Efficacy and Safety of TKI Plus PD-1 Inhibitors in Elderly uHCC Patients: A Retrospective Study

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Purpose: To explore the efficacy and safety of sorafenib- or lenvatinib-based combination therapy with PD-1 inhibitors in elderly patients aged ≥75 years with unresectable hepatocellular carcinoma (uHCC).

Patients and Methods: Systemic therapy-naïve uHCC patients who received first-line sorafenib- or lenvatinib-based combination therapy with PD-1 inhibitors were continually reviewed. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events (AEs) and immune-related AEs (irAEs) were also evaluated. Groups and subgroups were separated at the ages of 65 and 75 years and compared with 1:1 matching.

Results: Total 169 eligible patients were enrolled, including 24 aged ≥75 years. Median progression-free survival (PFS) and overall survival (OS) in these 24 elderly patients were 4.6 (95% CI: 2.6–6.6) months, and 17.0 (95% CI: 11.2–22.8) months, with 3-, 6-, 12-month OS rate at 82.90%, 73.70%, and 57.50%. Age ≥75 years was confirmed to be a risk factor influencing PFS among patients aged ≥65 years. Adverse events (AEs) were recorded in all these 24 elderly patients, with seven patients experiencing immune-mediated AEs (irAEs). Nearly 30% of elderly patients stopped treatment due to AEs (16% of these due to irAEs). No statistical differences were found in all efficacy endpoints at the cutoff age of 65 years.

Conclusion: For patients aged ≥75 years, application of PD-1 inhibitors in combination with sorafenib or lenvatinib is promising, but this has to be done with caution and needs to be confirmed by future prospective studies.

Keywords: hepatocellular carcinoma, elderly, PD-1 inhibitors, efficacy, safety

Introduction

Hepatocellular carcinoma (HCC) is a highly malignant gastrointestinal carcinoma with a high incidence rate.1 Moreover, most patients are not amenable to curative treatment at the time of diagnosis. For unresectable HCC (uHCC), the prognosis remains poor. Fortunately, sorafenib and lenvatinib, two traditional tyrosine kinase inhibitors (TKIs), have greatly improved overall survival (OS) of patients with uHCC.2

Programmed cell death protein 1 (PD-1), a traditional immune checkpoint molecule, contributes significantly to immune evasion of tumors.3 Blockade of PD-1 and its ligand can break the conditions of immune evasion in the tumor microenvironment and its efficacy has been observed in multiple tumors.4 Atezolizumab plus bevacizumab (A+T) is the first approved first-line treatment consisting of targeted drugs plus immune checkpoint inhibitors (ICIs) in uHCC.5 The application of first-line TKIs plus PD-1 inhibitors in uHCC patients has reached the consensus of Chinese hepatobiliary
clinical experts\textsuperscript{6–8} and is wildly used in clinical practice. The efficacy, potential downstaging, and conversion ability of TKIs plus PD-1 inhibitors was explored in previous studies.\textsuperscript{9–17}

Aging is a major global trend that has raised great concerns worldwide. With the increasing number of aging citizens, the age-adjusted HCC mortality rate has risen,\textsuperscript{18–20} including in mainland China.\textsuperscript{21} Though previous clinical trials related to uHCC did not limit the upper boundary of age, considering relatively complicated physical conditions in elderly patients, they might not be fully included in studies. Therefore, participants from clinical trials might not accurately represent real-world situation of elderly patients, especially for whose age is \(\geq 75\) years.\textsuperscript{22–24} Although previous studies have already investigated the application of sorafenib, lenvatinib monotherapy, or A+T in elderly patients with uHCC,\textsuperscript{25–28} whether this group of patients would benefit from sorafenib or lenvatinib plus PD-1 inhibitors, needs to be clarified. In order to explore the efficacy and safety of sorafenib- or lenvatinib-based combination therapy with PD-1 inhibitors in elderly patients with uHCC, we conducted this study.

Materials and Methods

Study Design and Patients

This study conformed to the Declaration of Helsinki and was approved by Ethics Committee of the Fifth Center of Chinese PLA General Hospital. Informed consents were signed from patients before studies. This study has already registered in NCT03892577.

We retrospectively included systemic therapy-naïve uHCC patients who received sorafenib or lenvatinib combined with PD-1 inhibitors treatment from October 2018 to October 2021 at the Fifth Center of the General Hospital of the People’s Liberation Army. Patients were excluded if they [1] had secondary HCC or end-stage HCC (defined as BCLC stage D),\textsuperscript{5} [2] were amenable to curative surgical or regional therapy, [3] had other tumors simultaneously, [4] had no evaluable target regions (in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), and [5] had no effective follow-up, [6] without sufficient liver function (defined as Child-Pugh Score higher than B7).\textsuperscript{7}

Patients were recommended to receive sorafenib or lenvatinib according to their standard dose (oral: 400 mg sorafenib twice daily, 12 mg or 8 mg lenvatinib according to the patients’ body weight). Tolerated doses of sorafenib or lenvatinib were allowed. Patients received PD-1 inhibitors (pembrolizumab 200mg, sintilimab 200mg, or camrelizumab 200mg) intravenously once every three weeks.

Assessments and Endpoints

Responses were assessed once every 6–8 weeks according to the RECIST v1.1, by two senior imaging doctors independently. Combination treatment continued until the progression of the disease (PD) was confirmed by radiology, adverse events, death, or other reasons (including conversion therapy, patients’ intention, etc.).

The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). OS was defined as the time from treatment initiation to death from any cause. PFS was defined as the time from treatment initiation to progressive disease or death for any reason, whichever came first.\textsuperscript{29} Adverse events (AEs) and immune-related AEs (irAEs) were evaluated in all patients using common Terminology Criteria for Adverse Events v5.0.

Data Collection and Group

Demographic data (including sex, age, and alcohol consumption), etiology of hepatitis (including HBV or HCV infection), Eastern Cooperative Oncology Group (ECOG), Charlson comorbidity index (CCI),\textsuperscript{30} chronic disease (hypertension or diabetes), liver function, radiological characteristics of HCC (tumor size, macroscopic vascular invasion, and extrahepatic metastasis), serum alpha-fetoprotein (AFP) levels, and data on previous regional therapy were collected at baseline. Combinations of locoregional therapies during treatment were also recorded.

