	0.68–1.27	0.63	—
	Sorafenib vs. atezo/bev	0.98	0.74–1.31	0.90	—

PH p indicates the p-value of the scaled Schoenfeld residual test for the proportional-hazards assumption in the two-arm PSM analyses; it is not applicable to the secondary three-arm IPTW analyses. Three-arm IPTW findings, including sorafenib, should be interpreted as secondary contextual analyses rather than primary causal comparisons. Atezo/bev: atezolizumab plus bevacizumab; HR: hazard ratio; PSM: propensity score matching; IPTW: stabilized inverse probability of treatment weighting (1st/99th percentile truncated); TTD: time to treatment discontinuation; ICU: intensive care unit. For the ICU outcome, patients with ICU admission during the 30 days before index were excluded from the outcome-specific analysis; the two-arm PSM ICU risk set was 459 atezo/bev versus 445 lenvatinib recipients.

3.3 *Time to treatment discontinuation*

The composite TTD endpoint was reached earlier in the lenvatinib group than in the atezo/bev group. In the matched cohort, the HR comparing lenvatinib with atezo/bev was 1.41 (95% CI, 1.24–1.61; $p < 0.001$). In the three-arm IPTW analysis, the corresponding HRs were 1.39 (95% CI, 1.23–1.56) for lenvatinib and 2.27 (95% CI, 2.00–2.57) for sorafenib versus atezo/bev. TTD was a pragmatic composite endpoint of treatment gaps, switching or addition of another systemic agent, and death; it should not be

interpreted as radiographic progression-free survival or as a treatment-specific toxicity endpoint. The proportional-hazards assumption was marginally violated for TTD (Schoenfeld test, p = 0.018).

3.4 Time to intensive care unit admission

For the exploratory healthcare utilization endpoint, time to ICU admission did not differ significantly between atezo/bev and lenvatinib (PSM HR, 0.82; 95% CI, 0.57–1.16; p = 0.26) (Table 3, Fig. 2c). The proportional-hazards assumption was met (Schoenfeld test, p = 0.089). Three-arm IPTW estimates were also null (lenvatinib vs. atezo/bev: HR, 0.93; 95% CI, 0.68–1.27; sorafenib vs. atezo/bev: HR, 0.98; 95% CI, 0.74–1.31). ICU admission was retained as an exploratory utilization outcome and not interpreted as a validated measure of HCC progression or treatment safety. After excluding patients with an ICU admission during the 30-day baseline window, the outcome-specific PSM risk set comprised 459 atezo/bev recipients and 445 lenvatinib recipients.

3.5 *Age-stratified associations*

In prespecified analyses by age (< 65 vs. ≥65 years), adjusted associations for OS were similar across strata (Table 4). Among patients aged < 65 years, the HR for lenvatinib versus atezo/bev was 1.51 (95% CI 1.23–1.84), whereas among those aged ≥ 65 years, it was 1.43 (95% CI 1.18–1.75), and treatment-by-age interaction was not significant (p = 0.83). Findings for TTD were similarly consistent (interaction p = 0.38), as were ICU outcomes (interaction p = 0.15). Three-arm IPTW subgroup estimates for OS and TTD were similar in direction to the primary analysis, with only a borderline interaction for TTD (p = 0.052), driven by a slightly greater lenvatinib-associated discontinuation hazard among patients aged ≥ 65 years. These subgroup findings are descriptive and should not be used to infer equivalent causal effects across age groups.

Table 4
Age subgroup analysis (< 65 vs. ≥65 years) for the primary two-arm PSM and three-arm IPTW comparisons.

Analysis	Outcome	Comparison	< 65 years HR (95% CI)	≥ 65 years HR (95% CI)	Interaction p
Two-arm PSM	OS	Lenvatinib vs. atezo/bev	1.51 (1.23–1.84)	1.43 (1.18–1.75)	0.83
	TTD	Lenvatinib vs. atezo/bev	1.33 (1.11–1.60)	1.48 (1.22–1.78)	0.38
	ICU	Lenvatinib vs. atezo/bev	1.08 (0.67–1.74)	0.58 (0.34–1.00)	0.15
Three-arm IPTW	OS	Lenvatinib vs. atezo/bev	1.43 (1.20–1.70)	1.39 (1.17–1.66)	0.63
	OS	Sorafenib vs. atezo/bev	2.10 (1.77–2.50)	1.87 (1.57–2.23)	0.63
	TTD	Lenvatinib vs. atezo/bev	1.28 (1.07–1.53)	1.49 (1.26–1.77)	0.052
	TTD	Sorafenib vs. atezo/bev	2.47 (2.07–2.95)	2.10 (1.76–2.50)	0.052

Interaction p-value derived from the treatment × age cross-product term in the Cox model fitted on the matched (or weighted) cohort. Atezo/bev: atezolizumab plus bevacizumab; HR: hazard ratio; OS: overall survival; TTD: time to treatment discontinuation; ICU: intensive care unit; PSM: propensity score matching; IPTW: stabilized inverse probability of treatment weighting; CI: confidence interval.

