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ORIGINAL RESEARCH

Survival Outcomes and Prognostic Factors of Systemic Therapy for Advanced Hepatocellular Carcinoma: A Multidisciplinary Clinic Experience from Saudi Arabia

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Purpose: To investigate survival outcomes and prognostic factors of systemic therapies in advanced hepatocellular carcinoma (HCC) within Saudi Arabia, addressing the limited regional data.

Patients and Methods: A retrospective review of 670 HCC patients was utilized. 130 patients with advanced HCC who received first-line systemic therapy were identified, and data on demographics, tumor characteristics, treatment regimens, laboratory findings, and survival outcomes were collected. Treatment response and survival outcomes were evaluated using RECIST criteria and the Kaplan-Meier method, respectively.

Results: Our population's mean age was 70.4, majority being males. Sorafenib was the most frequently used, then nivolumab and the atezolizumab-bevacizumab (Atezo+Bev) combination. Median overall survival (OS) varied by treatment: patients receiving Atezo +Bev showed the longest OS, followed by nivolumab and sorafenib. No statistically significant difference was observed in survival. Despite the small sample size, this trend suggests a potential OS benefit with Atezo+Bev, particularly in patients with advanced hepatic dysfunction. Furthermore, 39.1% of patients had elevated alpha-fetoprotein (AFP) levels and 26.8% had sarcopenia. Multivariate analysis highlighted the elevated neutrophil-to-lymphocyte ratio (NLR) as a significant predictor of worse survival, reinforcing its relevance as a prognostic marker in HCC. Although sarcopenia demonstrated an improved survival trend, it was not statistically significant. Adverse events were consistent, with elevated AST, anorexia, and fatigue frequently observed.

Conclusion: This study illustrated Atezo+Bev's potential in improving OS in advanced HCC, with an elevated NLR identified as a key marker for poor prognosis. These findings support the need for prospective studies to confirm and expand regional insights into the management of HCC.

Keywords: hepatocellular carcinoma, neutrophil-to-lymphocyte ratio, sarcopenia, systemic therapy

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and a leading cause of cancer-related mortality in the United States.[1] In Saudi Arabia, liver cancer accounted for up to 3.3% of all cancer diagnoses in 2020 and ranked seventh most common cancer in men and 10th in women according to the latest national cancer registry, with hepatocellular carcinoma morphology being the dominant type.[2] Diagnosis and classification rely

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heavily on imaging and laboratory values and rarely on biopsy.[3] It often occurs in the background of a diseased liver, most commonly owing to alcohol consumption or viral illness, depending heavily on the geography.[3,4]

In our region, HCC etiology shows a pattern different from that of the global trends. For example, one study found a substantially higher proportion of HBV-related HCC cases in Saudi Arabia, which increased from 0.7% in 2010 to 11.9% in 2015, indicating an increasing impact of HBV as a risk factor in the region.[5] HCV remains a major contributor to HCC, accounting for 35–50% of HCC cases in Saudi Arabia.[6] Metabolic dysfunction-associated fatty liver disease (MAFLD), associated with diabetes and obesity, is another growing concern that contributes to the risk of HCC in this region, mirroring the global increase in MAFLD-related liver diseases.[7] In addition, the COVID-19 pandemic has affected global cancer care from multiple angles, importantly, diagnosis, screening, and treatment. A multicenter international study (CERO-19) reported that during the first wave of the COVID-19 pandemic, 87% of liver cancer centers worldwide modified their clinical practice—40% altered diagnostic procedures, 80% changed screening programs, 50% delayed curative or palliative treatments, and 41% adjusted liver transplantation schedules—highlighting a significant disruption in HCC care delivery.[8] The treatment approach depends on staging, most prominently, the Barcelona Clinic Liver Cancer (BCLC) framework.[9] This system utilizes tumor size and number, local invasion, extrahepatic spread, Child-Pugh grade, and performance status using the Eastern Cooperative Oncology Group (ECOG) grading. It classifies patients into one of five stages, and the treatment choice depends on the stage and clinical acumen. In general, treatment is represented on a spectrum, with one end having a better prognosis (BCLC stage 0, A, B) than the advanced cases reflecting worse outcomes (BCLC stages C and D). Furthermore, advancements in selective and super-selective TACE have enhanced both efficacy and safety, and transient post-TACE hypertransaminasemia—such as a $\geq$46% rise in AST or $\geq$52% in ALT—has recently been identified as an early predictor of objective radiological response in HCC patients.[10] Treatment in the early stages is curative and relies on resection, radiofrequency ablation, and transplantation.[11] Patients with advanced disease require systemic therapy. Frequently used medications for advanced unresectable cases include immune checkpoint inhibitors, tyrosine kinase inhibitors, and monoclonal antibodies targeting the VEGF pathway. More often, a combination of two drugs is employed, such as the atezolizumab-bevacizumab combination, as first-line treatment. Furthermore, important emerging prognostic factors include alpha-fetoprotein (AFP) level, albumin-bilirubin (ALBI) score, neutrophil-to-lymphocyte ratio (NLR), and sarcopenia, which is defined as skeletal muscle loss measured through imaging.[12–14]