Because most HCC-related prospective clinical trials set a cut-off age of 65 years, we followed this standard. We divided patients into young patients (marked as YPs, defined as patients younger than 65 years old, with group’s name: YP) and old patients (marked as OPs, opposite from YPs, with group’s name: OP). Moreover, considering the lack of...
real-world efficacy data for ICIs in HCC patients over 75 years of age [16]; and recently, Vithayathil et al have used a similar age division when exploring the efficacy and safety of A+T in elderly uHCC patients;\(^{28}\) we performed a subgroup analysis in OPs. We further divided OPs into OP1s (for old patients aged from 65 to 74 years old, with group’s name: OP1) and OP2s (for patients aged 75 or older, with group’s name: OP2).

Considering the heterogeneity of patients with ECOG 2 and/or Child-Pugh B, we report the efficacy and safety of these two subgroups separately.

**Statistical Analyses**

All data calculations were performed using R language version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Medical Pack for Windows (version 25.0; SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations, and categorical variables were summarized using numbers and percentages. We used package “compareGroups” to test the statistical difference of index at baseline automatically.\(^{31}\) To reduce confounding, we performed 1:1 matching using the nearest-neighbor marching method, considering those variables showing P < 0.1 by package “MatchIt”.\(^{32}\)

Survival data were analyzed using the Kaplan–Meier method and compared between groups using two-tailed Log rank tests. ORR and DCR were expressed as ratios with 95% confidence intervals (CI) and compared using Pearson’s chi-square analysis or Fisher’s exact test. Cox proportional hazards models were used to explore the association between the covariates and PFS or OS. Variables showing P < 0.1 in univariate analysis were subjected to stepwise multivariate analysis. A summary of each model for OS and PFS is presented as hazard ratios (HR) and 95% CI. Survival analysis, survival plots, and Cox proportional hazards models were conducted with the help of packages “survival”, “survminer”, “MASS” and “ggplot2”.\(^{33–36}\)

**Results**

**Baseline Characteristics of the Study Population**

From October 2018 to October 2021, a total of 169 eligible patients were consecutively enrolled in our study: 121 were in the YP group and the other 48 in the OP group. For OPs, 24 were in OP1 and 24 in OP2.

As shown in Table 1, the percentage of male patients (86.8% vs 70.8%, p = 0.026), those with HBV infection (92.6% vs 68.8%, p < 0.001), macroscopic vascular invasion (78.5% vs 60.4%, p = 0.027), and having tumor sizes ≥5 cm (22.3% vs 45.8%, p = 0.004) was statistically higher in YPs compared to OPs, with relatively lower percentage of hypertension (22.3% vs 45.8%, p = 0.004) and a tendency to receive lenvatinib being higher (86.8% vs 70.8%, p = 0.026).

Subgroup analysis of OPs suggested that CCI was higher [(7.5±1.9) vs (9.0±1.8), p = 0.007], with higher percentages of hypertension (25.0% vs 66.7%, p = 0.009) and ECOG 1–2 (79.2% vs 33.3%, p = 0.005) in OP2s compared to OP1s, with similar demographics and characteristics of tumors between the two subgroups (Table 1).

**Overall Efficacy**

At the data cut-off (May 2022), following a median follow-up of 16.7 months (95% CI: 15.4–18.0) and a median duration of treatment (DOT) of 5.7 (95% CI: 4.1–7.3) months, a total of 140 (82.8%) patients had stopped combination treatment. PD, including death, was the main reason for discontinuation of treatment (79.3%), followed by AEs (12.9%), and other reasons (7.9%) for these 140 patients (Supplementary Table 1). In OP2s, a total of 20 (87.5%) patients discontinued first-line antitumor treatment, 13 (65.0%) due to PD, six (30.0%) due to adverse events (four of them due to irAEs), and one (5%) due to other reasons (Supplementary Table 1). Total 4 patients (2.3%) in our study were lost to follow-up. Overall median OS and PFS were 27.3 months (95% CI: 14.7–39.9) and 5.8 (95% CI: 4.4–7.2) months, respectively. Overall ORR and DCR were 20.7% (95% CI: 15–27%) and 72.2% (95% CI: 65–79%), respectively (Table 2).

**Comparison of Efficacy Between YP and OP**

For the raw data before matching, no significant difference was found among all efficacy indices between the YP and OP groups (Figure 1 and Table 2). After matching, 92 patients remained in the study. Median DOT was 5.5 (95% CI: 3.7–
Table 1 Baseline Characteristics of All Patients

|                        | Overall | Before Matching | p-value | After Matching | p-value | Subgroup Analysis of OP | p-value |
|------------------------|---------|-----------------|---------|----------------|---------|------------------------|---------|
|                        | N = 169 | N = 121 | N = 48 | N = 48 | N = 48 | N = 48 | N = 24 | N = 24 |
| Gender:                |         |         |       |       |       |       |       |       |
| Female                 |         |         |       |       |       |       |       |       |
| Male                   |         |         |       |       |       |       |       |       |
| Hepatitis:             |         |         |       |       |       |       |       |       |
| HBV                    |         |         |       |       |       |       |       |       |
| HCV                    |         |         |       |       |       |       |       |       |
| NBNC                   |         |         |       |       |       |       |       |       |
| Alcohol Consumption    |         |         |       |       |       |       |       |       |
| Hypertension           |         |         |       |       |       |       |       |       |
| Diabetes               |         |         |       |       |       |       |       |       |
| Charlson Comorbidity Index |     |         |       |       |       |       |       |       |
| ECOG:                  |         |         |       |       |       |       |       |       |
| Child-Pugh:            |         |         |       |       |       |       |       |       |
| A                      |         |         |       |       |       |       |       |       |
| B*                     |         |         |       |       |       |       |       |       |
| BCLC:                  |         |         |       |       |       |       |       |       |
| Tumor size (cm):       |         |         |       |       |       |       |       |       |
| AFP (ng/mL):           |         |         |       |       |       |       |       |       |
| Tyrosine Kinase Inhibitor: |       |         |       |       |       |       |       |       |
| Lenvatinib             |         |         |       |       |       |       |       |       |
| Sorafenib              |         |         |       |       |       |       |       |       |
| Previous Locoregional Therapy | |         |       |       |       |       |       |       |
| Combination of Locoregional Therapy | |         |       |       |       |       |       |       |

Note: *For patients with Child-Pugh B7.