3.6 *Sensitivity analysis: E-value*

For the primary OS estimate (HR 1.49), the E-value was 2.34 for the point estimate and 1.91 for the lower confidence limit. This means that an unmeasured confounder would need to be associated with both treatment selection and mortality, with risk ratios of at least 2.34 (or 1.91 to shift the CI to the null), to explain the observed association. Given the strong prognostic influence of Child–Pugh class, BCLC stage, ECOG performance status, tumor burden, vascular invasion, extrahepatic metastasis, and bevacizumab eligibility, this E-value should be viewed as quantifying sensitivity to unmeasured confounding rather than excluding clinically important residual bias. The corresponding E-value for the lenvatinib versus atezo/bev OS comparison in the three-arm IPTW analysis was 2.20 (1.83 for the lower confidence limit) (Supplementary Table S4). All hazard ratio estimates from the two-arm PSM, three-arm IPTW, and age-stratified analyses are summarized in Fig. 3.

4. Discussion

In this nationwide Korean claims-based cohort of patients with HCC who initiated systemic therapy shortly after diagnosis without prior locoregional treatment, recipients of atezo/bev had longer observed OS and TTD than recipients of lenvatinib. These findings are observational and apply to a selected

population that proceeded directly to systemic therapy rather than the broader HCC population, in which sequential locoregional and systemic approaches are common. Because atezo/bev became reimbursed only from May 2022, the primary comparison also spans different treatment eras. Claims data do not capture several major prognostic and treatment-selection factors; therefore, the observed associations should not be interpreted as definitive comparative efficacy.

The estimated higher mortality hazard in the lenvatinib group (HR 1.49 vs. atezo/bev) was consistent across age strata and similar in the three-arm IPTW analysis, with sorafenib serving as a historical reference. However, the magnitude of this association may reflect differences in baseline clinical status that could not be measured, particularly hepatic reserve, tumor burden, vascular invasion, extrahepatic spread, performance status, and bevacizumab eligibility. Patients selected for atezo/bev in routine practice may have been more likely to have adequate hepatic reserve, controlled variceal risk, and no recent bleeding, whereas patients receiving lenvatinib may have included those with contraindications to bevacizumab or more complex clinical profiles. This explanation is clinically plausible and cannot be fully addressed by PSM when the relevant variables are unavailable.

Our findings are consistent with those of the IMbrave150 trial, in which atezolizumab plus bevacizumab prolonged median OS compared with sorafenib (19.2 vs. 13.4 months in the updated analysis), as well as with previous real-world comparisons between atezo/bev and lenvatinib, which generally favored atezo/bev, although not uniformly [1, 2, 5–9]. The present study differs from those analyses in its nationwide claims-based design and its intentional restriction to patients initiating systemic therapy without prior locoregional treatment. This restriction improves clinical coherence but also defines a specific advanced-presentation subgroup rather than a broadly generalizable HCC population.

The study design supports interpretation of real-world treatment outcomes in routine practice. First, incident HCC was identified after excluding any previous HCC record across the available database history. Second, any locoregional therapy recorded before the first systemic dose triggered exclusion, reducing heterogeneity from previous resection, ablation, transarterial treatment, transplantation, or radiotherapy. Third, requiring systemic treatment initiation within 30 days of diagnosis defined patients who began systemic therapy shortly after diagnosis without prior locoregional treatment. Finally, nationwide data reduced referral-center bias and captured routine practice across Korean health care settings. These design features improve cohort specificity but do not remove confounding from clinical variables unavailable in claims data.

Current international and Korean guideline frameworks, as well as contemporary reviews of HCC immunotherapy, emphasize that first-line systemic treatment should be considered in the context of tumor stage, liver function, performance status, and treatment eligibility, including bleeding risk and bevacizumab suitability [19–26]. Prior global and Korean real-world reports of HCC management also indicate that treatment pathways frequently involve sequential locoregional and systemic strategies, underscoring the importance of explicitly distinguishing patients who begin systemic therapy without prior locoregional treatment [27, 28]. The current analysis contributes to this literature by documenting

treatment outcomes in patients who began systemic therapy without prior locoregional treatment rather than by establishing comparative drug efficacy.