Despite many advances in the Western and Far East literature on HCC, detailed reporting in the Middle East, specifically in Saudi Arabia, remains scarce.[15,16] Additionally, there is a significant gap in treatment outcomes from retrospective studies and an unfortunate lack of prospective trials. A few published retrospective studies have not focused on comparing systemic therapy and prognostic values, such as NLR or sarcopenia.[17,18] Recently, a consensus on the management of HCC was published by our leading multidisciplinary specialized clinic.[19] This clinic in King Abdulaziz Medical City, Riyadh, has one of the largest HCC cohorts in the Arab region. Here, we report the outcomes of various systemic treatment lines along with numerous factors that influence survival, making it the first detailed report from Saudi Arabia.

Materials and Methods

Assembly and Variables

A retrospective chart review was conducted at King Abdulaziz Medical City, National Guard Health Affairs in Riyadh, Saudi Arabia, to assess every patient with HCC diagnosed between 2016 and 2022. Our final cohort included advanced patients who underwent first-line systemic therapy alone or after radiotherapy and excluded patients under 18 years of age. The recorded data included patient demographics, underlying diseases, tumor features, treatment approaches, laboratory values, and mortality outcomes. Data were collected on Excel sheets from BestCare 2.0, an electronic medical record system used at our institution.

The treatment response was evaluated using cross-sectional computed tomography or magnetic resonance imaging (MRI). The modified RECIST (mRECIST) criteria for HCC were used in this study, in accordance with established radiological response parameters specific to HCC. The responses were categorized as Complete Response (CR), Partial

Response (PR), Stable Disease (SD), or Progressive Disease (PD).Metastasis and vascular invasion were measured using this protocol.

The albumin-bilirubin grading was categorized as grades 1–3. The formula used for the score is as follows: ALBI score = (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.0852). The grades were developed as follows: ALBI score ≤ −2.60 (ALBI grade 1), > −2.60 to ≤ −1.39 (ALBI grade 2), and > −1.39 (ALBI grade 3).[20] Sarcopenia was assessed by measuring the skeletal muscle index in centimeters (cm) squared over meters (m) squared and total muscle area in cm squared through MRI of various muscles, and sarcopenia cutoff used was below 40.31 for men and 30.88 for women.[21] For AFP levels, a cutoff value of 400 ng/mL was considered significantly elevated. A neutrophil-to-lymphocyte ratio of 3 or higher was considered elevated. Given the retrospective design and varying frequency of drug utilization, the number of patients in some treatment arms was relatively small, which may introduce potential selection bias. This was taken into account during the analysis and interpretation of subgroup comparisons.

Statistical Plan

The statistical analysis was conducted as follows: continuous variables were presented as means (±standard deviations (SD)) or as median (interquartile range (IQR)) based on the normality of the distribution, which was assessed using the Shapiro–Wilk test. The paired Student's *t*-test or Wilcoxon matched-pair signed-rank test was used to compare related continuous variables when suitable The unpaired Student's *t*-test or Mann–Whitney *U*-test was used to compare independent continuous variables when appropriate. Categorical variables are presented as frequencies and percentages. Pearson's Chi-square test or Fisher's exact test was used for categorical variables when applicable. The Kaplan-Meier method was used to examine the differences in survival outcomes, and logistic regression analysis was used for multivariate analysis to determine outcome predictors. The Statistical Package for the Social Sciences (IBM SPSS Statistics version 26) was used to analyze the variables. All P-values were two-tailed. Statistical significance was set at $p < 0.05$.