Abbreviations: YP, younger patients aged <65 years; OP, older patients aged ≥65 years; OP1, older patients aged 65–74 years; OP2, older patients aged ≥75 years; HBV, Hepatitis B virus; HCV, Hepatitis C virus; NBNC, none-HBV and none-HCV infection; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-feto-protein.
|                | Raw Data | Before Matching | After Matching | Subgroup Analysis |
|----------------|----------|-----------------|----------------|-------------------|
|                | Overall N = 169 | YP N = 121 | OP N = 48 | p-value | YP N = 48 | OP N = 48 | p-value | OP1 N = 24 | OP2 N = 24 | p-value |
| Response       |          |                 |                |         |          |                |         |            |              |         |
| PR             | 35       | 24              | 11             | 0.656   | 6        | 11             | 0.181   | 9           | 2           | 0.016   |
| SD             | 87       | 66              | 21             | 0.411   | 29       | 21             | 0.606   | 10          | 11          | 0.066   |
| PD             | 43       | 30              | 13             | 0.018   | 13       | 13             | 0.99    | 4           | 9           | 0.009   |
| NE             | 4        | 1               | 3              |          | 0        | 3              |          | 1           | 2           |         |
| ORR, % (95% CI)| 20.7% (15–27%) | 19.8% (13–27%) | 22.9% (11–35%) | 0.656   | 12.5% (3–22%) | 22.9% (11–35%) | 0.181   | 37.5% (18–57%) | 8.3% (0–19%) | 0.016   |
| DCR, % (95% CI)| 72.2% (65–79%) | 74.3% (67–82%) | 66.7 (53–80%) | 0.411   | 72.9% (60–85%) | 66.7 (53–80%) | 0.606   | 79.2% (63–95%) | 54.2% (45–83%) | 0.066   |
| DOT, median (95% CI) months | 5.7 (4.1–7.3) | 5.8 (4.0–7.6) | 5.1 (2.1–8.1) | 0.818   | 5.5 (3.7–7.3) | 5.1 (2.1–8.1) | 0.671   | 9.1 (2.9–15.3) | 4.0 (2.1–5.9) | 0.009   |
| PFS, median (95% CI) months | 5.8 (4.4–7.2) | 6.1 (4.7–7.5) | 5.2 (2.6–7.8) | 0.426   | 6.6 (3.6–9.6) | 5.2 (2.6–7.8) | 0.99    | 11.5 (8.2–14.8) | 4.6 (2.6–6.6) | 0.006   |
| 3-months PFS rate, % (95% CI) | 80.30% | 81.40% | 77.10% |          | 85.40% | 77.10% |          | 95.70% | 57.90% |         |
| 6-months PFS rate, % (95% CI) | 49.50% | 50.40% | 46.60% |          | 56.00% | 46.60% |          | 67.80% | 22.10% |         |
| 12-months PFS rate, % (95% CI) | 18.80% | 16.10% | 27.70% |          | 22.60% | 27.70% |          | 40.20% | 14.70% |         |
| OS, median (95% CI) months | 27.3 (14.7–39.9) | 27.3 (9.8–44.8) | 21.9 (NE-NE) | 0.374   | 27.3 (11.0–43.6) | 21.9 (NE-NE) | 0.44    | NE (NE-NE) | 17.0 (11.2–22.8) | 0.026   |
| 3-months OS rate, % (95% CI) | 91.10% | 92.60% | 91.60% |          | 97.90% | 91.60% |          | 95.70% | 82.90% |         |
| 6-months OS rate, % (95% CI) | 80.80% | 78.30% | 84.90% |          | 91.70% | 84.90% |          | 95.70% | 73.70% |         |
| 12-months OS rate, % (95% CI) | 64.10% | 62.10% | 69.60% |          | 78.40% | 69.60% |          | 81.10% | 57.50% |         |

Abbreviations: YP, younger patients aged <65 years; OP, older patients aged ≥65 years; OP1, older patients aged 65–74 years; OP2, older patients aged ≥75 years; PR, partial response; SD, stable disease; PD, progression of disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate.
Figure 1 Survival outcomes for different groups of patients who received first-line sorafenib or lenvatinib plus PD-1 inhibitors. (A) OS for all patients before matching; (B) OS for all patients after matching; (C) PFS for all patients before matching; (D) PFS for all patients after matching; (E) OS for elderly patients; (F) PFS for elderly patients. Abbreviations: YP, younger patients aged <65 years; OP, older patients aged ≥65 years; OP1, older patients aged 65–74 years; OP2, older patients aged ≥75 years; PFS, progression-free survival; OS, overall survival.
7.3) and 5.1 (95% CI: 2.1–8.1) months for the YP and OP groups, with no significant difference (Table 2). Median OS and PFS in the YP and OP were 27.3 (95% CI: 11.0–43.6) vs 21.9 (95% CI: NE–NE) months (p = 0.44) and 6.6 (95% CI: 3.6–9.6) vs 5.2 (95% CI: 2.6–7.8) months (p = 0.99), respectively. ORR and DCR in the two cohorts were 12.5% (95% CI: 3–22%) and 22.9% (95% CI: 11–35%), respectively (p = 0.181), and 72.9% (95% CI: 60–85%) and 66.7% (95% CI: 53–80%), respectively (p = 0.606) (Figure 1 and Table 2).

**Subgroup Analysis of Efficacy in OP1 and OP2**

Subgroup analysis demonstrated that efficacy in OP1 was statistically better than that in OP2 in terms of OS (median with 95% CI: NE [NE–NE] vs 17.0 [11.2–22.8] months, p = 0.026) and PFS (median with 95% CI: 11.5 [8.2–14.8] vs 4.6 [2.6–6.6] months, p = 0.006). Three-month, 6-month, and 12-month PFS and OS rates in OP1 were 95.70%, 67.80%, and 40.20% and 95.70%, 95.70% and 40.20% respectively. Those in OP2 were 57.90%, 22.10%, and 14.70%, respectively. ORR and DCR in OP1 and OP2 were 37.5% (95% CI: 18–57%) vs 8.3% (95% CI: 0–19%), p = 0.016 and 79.2% (95% CI: 63–95%) vs 54.2% (95% CI: 45–83%), p = 0.066, respectively (Figure 1 and Table 2). Median DOT in OP1 and OP2 was 9.1 (95% CI: 2.9–15.3) and 4.0 (95% CI: 2.1–5.9) months, with statistical difference (p = 0.009) (Figure 1 and Table 2).