In addition to OS, the TTD association provides information on real-world treatment persistence but requires caution. The endpoint combined a prescription gap of at least 30 days, switching or addition of a non-index systemic agent, and death. Thus, it may reflect progression, toxicity, clinical deterioration, mortality, physician preference, treatment scheduling, or reimbursement practice. Alternative 60- or 90-day gap definitions, death-censored or competing-risk discontinuation analyses, and detailed subsequent-treatment sequencing were not available in the present analysis. Therefore, TTD should not be interpreted as progression-free survival or as a direct comparison of regimen tolerability.

Time to ICU admission should be interpreted even more cautiously. In this study, ICU admission was analyzed as an exploratory health care utilization endpoint rather than a validated measure of severe HCC deterioration. The absence of a difference in time to ICU admission, despite the relatively low event rate, suggests that there was no claims-based signal of increased critical care utilization with atezo/bev. However, whether this reflects improved disease control with atezo/bev, comparable safety profiles in selected patients, or differences in the timing of ICU admission (e.g., end-of-life admissions) cannot be determined from claims data and requires prospective investigation.

The age-stratified findings were similar across strata, with no statistically significant treatment-by-age interaction for OS, TTD, or ICU outcomes. This is relevant given the aging HCC population in Korea, where the proportion of patients aged ≥ 70 years has risen markedly over the past decade [4]. These results should be considered descriptive. Age alone cannot supplant individualized assessment of liver reserve, frailty, performance status, tumor burden, and bleeding risk. The absence of a statistically significant interaction also does not prove that treatment effects are identical across age groups. This interpretation is supported by multicenter data suggesting that atezo/bev is feasible in selected older patients, although age alone should not supplant formal clinical assessment of liver reserve, frailty, and bleeding risk [29].

This study has some limitations. First, claims data lacked major prognostic and treatment-selection variables, including Child–Pugh class, ALBI grade, bilirubin, albumin, INR, ECOG performance status, BCLC stage, alpha-fetoprotein, tumor size and number, vascular invasion, extrahepatic metastasis, and direct assessment of varices, bleeding risk, and bevacizumab eligibility. PSM therefore balanced only measured claims-based variables. Baseline hepatic-decompensation and treatment-eligibility proxies were not included in the prespecified primary PS model, although their post-matching balance was reported; residual confounding by disease severity remains possible. The E-value quantified the strength of unmeasured confounding required to explain the observed OS association but cannot exclude clinically plausible residual bias.

Second, atezo/bev reimbursement began in May 2022, whereas lenvatinib and sorafenib were available throughout the cohort-entry period. The prespecified PS models did not adjust for calendar quarter, and no common-era reanalysis was available. Residual confounding from treatment era, evolving supportive

care, differences in follow-up, subsequent treatment availability, and physician selection therefore cannot be excluded (Supplementary Fig. S1). Sorafenib results should be interpreted only as secondary historical context. Third, the proportional-hazards assumption was violated for OS and TTD (Supplementary Fig. S2); HRs therefore represent average associations over follow-up rather than constant relative effects. Fourth, the 30-day TTD gap may classify temporary interruptions as discontinuations, and alternative gap or competing-risk analyses were not performed. Fifth, ICU admission is an exploratory utilization endpoint influenced by institutional and end-of-life care practices. Sixth, generalizability beyond the Korean health care system and its HBV-predominant HCC population requires external validation.

5. Conclusions

In this nationwide cohort of patients with incident HCC who initiated systemic therapy without any prior locoregional treatment, atezo/bev initiation was associated with longer observed OS and time to treatment discontinuation than lenvatinib initiation. This nationwide claims analysis describes treatment-associated outcomes after initial systemic therapy in routine Korean practice. Because key clinical prognostic variables, bevacizumab eligibility, and calendar-time effects were not fully captured, the findings should not be interpreted as definitive comparative efficacy estimates.