Results

Basic Demographic

Among 670 patients with HCC diagnosed and treated at our institute, one hundred and thirty underwent first-line systemic therapy (Table 1). Sorafenib was the most commonly used systemic therapy (n = 72), followed by nivolumab (n = 33), Atezo+Bev (n = 22), and others (Atezolizumab, Lenvatinib, Pembrolizumab Ramucirumab) (n = 11). The patients' mean age was 70.4 (±10.95), and 18.1% were female. The mean age and sex of the cohort were not significantly different between the groups (p = 0.2304) (p = 0.8685, respectively). The patients mean Child-Pugh Score was 6.4 (±1.33), and those with the highest mean Child-Pugh Score were found to be highest in the other cohorts 6.8 (±1.64). The difference between the cohorts' mean Child Pugh Scores was significant (p = 0.0354). Forty-three and a half percent of the patients were categorized as BCLC C, whereas the rest were categorized as BCLC B (47.2%; p = 0.380). Fifty-six percent of patients categorized as having BCLC were treated with sorafenib (p = 0.380). Vascular invasion and extrahepatic spread were observed in 21.0% and 29.7% of patients, respectively. Patients receiving sorafenib were found to have more vascular invasion (75.9%) (p = 0.1513) and extrahepatic spread (48.7%) (p = 0.1765). Most patients (62.9%) had an ALBI Grade 2. The Atezo+Bev arm had the highest percentage of ALBI Grade 3 (40.9%) (p = 0.0280), with the remainder having Grade 2 (63.6%). The most common HCC etiology was Cryptogenic (44.2%), followed by Viral (Hepatitis A or B) (36.2%). It was found that 39.1% and 18.8% of the patients had elevated AFP and NLR, respectively, and 26.8% of the patients had sarcopenia. The most common interventions were liver resection and transarterial chemoembolization (TACE) being done in 12.3%), followed by transarterial radioembolization (8.7%). Most of the patients undergoing TACE were subsequently treated with sorafenib (94.1%) (p = 0.0037).

Recist

One hundred and eleven patients underwent disease assessment using the RECIST criteria during follow-up visits, as shown in Table 2. Sixty-one percent were categorized as having PD, 10.1% as having SD, 8% as having PR, and 1.4% as having CR. Most patients who were on nivolumab were categorized as having PD (78.3%), followed by Atezo+Bev

Table 1 Baseline Characteristics of Systemic Treatment Groups: Others (Lenvatinib =4, Ramucirumab =4, Atezolizumab =2, Pembrolizumab =1)