**Factors Influencing Efficacy**

Examinations of the prognostic factors for OS and PFS stratified by age with Cox hazard multivariable analysis showed that for YPs, ECOG 1–2 (HR: 9.5, 95% CI: [2.4–38], p = 0.001), AFP ≥200 ng/mL (HR: 9.5, 95% CI: [2.4–38], p = 0.001), and Child-Pugh B (HR: 4.6, 95% CI: [1.4–15], p = 0.012) were risk factors for OS and HBV infection (HR: 3.5, 95% CI: [1.01–12.2], p = 0.048) to be risk factors for PFS. While for OPs, ECOG 1–2 (HR: 5.3, 95% CI: [1.1–26], p = 0.04) and AFP ≥200 ng/mL (HR: 4.6, 95% CI: [1.2–17], p = 0.023) were found to be unfavorable factors for OS and age ≥75 years (HR: 3.1, 95% CI: [1.28–7.3], p = 0.012) to be risk factors for PFS (Table 3). The results of univariate Cox analysis are described in Supplementary Tables 2 and 3.

**Post-Progression Therapy**

Of the 106 patients with PD (12 in OP2), 66 continued antitumor therapies (7 in OP2). Among these 106 patients, compared to the 40 patients who discontinued systemic therapy after first-line systemic therapy, the 66 patients who received post-progression systemic therapy tended to have a better baseline situation: ECOG 0 (57.6% vs 22.5%, p = 0.001), Child-Pugh A (68.2% vs 45.0%, p = 0.031), BCLC stage B (13.6% vs 0%, p = 0.013), AFP < 200 (60.6% vs 35.0%, p = 0.018), and combination of regional therapy (65.2% vs 40.0%, p = 0.020) (Supplementary Table 4). Of the 66 patients, 14 and 52 received TKIs monotherapy (21.2%) and TKIs plus ICIs therapy (78.8%), respectively. In OP2, 2 and 5 patients received TKIs monotherapy and TKIs plus ICIs, respectively (Supplementary Table 5). Those 66 patients who received post-progression therapy tended to survive better than the other 40 patients (median OS: NE [95% CI: NE–NE] vs 6.4 [95% CI: 4.4–8.4], p < 0.001). Similar trend was found in OP2, with marginal statistical difference (median OS: 21.9 [95% CI: NE–NE] vs 17.0 [95% CI: NE–NE], p = 0.056) (Supplementary Figure 1).

**Safety**

All patients were assessed for safety. The overall incidence of AEs was 100%. The details of the AEs are described in Table 4.

Hypertension, decreased appetite and fatigue were the top three AEs for all patients. The most frequent grades 3–4 AEs (>5%) were hypertension, decreased platelet count, drug-related hepatic injury, proteinuria, and increased blood bilirubin for all patients and hypertension, drug-related hepatic injury, decreased appetite, dermatologic events, and nausea for OP2.

In our study, we monitored and recorded immune-mediated hepatitis, adrenal insufficiency, skin reaction, immune-mediated hepatitis, and four kinds of irAEs, which were closely related to discontinuation of treatment. These irAEs occurred in 25 patients (14.8%, including seven patients in OP2). The most common irAEs were skin reactions (7.1%), followed by immune-mediated hepatitis (4.1%), immune-mediated pneumonitis (3.6%), and adrenal insufficiency (1.2%).
The most common irAEs in OP2 were immune-mediated hepatitis (16.7%), following skin reaction (8.3%) and adrenal insufficiency (4.2%). Nearly all irAEs in OP2 were severe irAEs. Four of the patients in OP2 discontinued treatment owing to irAEs (Table 5 and Supplementary Table 1).

**Efficacy and Safety of Patients with Child-Pugh B and/or ECOG 2**

For patients with an ECOG 2 performance status, both OS and PFS were significantly lower than those in patients with ECOG 0–1 [median OS with 95% CI: 6.2 (2.4–10.0) vs 27.3 (17.6–37.0), p < 0.0001 and median PFS with 95% CI: 4.0 (3.2–4.8) vs 6.6 (5.2–8.0), p = 0.0011] (Supplementary Figure 2). For patients with Child-Pugh B, OS was significantly shorter than patients with Child-Pugh A [median with 95% CI: 13.7 (7.3–20.1) vs NE (NE-NE), p = 0.015]. However,
Table 4 Adverse Events

| AEs, n (%)                        | All Patients (N = 169) | Patients < 75 Years (N = 145) | OP2 (N = 24) |
|----------------------------------|------------------------|-------------------------------|--------------|
| **Abdominal pain**               |                        |                               |              |
| Any grade                        | 34 (20.1)              | 33 (22.8)                     | 1 (4.2)      |
| Grade 3/4                        | 5 (3.0)                | 5 (3.4)                       | 0            |
| **Abnormal Thyroid Function**    |                        |                               |              |
| Any grade                        | 63 (37.3)              | 54 (37.2)                     | 9 (37.5)     |
| Grade 3/4                        | 0                      | 0                             | 0            |
| **Decreased appetite**           |                        |                               |              |
| Any grade                        | 80 (47.3)              | 66 (45.5)                     | 14 (58.3)    |
| Grade 3/4                        | 8 (4.7)                | 6 (4.1)                       | 2 (8.3)      |
| **Decreased platelet count**     |                        |                               |              |
| Any grade                        | 63 (37.3)              | 61 (42.1)                     | 2 (8.3)      |
| Grade 3/4                        | 14 (8.3)               | 14 (9.7)                      | 0            |
| **Decreased weight**             |                        |                               |              |
| Any grade                        | 58 (34.3)              | 49 (33.8)                     | 9 (37.5)     |
| Grade 3/4                        | 3 (1.8)                | 2 (1.4)                       | 1 (4.2)      |
| **Decreased white blood cell count** |                     |                               |              |
| Any grade                        | 65 (38.5)              | 59 (40.7)                     | 6 (25.0)     |
| Grade 3/4                        | 3 (1.8)                | 3 (2.1)                       | 0            |
| **Dermatologic events**          |                        |                               |              |
| Any grade                        | 65 (38.5)              | 60 (41.4)                     | 5 (20.8)     |
| Grade 3/4                        | 8 (4.7)                | 6 (4.1)                       | 2 (8.3)      |
| **Diarrhea**                     |                        |                               |              |
| Any grade                        | 68 (40.2)              | 60 (41.4)                     | 8 (33.3)     |
| Grade 3/4                        | 6 (3.6)                | 5 (3.4)                       | 1 (4.2)      |
| **Drug-related Hepatic Injury**  |                        |                               |              |
| Any grade                        | 15 (8.9)               | 10 (6.9)                      | 5 (20.8)     |
| Grade 3/4                        | 14 (8.3)               | 9 (6.2)                       | 5 (20.8)     |
| **Elevated aspartate aminotransferase** |                     |                               |              |
| Any grade                        | 35 (20.7)              | 32 (22.1)                     | 3 (12.5)     |
| Grade 3/4                        | 7 (4.1)                | 7 (4.8)                       | 0            |
| **Fatigue**                      |                        |                               |              |
| Any grade                        | 77 (45.6)              | 66 (45.5)                     | 11 (45.8)    |
| Grade 3/4                        | 5 (3.0)                | 5 (3.4)                       | 0            |
| **Gastrointestinal hemorrhage**  |                        |                               |              |
| Any grade                        | 14 (8.3)               | 14 (9.7)                      | 0            |
| Grade 3/4                        | 7 (4.1)                | 7 (4.8)                       | 0            |
| **Hyperamylasemia**             |                        |                               |              |
| Any grade                        | 13 (7.7)               | 12 (8.3)                      | 1 (4.2)      |
| Grade 3/4                        | 0                      | 0 (0)                         | 0            |
| **Hypertension**                | 110 (65.1)             | 93 (64.1)                     | 17 (70.8)    |
| Grade 3/4                        | 31 (18.3)              | 24 (16.6)                     | 7 (29.2)     |
| **Pneumonitis**                 |                        |                               |              |
| Any grade                        | 6 (3.6)                | 6 (4.1)                       | 0            |
| Grade 3/4                        | 4 (2.4)                | 4 (2.8)                       | 0            |
| **Increased blood bilirubin**    |                        |                               |              |
| Any grade                        | 64 (37.9)              | 57 (39.3)                     | 7 (29.2)     |
| Grade 3/4                        | 9 (5.3)                | 9 (6.2)                       | 0            |
| **Nausea**                      |                        |                               |              |
| Any grade                        | 48 (28.4)              | 41 (28.3)                     | 7 (29.2)     |
| Grade 3/4                        | 3 (1.8)                | 1 (0.7)                       | 2 (8.3)      |