Declarations

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Author contributions

Conceptualization, J.-Y.S. and W.S.; methodology, S.-H.Y., J.-Y.S. and W.S.; formal analysis, S.-H.Y. and W.S.; investigation, S.-H.Y., A.Y.L., S.K., K.L., J.A. and W.S.; data curation, S.-H.Y., A.Y.L., S.K., K.L., J.A. and W.S.; writing—original draft preparation, S.-H.Y., A.Y.L. and W.S.; writing—review and editing, all authors; visualization, S.-H.Y., J.A. and W.S.; supervision, J.-Y.S. and W.S.; project administration, J.-Y.S. and W.S. All authors have read and agreed to the submitted version of the manuscript.

Data availability

The data that support the findings of this study were obtained from the Korean National Health Insurance Service (NHIS) under approval for this study (NHIS-2025-08-1-049). Individual-level data are not publicly available and cannot be shared directly by the authors because access is governed by the NHIS and applicable Korean privacy regulations. Requests for access to the study data should be directed to the Korean National Health Insurance Service (NHIS) through its official data-access application process; access is subject to independent NHIS review and approval. For questions

regarding the dataset used in this study or the access process, please contact the corresponding author, Wonsuk Shin (wonsug89@chamc.co.kr).

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Competing interests

The authors declare no competing interests.

Ethics Approval

The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments and was approved by the Institutional Review Board of CHA University Bundang Medical Center, Seongnam, Republic of Korea (IRB No. CHAMC 2024-05-051).

Consent to Participate

The requirement for informed consent was waived by the Institutional Review Board of CHA University Bundang Medical Center because anonymized administrative claims data were used.

Consent for Publication

Not applicable.

Supplementary Information

The following supporting information is available with this article: Table S1, operational definitions and code lists; Table S2, unmatched baseline characteristics; Table S3, additional Cox models; Table S4, E-value analyses; Figure S1, treatment initiation by calendar quarter; and Figure S2, scaled Schoenfeld residuals.