Variables	Total=138	Sorafenib=72	Atezo+Bev=22	Nivolumab=33	Others=11	P-value
Age, Mean (±SD) y	70.4 ± 10.95	71.2 ± 10.90	68.6 ± 11.89	71.6 ± 10.42	65.2 ± 10.27	0.2304
Female, n (%)	25 (18.1%)	15 (20.8%)	4 (18.2%)	5 (21.7%)	1 (9.1%)	0.8685
BMI, Mean (±SD)	25.4 ± 6.29	25.8 ± 7.18	24.9 ± 4.60	25.2 ± 4.71	24.8 ± 7.06	0.9973
Diabetes Mellitus, n (%)	74 (53.6%)	43 (59.7%)	11 (50.0%)	16 (48.5%)	4 (36.4%)	0.5232
Hypertension, n (%)	66 (47.8%)	41 (56.9%)	9 (40.9%)	14 (42.4%)	2 (18.2%)	0.2911
Cardiovascular disease, n (%)	24 (17.4%)	14 (19.4%)	3 (13.6%)	5 (15.2%)	2 (18.2%)	0.5674
Chronic Kidney Disease, n (%)	14 (10.1%)	7 (9.7%)	2 (9.1%)	3 (9.1%)	2 (18.2%)	0.2382
Cirrhosis, n (%)	86 (62.3%)	48 (66.7%)	13 (59.1%)	18 (54.5%)	7 (63.6%)	0.0417
AFP ≥400, n (%)	54 (39.1%)	28 (38.9%)	7 (31.8%)	14 (42.4%)	5 (45.5%)	0.5240
Sarcopenia, n (%)	37 (26.8%)	10 (13.9%)	13 (59.1%)	13 (39.4%)	1 (9.1%)	0.1109
NLR >3, n (%)	26 (18.8%)	22 (30.6%)	1 (4.5%)	2 (6.1%)	1 (9.1%)	0.6184
Vascular Invasion, n (%)	29 (21.0%)	22 (30.6%)	1 (4.5%)	3 (9.1%)	3 (27.3%)	0.1513
Extrahepatic Spread, n (%)	41 (29.7%)	20 (27.8%)	5 (22.7%)	14 (42.4%)	2 (18.2%)	0.1765
ECOG 0–2, n (%)	21 (15.2%)	11 (15.3%)	2 (9.1%)	7 (21.2%)	1 (9.1%)	1.000
BCLC-C, n (%)	60 (43.5%)	34 (47.2%)	6 (27.3%)	15 (45.5%)	5 (45.5%)	0.380
Child-Pugh Score, Mean (±SD)	6.4 ± 1.33	6.4 ± 1.28	5.6 ± 0.93	6.6 ± 1.45	6.8 ± 1.64	0.0354
ALBI Grades, n (%)						0.0280
Grade 1	23 (16.7%)	15 (20.8%)	0 (0%)	5 (15.2%)	3 (27.3%)	
Grade 2	88 (63.8%)	46 (63.9%)	14 (63.6%)	21 (63.6%)	7 (63.6%)	
Grade 3	27 (19.6%)	11 (15.3%)	9 (40.9%)	7 (21.2%)	0 (0%)	
Etiology, n (%)						0.532
Viral hepatitis	50 (36.2%)	28 (38.9%)	6 (27.3%)	13 (39.3%)	3 (27.3%)	
MASH	2 (1.4%)	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	
Cryptogenic cirrhosis	61 (44.2%)	31 (43.1%)	13 (59.1%)	10 (30.3%)	7 (63.6%)	
Surgical Interventions, n (%)						0.0037
Resection	17 (12.3%)	5 (6.9%)	4 (18.2%)	6 (18.2%)	2 (18.2%)	
Radiation	8 (5.8%)	5 (6.9%)	2 (9.1%)	1 (3.0%)	0 (0%)	
TACE	17 (12.3%)	16 (22.2%)	0 (0%)	0 (0%)	1 (9.1%)	
TARE	12 (8.7%)	6 (8.3%)	0 (0%)	3 (9.1%)	3 (27.3%)	

Table 2 Tumor Response to Systemic Therapy According to mRECIST; Others (Lenvatinib, 4; Ramucirumab, 4; Atezolizumab, 2; Pembrolizumab, 1) p = 0.056

Variables	Total=138	Sorafenib=72	Atezo+Bev=22	Nivolumab=33	Others=11
CR	2 (1.4%)	0 (0%)	0 (0%)	2 (6.0%)	0 (0%)
PD	84 (60.9%)	47 (65.3%)	15 (68.2%)	18 (78.3%)	4 (36.4%)
PR	11 (8.0%)	5 (6.9%)	3 (13.6%)	2 (6.0%)	1 (9.1%)
SD	14 (10.1%)	6 (8.3%)	3 (13.6%)	1(3.0%)	4 (36.4%)

(68.2%), Sorafenib (65.3%), whereas others were only 36.4%. CR was exclusively observed in patients treated with Nivolumab (6.0%).

Adverse Events

The most notable adverse events associated with each treatment line are listed in Table 3. Grading was done according to the Common Terminology Criteria for Adverse Events (CTCAE) guidelines, as shown in Table 4. The most common adverse events across all treatments were AST elevation (60.1%), followed by anorexia (34.1%) and fatigue (30.4%). There was no statistically significant difference in the occurrence of adverse events between the different drugs. There were 14 grade 3 events across all medications, and no grade 4 or 5 events were observed (Table 4).