(Continued)
PFS in Child-Pugh B resembled that in Child-Pugh A [median PFS with 95% CI: 5.8 (2.7–8.9) vs 6.1 (4.7–7.5), \( p = 0.63 \)].

With regard to safety, hypertension, decreased appetite and fatigue were the top 3 AEs for all grade for either Child-Pugh B or ECOG 2. Decreased platelet count (12.9% for Child-Pugh B and 9.1% for ECOG 2), drug-related hepatic injury (12.9% for Child-Pugh B and 6.1% for ECOG 2), gastrointestinal hemorrhage (10.0% for Child-Pugh B and 9.1% for ECOG 2), hypertension (14.3% for Child-Pugh B and 18.2% for ECOG 2), increased blood bilirubin (5.7% for Child-Pugh B and 9.1% for ECOG 2), and proteinuria (5.7% for Child-Pugh B and 6.1% for ECOG 2) were the most common (>5%) severe AEs (Supplementary Table 6).

### Table 4 (Continued).

| AEs, n (%) | All Patients (N = 169) | Patients < 75 Years (N = 145) | OP2 (N = 24) |
|-----------|------------------------|-------------------------------|-------------|
| **Periodontal disease** |                        |                               |             |
| Any grade | 15 (8.9)               | 14 (9.7)                      | 1 (4.2)     |
| Grade 3/4 | 1 (0.6)                | 1 (0.7)                       | 0           |
| **Proteinuria** |                        |                               |             |
| Any grade | 61 (36.1)              | 55 (37.9)                     | 6 (25.0)    |
| Grade 3/4 | 10 (5.9)               | 10 (6.9)                      | 0           |
| **Vomiting** |                        |                               |             |
| Any grade | 29 (17.2)              | 25 (17.2)                     | 4 (16.7)    |
| Grade 3/4 | 3 (1.8)                | 2 (1.4)                       | 1 (4.2)     |

**Notes:** *Considering the impact of targeted drugs, it was hard to distinguish whether AEs were caused by targeted drugs or immune drugs. **Dermatologic events included hand-foot syndrome, rash and reactive cutaneous capillary endothelial proliferation (RCCEP). ***Drug-related hepatic injury was diagnosed after excluding other possible reasons, including viral flare, biliary or vascular obstruction, infection, alcohol consumption or progression of tumor.

### Table 5 AE of Special Interest, Immune-Mediated (Any Attribution)

| irAEs, n (%) | All Patients (N = 169) | Patients < 75 Years (N = 145) | OP2 (N = 24) |
|-------------|------------------------|-------------------------------|-------------|
| **Adrenal insufficiency** |                        |                               |             |
| Any grade   | 2 (1.2)                | 1 (0.7)                       | 1 (4.2)     |
| Grade 3/4   | 1 (0.6)                | 0                             | 1 (4.2)     |
| **Immune-mediated hepatitis** |                    |                               |             |
| Any grade   | 7 (4.1)                | 3 (2.1)                       | 4 (16.7)    |
| Grade 3/4   | 6 (3.6)                | 2 (1.4)                       | 4 (16.7)    |
| **Immune-mediated pneumonitis** |                  |                               |             |
| Any grade   | 6 (3.6)                | 6 (4.1)                       | 0           |
| Grade 3/4   | 4 (2.4)                | 4 (2.8)                       | 0           |
| **Skin reaction** |                    |                               |             |
| Any grade   | 12 (7.1)               | 10 (6.9)                      | 2 (8.3)     |
| Grade 3/4   | 4 (2.4)                | 3 (2.1)                       | 1 (4.2)     |

**Notes:** *Including reactive cutaneous capillary endothelial proliferation (RCCEP) and immune-mediated rash.

PFS in Child-Pugh B resembled that in Child-Pugh A [median PFS with 95% CI: 5.8 (2.7–8.9) vs 6.1 (4.7–7.5), \( p = 0.63 \)].

With regard to safety, hypertension, decreased appetite and fatigue were the top 3 AEs for all grade for either Child-Pugh B or ECOG 2. Decreased platelet count (12.9% for Child-Pugh B and 9.1% for ECOG 2), drug-related hepatic injury (12.9% for Child-Pugh B and 6.1% for ECOG 2), gastrointestinal hemorrhage (10.0% for Child-Pugh B and 9.1% for ECOG 2), hypertension (14.3% for Child-Pugh B and 18.2% for ECOG 2), increased blood bilirubin (5.7% for Child-Pugh B and 9.1% for ECOG 2), and proteinuria (5.7% for Child-Pugh B and 6.1% for ECOG 2) were the most common (>5%) severe AEs (Supplementary Table 6).