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Figures

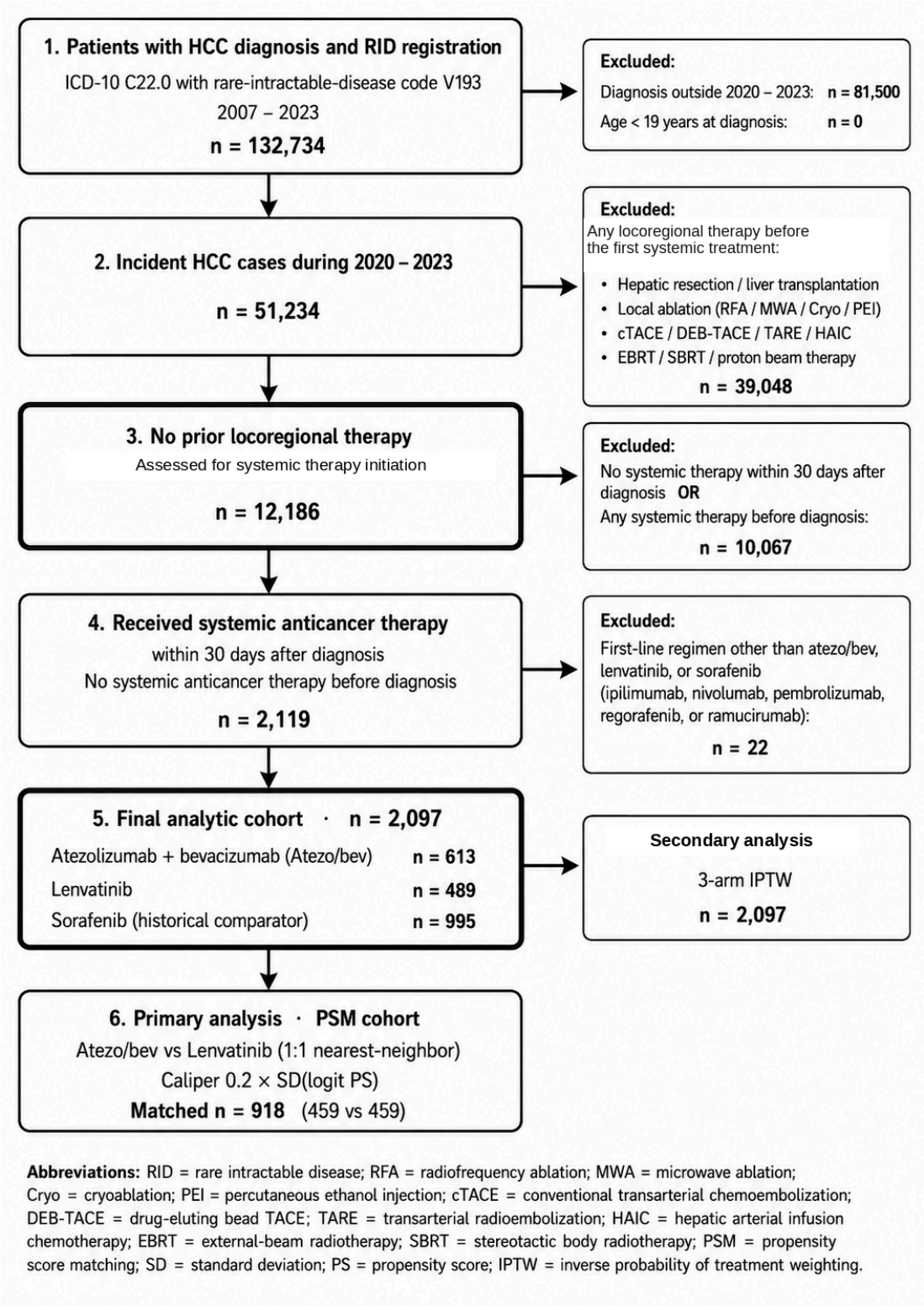


Figure 1

Study cohort selection flow diagram. Incident HCC required no previous HCC record, and any locoregional therapy before the first systemic dose triggered exclusion. The final cohort comprised 2,097 patients; 918 were included in the 1:1 PSM comparison.

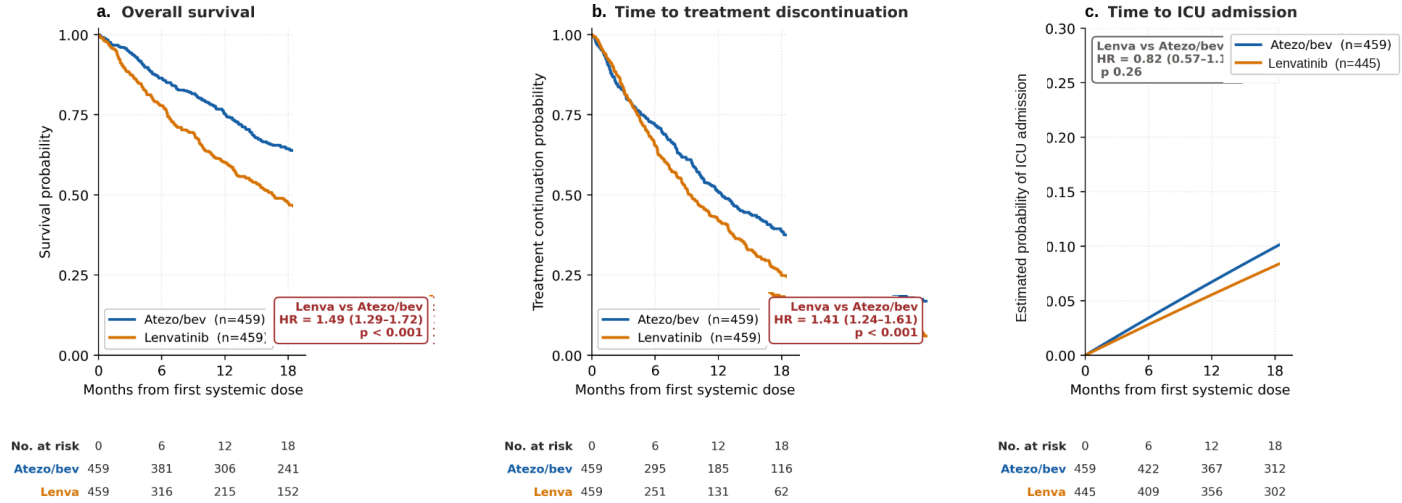


Figure 2

Time-to-event curves in the propensity-score-matched cohort. (a) Overall survival; (b) time to treatment discontinuation; and (c) estimated probability of ICU admission, derived as one minus the Kaplan–Meier estimate of ICU-admission-free probability. Curves and numbers at risk are displayed through 18 months for visual presentation; HRs and statistical tests were estimated using the full available follow-up through 31 December 2024. HRs were obtained from Cox models with robust standard errors clustered by matched pairs. ICU admission was evaluated as an exploratory claims-based utilization endpoint. For the ICU outcome, patients with an ICU admission during the 30 days before the index date were excluded; therefore, the outcome-specific risk set was 459 atezo/bev and 445 lenvatinib recipients.