Table 3 Adverse Events of Systemic Treatments: Others (Lenvatinib =4, Ramucirumab =4, Atezolizumab =2, Pembrolizumab =1)

Variables	Total=138	Sorafenib=72	Nivolumab=33	Atezo+Bev=22	Others=11	P-value
ALT elevation	39 (28.3%)	22 (15.9%)	7 (21.2%)	5 (22.7%)	5 (45.4%)	0.402
Anorexia	47 (34.1%)	30 (41.7%)	8 (24.2%)	5 (22.7%)	4 (36.4%)	0.207
AST elevation	83 (60.1%)	42 (58.3%)	18 (54.5%)	13 (59.1%)	10 (90.9%)	0.181
Confusion	16 (11.6%)	9 (12.5%)	4 (12.1%)	1 (4.5%)	2 (18.2%)	0.660
Constipation	23 (16.7%)	14 (19.4%)	6 (18.2%)	1 (4.5%)	2 (18.2%)	0.423
Creatinine elevation	17 (12.3%)	8 (11.1%)	7 (21.2%)	1 (4.5%)	1 (9.1%)	0.278
Diarrhea	20 (14.5%)	15 (20.8%)	4 (12.1%)	1 (4.5%)	0 (0%)	0.107
Fatigue	42 (30.4%)	25 (34.7%)	11 (33.3%)	2 (9.1%)	4 (36.4%)	0.129
Itching	18 (13.0%)	9 (12.5%)	6 (18.2%)	2 (9.1%)	1 (9.1%)	0.743

Table 4 Adverse Event Grading; Others (Lenvatinib =4, Ramucirumab =4, Atezolizumab =2, Pembrolizumab =1)

Variables	Total=138	Sorafenib=72	Nivolumab=33	Atezo+Bev=22	Others=11
Grade 1					
Anorexia	15 (10.9%)	9 (12.5%)	4 (12.1%)	1 (4.5%)	1 (9.1%)
Confusion	10 (7.2%)	5 (6.9%)	4 (12.1%)	1 (4.5%)	0
Constipation	13 (9.4%)	7 (9.7%)	4 (12.1%)	1 (4.5%)	1 (9.1%)
Diarrhea	9 (6.5%)	6 (8.3%)	2 (6.1%)	1 (4.5%)	0
Fatigue	28 (20.3%)	14 (19.4%)	9 (27.3%)	3 (13.6%)	2 (18.2%)
Itching	13 (9.4%)	6 (8.3%)	5 (15.2%)	2 (9.1%)	0
Grade 2					
Anorexia	29 (21%)	20 (27.8%)	4 (12.1%)	3 (13.6%)	2 (18.2%)
Confusion	4 (2.9%)	3 (4.2%)	0	0	1 (9.1%)
Constipation	10 (7.2%)	6 (8.3%)	2 (6.1%)	1 (4.5%)	1 (9.1%)
Diarrhea	8 (5.8%)	6 (8.3%)	2 (6.1%)	0	0
Fatigue	13 (9.4%)	10 (13.9%)	2 (6.1%)	0	1 (9.1%)
Itching	5 (3.6%)	2 (2.8%)	1 (3%)	1 (4.5%)	1 (9.1%)
Grade 3					
Anorexia	4 (2.9%)	2 (2.8%)	0	1 (4.5%)	1 (9.1%)
Confusion	3 (2.2%)	1 (1.4%)	0	1 (4.5%)	1 (9.1%)
Constipation	1 (0.7%)	1 (1.4%)	0	0	0
Diarrhea	3 (2.2%)	3 (4.2%)	0	0	0
Fatigue	2 (1.4%)	1 (1.4%)	0	0	1 (9.1%)
Itching	1 (0.7%)	1 (1.4%)	0	0	0

Multivariate & Survival Analysis

We conducted a multivariate regression analysis to adjust for confounders predicting survival (Table 5). Notably, an increased NLR was associated with worse survival (HR 95% 2.468, p=0.0324). In addition, sarcopenia was significantly associated with better survival (hazard ratio [HR], 95% confidence interval [CI] 0.49; p=0.0499). However, because the upper confidence interval nearly crossed the interval of 1.0, and considering the small sample size of our cohort, we can safely conclude that this value is insignificant and not sufficiently powered to show a concrete survival benefit.

The Kaplan-Meier survival method was used to calculate the overall survival (OS) by comparing the three major systemic treatment arms used in the first-line setting (Figure 1) (Table 6). During the 24-months follow-up, Atezo+Bev had a median OS of 20.94 months, followed by nivolumab at 19.79 months, and finally sorafenib at 11.77 months (HR 1.014, 95% CI 0.79–1.31, p = 0.918).