### Discussion

HCC is a malignant carcinoma with poor prognosis. Sorafenib, lenvatinib, and A+T is the standard first-line systemic therapy for uHCC. To date, the application of first-line TKIs plus PD-1 inhibitors in uHCC patients has received the consensus of the Chinese hepatobiliary clinical experts and is widely used in clinical practice. Although previous studies have clarified the efficacy and safety of sorafenib or lenvatinib monotherapy and A+T in aging patients with uHCC, and the efficacy and potential downstaging and conversion ability of TKIs plus PD-1 inhibitors have been explored in previous studies, whether aging patients would benefit from TKIs plus PD-1 inhibitors, especially for PD-1 inhibitors used in patients aged ≥75 years old, remains unclear before our study. In our study, we found median OS to
be 17.0 (95% CI: 11.2–22.8) months in this group of elderly patients treated with first-line sorafenib or lenvatinib plus PD-1 inhibitors, with nearly 30% discontinuing first-line systemic therapy due to AEs (25.0% due to irAEs), which suggested that the use of target drugs with PD-1 inhibitors, was promising but has to be done with caution in elderly patients aged ≥75 years.

In our study, baseline characteristics differed between the age groups. Though some homogeneity was found between OP1 and OP2 considering relatively similar demographic and etiological background and characteristics of tumors, performance status and comorbidities, especially chronic cardiovascular disease such as hypertension, were more complicated in OP2, suggesting heterogeneity in old patients. In OP2, seven (29.2%) patients were ECOG 2, 16 (66.7%) had complications with hypertension, and mean CCI was 9.0 ± 1.8, higher than those in OP1 (Table 1). For this part of the population, ECOG >1, often accompanied by serious cardiovascular events, are usually not within the inclusion criteria of prospective clinical trials. In other words, the OP2 in our group can partially represent the characteristics of aging patients in the real-world clinical practice.

Nearly all efficacy endpoints in OP2 were worse than those in OP1. Median PFS in OP2 were 4.6 vs 11.5 months, with 12-months PFS rate of 14.7% vs 40.2% (p = 0.006) compared to OP1. Median OS in OP2 were 17.0 vs NE, with 12-months OS rate of 57.50% vs 81.10% (p = 0.026). Unbalanced baseline characteristics might be the primary reason for these differences. Multivariate cox regression model showed age ≥75 years to be an independent risk factor for PFS for OPs, which suggested that short-term efficacy of sorafenib or lenvatinib plus PD-1 inhibitors might not be satisfied.

However, opposite from short-term efficacy, though with more complicated baseline characteristics in OP2, median OS in OP2 was 17.0 months, still longer than uHCC patients who received sorafenib or lenvatinib alone in REFLECT clinical trial (median OS in sorafenib arm and lenvatinib arm were 12.3 and 13.6 months, respectively). Application of sorafenib or lenvatinib monotherapy in OP2 with uHCC has also been reported in many manuscripts. Tada et al found cumulative overall survival at 50, 100, 150, and 200 days was 93.3%, 93.3%, 83.5%, and 79.3%, respectively, with unknown median OS in OP2 treated with first-line lenvatinib. A recent international cohort study summed up that median OS in OP2 treated with sorafenib was 7.2 months. OS for OP2 in our study was longer than that in REFLECT and real-world studies. In fact, a similar long-term outcome was found in all patients recruited in our study. Overall median OS reported in our study was 27.3 months, higher than uHCC patients who received lenvatinib plus pembrolizumab in phase 1b clinical trial (median OS: 22.0 months).

A possible explanation for this result could be the high proportion of post-progression therapies. In our cohort, for the 106 patients with radioologically confirmed PD (12 in OP2), 66 (62.3%, including 7 in OP2) continued post-progression antitumor therapy (Supplementary Tables 1 and 5). uHCC patients who received post-progression antitumor therapy were more likely to survive than those who did not, regardless of age (Supplementary Figure 1). Patients with post-progression therapies appeared have a better prognosis. However, further exploration of baseline among these 106 patients showed that patients who were to receive second-line systemic therapy tended to have better baseline liver function, better physical performance, and characteristics of carcinoma (Supplementary Table 4). This suggests that patients with better baseline conditions would have more opportunities to receive later-line systemic treatment, with more satisfying prognosis. In other words, the application of TKIs plus PD-1 inhibitors in patients with Child-Pugh B7 and ECOG >0 has to be cautious. However, for patients with permitted conditions, active later-line systemic therapy is still recommended, including OP2. Moreover, in our cohort, nearly half of the patients received locoregional therapies during first-line systemic therapy, including OP2 (54.2%). The synergistic effect of locoregional therapies on immunotherapy has been extensively reported in previous studies and LEAP-012 (NCT04246177) is still ongoing to prospectively explore it. Lastly, the efficacy of immunotherapy could be long-lasting and profound, even after discontinuation of PD-1 inhibitors.

In fact, chronological age itself might not be the primary reason for dismal prognosis. In our study, though great heterogeneity was found in YPs and OPs, following the traditional cutoff age at 65 years old, no differences were found in efficacy endpoints between the two groups (Table 2 and Figure 1), which is consistent with most previous studies. Application of ICIs in other solid tumors suggested similar long-term outcomes in aged patients, following cut-off age at 70, 75, or 80 years, which suggested promising prospect of application of ICIs in aging patients. However, age-related decreased performance status, complicated comorbidities, decreased function of solid...
organs (especially for aging liver with decreased ability of metabolism), immunosenescence, etc. could affect clinical decision-making and the efficacy of drugs. In our study, though age ≥75 years was confirmed to be a risk factor for poorer PFS, no direct correlation was found between age ≥75 years and OS (Table 3). However, ECOG >0 and AFP ≥200 ng/mL were risk factors for dismal prognosis (Table 3), further proving these opinions.

Interestingly, we found that the ORR in OP1 (37.5%) was slightly higher than that reported in the KEYNOTE-524 (36.0%). This result corroborated that of LEAP-002 (NCT03713593). The primary explanation for this phenomenon could be the different etiological backgrounds of chronic liver disease. HCV infection dominated in OP1 patients, unlike young patients, which might contribute to the relatively lower aggressiveness characteristics of HCC. Moreover, compared with OP2, these patients tended to have better performance status, which allowed them to receive more active and frequent locoregional therapies. Further mechanisms underpinning this phenomenon should be verified through basic research, prospective clinical trials, and epidemiology reports.