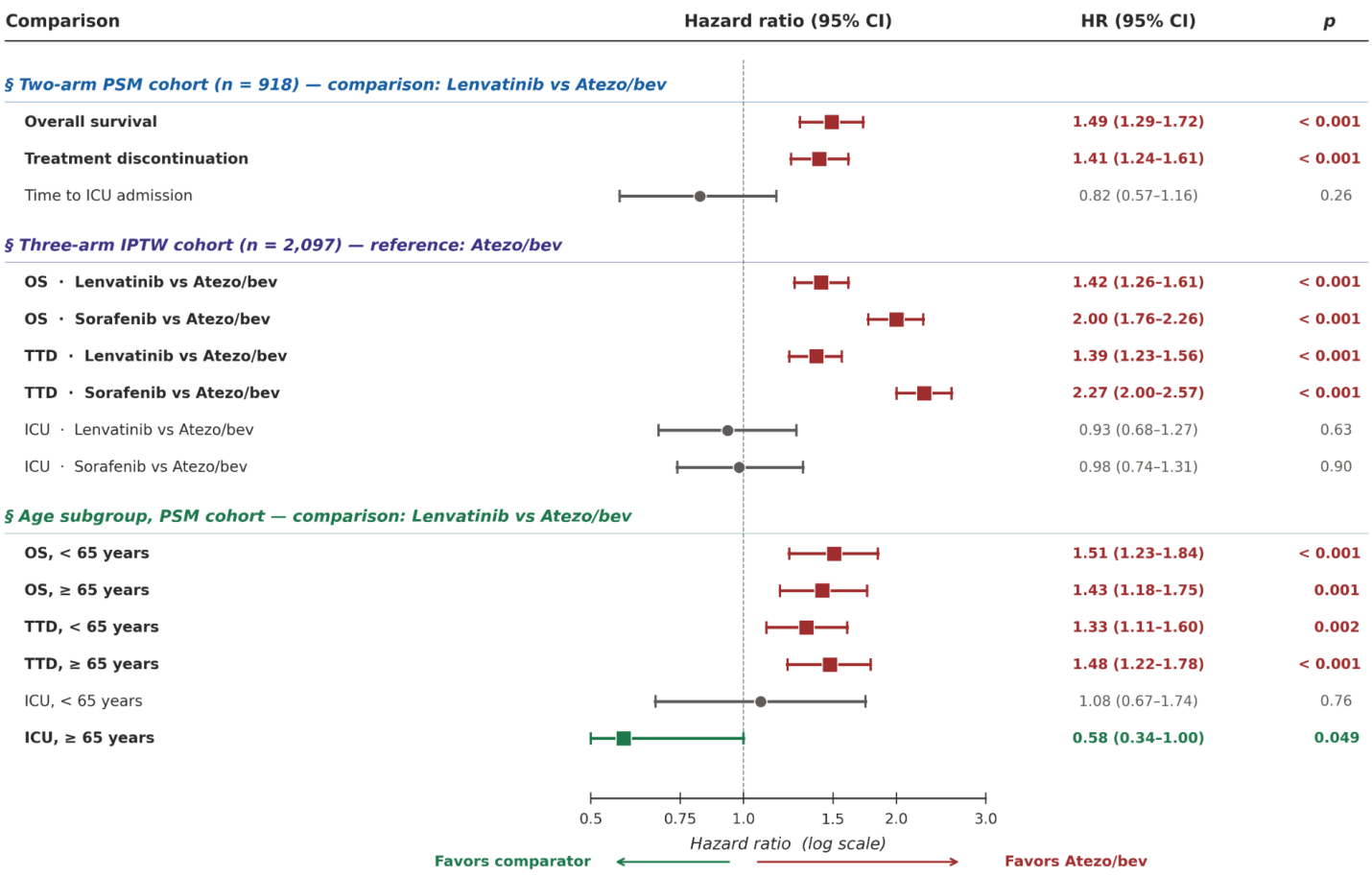


Figure 3

Forest plot of hazard ratios using atezo/bev as the reference. Results are shown for the two-arm PSM cohort, secondary three-arm IPTW cohort, and prespecified age-stratified analyses. Points represent hazard-ratio estimates and horizontal lines indicate 95% confidence intervals; the vertical dashed line denotes HR = 1. The treatment-by-age interaction for ICU admission was not significant, and the age-specific ICU finding is exploratory. CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; OS, overall survival; PSM, propensity score matching; TTD, time to treatment discontinuation.

Supplementary Files

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