Table 5 Multivariate Subgroup Analysis of Confounding Factors

Variables	Hazard Ratio (95% CI)	P-value
Age	1.026 (0.99, 1.06)	0.1464
Female gender	0.859 (0.34, 2.18)	0.7499
Nivolumab	0.470 (0.10, 2.16)	0.3319
Sorafenib	0.848 (0.21, 3.42)	0.8162
Atezolizumab+Bevacizumab	1.579 (0.34, 7.35)	0.5606
NLR >3	2.468 (1.08, 5.65)	0.0324
AFP ≥400	0.658 (0.35, 1.23)	0.1908
Sarcopenia	0.490 (0.24, 1.00)	0.0499
BCLC-C	0.289 (0.05, 1.76)	0.1786
Child-Pugh score ≥ 7	0.131 (0.00, 5.53)	0.2875
Child-Pugh class B	6.515 (0.16, 261.35)	0.3198
Child-Pugh class C	51.883 (0.71, 3795.96)	0.0714
ALBI Grade 2	1.636 (0.45, 6.01)	0.4585
ALBI Grade 3	2.154 (0.43, 10.86)	0.3527
Radiation	0.789 (0.26, 2.37)	0.6725
Resection	0.922 (0.39, 2.16)	0.8513
TACE	0.398 (0.11, 1.40)	0.1514
TARE	0.712 (0.25, 2.00)	0.5183

Discussion

Here, we present the first analysis of the use of various prognostic factors and systemic therapies in the Arab region. The incidence of HCC in Saudi Arabia was 5.2/100,000 in 2020, an increase from 4.5 per 100,000 in 2018.[22] This increasing incidence and mortality necessitates an increasing focus on improving prevention, treatment, and surveillance. Currently, the atezo+bev combination is the recommended first-line treatment for advanced unresectable HCC.[3] IMbrave 150 was the trial that showed significant OS with this regimen, surpassing that with sorafenib.[23] The trial demonstrated a 12-month OS rate of 67.2%, comparable to our 12-month OS rate of 78%. However, it is important to note that differences in numbers are expected owing to different patient populations and trial parameters. For example, we have less alcohol-induced cirrhosis and liver damage than in Western countries because of local cultural beliefs surrounding alcohol consumption. Additionally, the trial excluded patients with many comorbidities and underlying characteristics, such as attempted locoregional control before therapy, autoimmune diseases, and significant esophageal varices. Nivolumab was the second most commonly used first-line drug in our cohort of 33 patients. It was initially approved for second-line usage following sorafenib based on the CheckMate 040 trial.[24] Several studies, such as the CheckMate 459, have assessed its use as a first-line treatment against sorafenib.[25] This trial demonstrated a median OS of 16.4 months compared to 14.7 months for nivolumab and sorafenib, respectively, which yielded no statistical significance. However, its allure was its better tolerability, which raised the question of its use instead of sorafenib. In our study, nivolumab had a median OS of 19.79 months compared to 11.77 months for sorafenib, which is a better median than that in the trial. Our population in Saudi Arabia seemed to showed better response rates than those observed in the registration trials, which should be motivate the conduct of well-designed randomized trials in the Middle East. An important aspect that could impact our outcomes and might explain differences in patient responses is the underlying liver function reserve. Because most HCC patients also have underlying cirrhosis, their liver functional reserve is inherently limited, and although reserve has been well assessed in surgical settings to prevent postoperative failure, its role in guiding non-surgical treatments remains less defined.[26] Non-surgical treatments such as systemic therapy carry a risk of further hepatic impairment—highlighting the need for careful evaluation of liver functional reserve to preserve eligibility for subsequent lines of treatment.

A study by Dahlan et al in 2022 was one of only two Saudi HCC cohorts that analyzed survival outcomes and focused on radiological treatment rather than systemic therapy.[18] Badheeb et al conducted the second study that analyzed survival outcomes; however, they did not include systemic therapy.[17] Their study included only 52 patients, and showed that