However, for patients in OP2 with uHCC who received TKIs alone and aging patients with other solid tumors who received ICIs, incidence of AEs and irAEs tended to be higher, suggesting decreased tolerability to drugs. Similar results were found in OP2 patients with uHCC who received sorafenib or lenvatinib plus PD-1 inhibitors in our study, which had not been fully explored before. For all 169 patients included in our study, 10.7% of patients discontinued first-line systemic therapies due to AEs. But in OP2, the percentage of discontinuation of treatment increased to 30%, including irAEs (Supplementary Table 1). Severe hepatobiliary irAEs and severe irAEs tended to occur earlier and more frequently in OP2, correlating with Baldini et al’s results, which might contribute to relatively shorter DOT (median DOR in OP2: 4.0 months) (Table 2), thus negatively affecting the efficacy of drugs.

In fact, overall safety profiles of sorafenib or lenvatinib plus PD-1 inhibitors in our study were comparable to those reported in REFELECT and KEYNOTE-524 clinical trials. Overall incidence of irAEs in all patients was 14.8%, similar to overall incidence of irAEs in KEYNOTE-224. This demonstrated that in the general population, at least for those under the age of 75 years, application of PD-1 inhibitors was generally safe. However, considering the relatively higher incidence of irAEs in OP2, application of PD-1 inhibitors has to be done with caution.

To our knowledge, this is the first cohort study to summarize the efficacy and safety of sorafenib- or lenvatinib-based combination therapy with PD-1 inhibitors in elderly patients with uHCC in a real-world situation, as a supplement result as LEAP-002. However, considering that this was a retrospective study with very limited samples in one specialized hospital, information, admission, and immortal time biases could not be easily avoided. Due to the cross-sectional nature of adverse events between sorafenib, lenvatinib, and PD-1 inhibitors, the actual incidence of irAEs might be higher than we reported, which requires judgement of multi-disciplinary teams in future prospective clinical trials. However, considering its social value, this study could provide guidance for future clinical practice.

Conclusion
For patients aged ≥75 years, application of PD-1 inhibitors in combination with sorafenib or lenvatinib is promising, but this has to be done with caution and needs to be confirmed by future prospective studies.

Abbreviations
AE, adverse event; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; A+T, atezolizumab and bevacizumab; BCLC, Barcelona Clinic Liver Cancer; CCI, Charlson comorbidity index; CI, confidence intervals; DCR, disease control rate; DOT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; NE, not evaluable;

OPs, old patients, defined as patients aged ≥65 years, with group’s name: OP; OP1s, for old patients aged from 65 to 74 years, with group’s name: OP1; OP2s, for old patients aged ≥75 years, with group’s name: OP2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; uHCC, unresectable hepatocellular carcinoma; YPs, young patients, defined as patients aged <65 years, with group’s name: YP.
Data Sharing Statement
All the datasets on which the conclusions of this study relied were displayed in the manuscript.

Ethics Approval and Informed Consent
This study conformed to the Declaration of Helsinki and was approved by Ethics Committee of the Fifth Center of Chinese PLA General Hospital (approval number: KY-2022-4-25-1). Informed consents were signed from patients before studies. This study has already registered in NCT03892577.

Consent for Publication
All authors gave their consent for publication.

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Author Contributions
All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure
The authors have no conflicts of interest to declare in this work.

References
1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Villanueva A, Longo DL. Hepatocellular carcinoma. N Engl J Med. 2019;380(15):1450–1462. doi:10.1056/nejmra1713263
3. Alsaab HO, Sau S, Alzhrani R, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol. 2017;8:561. doi:10.3389/fphar.2017.00561
4. Jiang Y, Chen M, Nie H, Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. Hum Vaccin Immunother. 2019;15(5):1111–1122. doi:10.1080/21645515.2019.1571892
5. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76 (3):681–693. doi:10.1016/j.jhep.2021.11.018
6. Zhao HT, Cai JQ. Chinese expert consensus on neoadjuvant and conversion therapies for hepatocellular carcinoma. World J Gastroenterol. 2021;27 (47):8069–8080. doi:10.3748/wjg.v27.i47.8069
7. Chinese Chapter of the International Hepato-Pancreato-Biliary Association;Group of Liver Surgery, Surgical Society of Chinese Medical Association;Expert Committee on Liver Cancer, Chinese Society of Clinical Oncology. Chinese multidisciplinary expert consensus on combined immunotherapy based on immune checkpoint inhibitors for hepatocellular carcinoma(2021 version). Zhonghua Gan Dan Wai Ke Za Zhi. 2021;29 (7):636–647. doi:10.3760/cma.j.cn501113-20210604-00261
8. Professional Committee for Prevention and Control of Hepatobiliary and Pancreatic Diseases of Chinese Preventive Medicine Association, Chinese Society of Liver Cancer, Liver Study Group of Surgery Committee of Beijing Medical Association, Editorial Board of Chinese Journal of Hepatobiliary Surgery. Chinese expert consensus on conversion therapy of immune checkpoint inhibitors combined antiangiogenic targeted drugs for advanced hepatocellular carcinoma(2021 Edition) [J]. Zhonghua Gan Dan Wai Ke Za Zhi. 2021;27(4):241251. Chinese. doi:10.3760/cma.j.cn113884-20210415-00138
9. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38(26):2966–2970. doi:10.1200/JCO.20.00808
10. Wu JY, Yin ZY, Bai YN, et al. Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a multicenter retrospective study. J Hepatocell Carcinoma. 2021;8:1233–1240. doi:10.2147/JHC.S332420
11. Zhu XD, Huang C, Chen YH, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. Liver Cancer. 2021;10(4):320–329. doi:10.1159/000514313

12. He MK, Liang RB, Zhao Y, et al. Lenvatinib, sorafenib, plus hepatic arterial infusion chemotherpay versus sorafenib alone for advanced hepatocellular carcinoma. Ther Adv Med Oncol. 2021;17:588359211002720. doi:10.1177/17588359211002720

13. Chen S, Xu B, Wu Z, et al. Pembrolizumab plus lenvatinib with or without hepatic arterial infusion chemotherpay in selected populations of patients with treatment-naive unresectable hepatocellular carcinoma exhibiting PD-L1 staining: a multicenter retrospective study. BMC Cancer. 2021;21(1):1126. doi:10.1186/s12885-021-08838-6

14. Huang C, Zhu XD, Chen YH, et al. Organ specific responses to first-line lenvatinib plus anti-PD-1 antibodies in patients with unresectable hepatocellular carcinoma: a retrospective analysis. Biomark Res. 2021;9(1):19. doi:10.1186/s40634-021-00274-z

15. Li Q, Cao M, Yuan G, et al. Lenvatinib plus camrelizumab vs. lenvatinib monotherapy as first-line treatment for unresectable hepatocellular carcinoma: a multicenter retrospective cohort study. Front Oncol. 2022;12:89079. doi:10.3389/fonc.2022.89079

16. Chen S, Wu Z, Shi F, et al. Lenvatinib plus TACE with or without pembrolizumab for the treatment of initially unresectable hepatocellular carcinoma harbouring PD-L1 expression: a retrospective study. J Cancer Res Clin Oncol. 2022;148(8):2115–2125. doi:10.1007/s00432-021-03767-4

17. Cai M, Huang W, Huang J, et al. Transarterial chemoembolization combined with lenvatinib plus PD-1 inhibitor for advanced hepatocellular carcinoma: a retrospective cohort study. Front Immunol. 2022;13:84837. doi:10.3389/fimmu.2022.84837

18. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology. 2019;156(2):377–491.e1. doi:10.1053/j. gastro.2018.08.065

19. Ramani A, Tapper EB, Griffin C, Shankar N, Parikh ND, Asrani SK. Hepatocellular carcinoma-related mortality in the USA, 1999–2018. Dig Dis Sci. 2022;67(8):4100–4111. doi:10.1007/s10620-022-07433-8

20. Tateishi R, Uchino K, Fujisawa N, et al. A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011–2015 update. J Gastroenterol. 2015;50(4):367–376. doi:10.1007/s00535-015-1523-5

21. Wang F, Mubarak S, Zhang Y, et al. Long-term trends of liver cancer incidence and mortality in China 1990–2017: a jointpoint and age-period-cohort analysis. Int J Environ Res Public Health. 2019;16(16):2878. doi:10.3390/ijerph16162878

22. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. Nature. 2018;561(7721):45–56. doi:10.1038/s41586-018-0457-8

23. Macías RR, Monte MJ, Serrano MA, et al. Impact of aging on primary liver cancer: epidemiology, pathogenesis and therapeutics. Aging. 2021;13(19):23416–23434. doi:10.18632/aging.203620

24. Lyu N, Yi JZ, Zhao M. Immunotherapy in older patients with unresectable hepatocellular carcinoma. Eur J Cancer. 2022;162:76–98. doi:10.1016/j.ejca.2021.11.024

25. Tada T, Kumada T, Hiraoka A, et al. Safety and efficacy of lenvatinib in elderly patients with unresectable hepatocellular carcinoma: a multicenter analysis with propensity score matching. Hepatol Res. 2020;50(1):75–83. doi:10.1111/hepr.13427

26. Hajiev S, Allara E, Motedayen Aval L, et al. Correction: impact of age on sorafenib outcomes in hepatocellular carcinoma: an international cohort study. Br J Cancer. 2021;124(9):1611. doi:10.1038/s41416-020-02141-5

27. Marta GN, da Fonseca LG, Braghieri MI, Moura F, Hoff PM, Sabbaga J. Efficacy and safety of sorafenib in elderly patients with advanced hepatocellular carcinoma. Clinics. 2021;76(e2498):e2498. doi:10.6061/clinics/2021/e2498

28. Vithayathil M, D’Alessio A, Fulgenzi CAM, et al. Impact of older age in patients receiving atezolizumab and bevacizumab for hepatocellular carcinoma. Liver Int. 2022;42(11):2538–2547. doi:10.1111/liv.15405

29. Corbaux P, Maillet D, Boespflug A, et al. Older and younger patients treated with immune checkpoint inhibitors have similar outcomes in real-life setting. Eur J Cancer. 2019;121:192–201. doi:10.1016/j.ejca.2019.08.027

30. Charlson ME, Carozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom. 2022;91(1):8–35. doi:10.1159/000521288

31. Subirana I, Sanz H, Vila J. Building bivariate tables: the comparegroups package for R. J Stat Softw. 2014;57(12):1–6. doi:10.18637/jss.v057.i12

32. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Softw. 2011;42:8. doi:10.18637/jss.v042.i08

33. Therneau TM. A package for survival analysis in R: R Package Version 3.1–12. Rochester, MN: Mayo Clinic. 2021.

34. Wnawald R. Modern Applied Statistics with S. Springer; 2002.

35. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1

36. Osu A, Uenami T, Koyama S, et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. JCI Insight. 2018;3:19. doi:10.1172/jci.insight.59125

37. Xie D, Sun Q, Wang X, et al. Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world. Ann Transl Med. 2021;9(8):652. doi:10.21037/atm-20-7037

38. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–390. doi:10.1056/NEJMoa070858

39. Muchnik E, Loh KP, Strawderman M, et al. Immune checkpoint inhibitors in real-world treatment of older adults with non-small cell lung cancer: immune checkpoint inhibitors and older adults. J Am Geriatr Soc. 2019;67(5):905–912. doi:10.1111/jgs.15750

40. Fukui T, Okuma Y, Nakahara Y, et al. Activity of nivolumab and utility of neutrophil-to-lymphocyte ratio as a predictive biomarker for advanced non-small-cell lung cancer: a prospective observational study. Clin Lung Cancer. 2019;20(3):208–214.e2. doi:10.1016/j.cllc.2018.04.021

41. Baldini C, Martin Romano P, Voisin AL, et al. Impact of aging on immune-related adverse events generated by anti-programmed death (ligand) PD-(L)1 therapies. Eur J Cancer. 2020;129:71–79. doi:10.1016/j.ejca.2020.01.013

42. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. Oncologist. 2017;22(8):963–971. doi:10.1634/theoncologist.2016-0450

43. Hunt NJ, Kang SWS, Lockwood GP, Le Couteur DG, Cogger VC. Hallmarks of aging in the liver. Comput Struct Biotechnol J. 2019;17:1151–1161. doi:10.1016/j.csbj.2019.07.021

Dovepress
46. Cantarini MC, Trevisani F, Morselli-Labate AM, et al. Effect of the etiology of viral cirrhosis on the survival of patients with hepatocellular carcinoma. *Am J Gastroenterol*. 2006;101(1):91–98. doi:10.1111/j.1572-0241.2006.00364.x

47. Lee SH, Choi HC, Jeong SH, et al. Hepatocellular carcinoma in older adults: clinical features, treatments, and survival: hepatocellular carcinoma in older adults. *J Am Geriatr Soc*. 2011;59(2):241–250. doi:10.1111/j.1532-5415.2010.03273.x

48. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label Phase 2 trial. *Lancet Oncol*. 2018;19(7):940–952. doi:10.1016/S1470-2045(18)30351-6