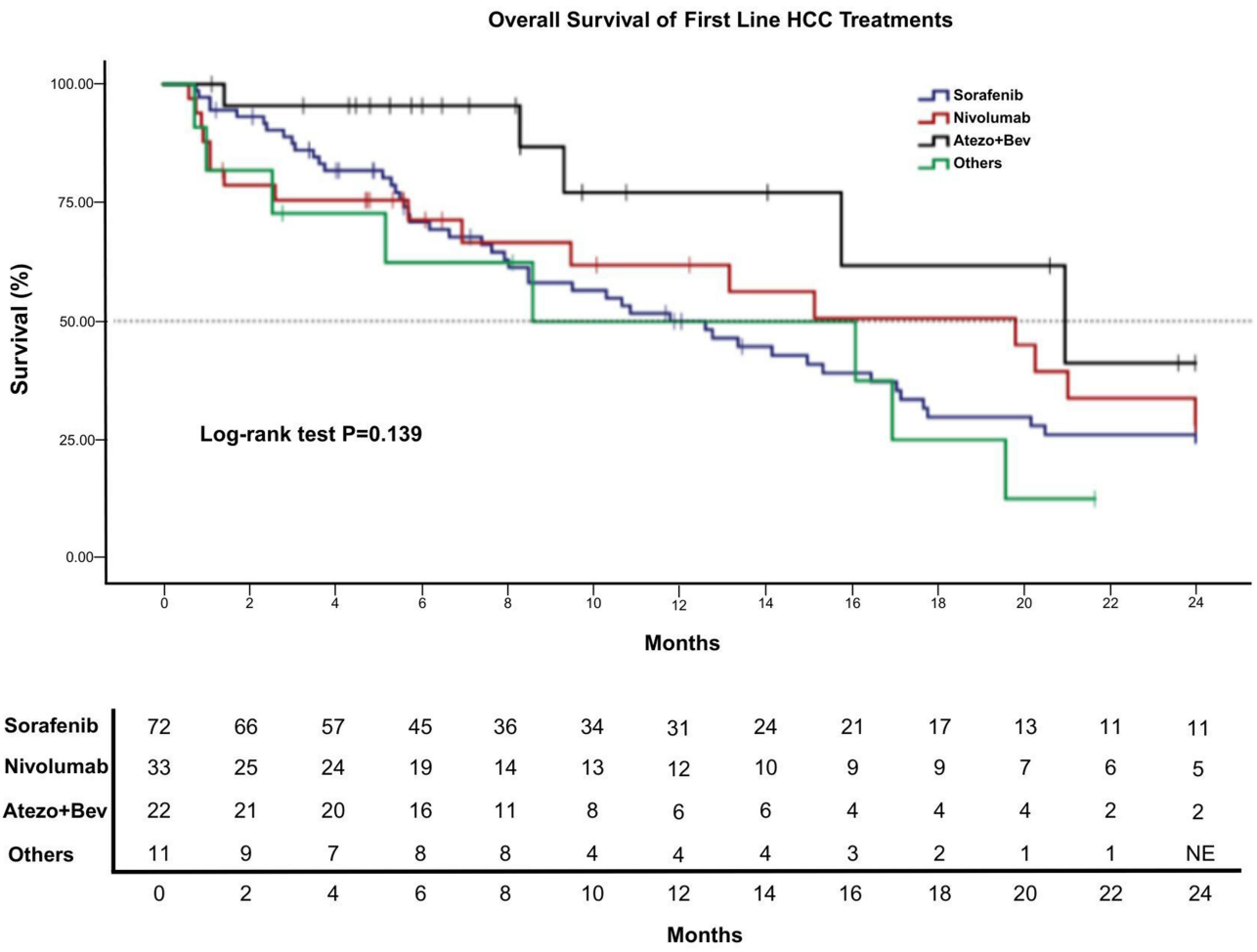

Figure 1 Kaplan-Meier Overall Survival of First Line HCC Treatments.

relapse, increased AFP levels, and ascites were associated with higher mortality. Finally, a study from our institute led by Alshammari et al specifically examined antibiotic exposure and anti-PD1 blockade therapy for Child-Pugh class A patients, which showed better survival for those who did not receive antibiotics during the course of treatment.[27]

Sarcopenia and elevated NLR are somewhat controversial in terms of their roles as relevant prognostic factors. Wang et al published a study in which 380 patients with HCC undergoing TACE alone were retrospectively assessed for NLR associations.[12] They found that an elevated NLR at a cutoff of >2.4 which is an independent prognostic parameter for poor OS. Similarly, a meta-analysis by Lin et al, which included nine studies, reported the same finding.[28] It is important

Table 6 First-Line HCC Treatment Survival

	Sorafenib (n=72)	Nivolumab (n=33)	Atezo+Bev (n=22)	Others* (n=11)
OS events, n (%)	46 (63.9)	17 (51.5)	5 (22.7)	3 (27.3)
Median OS, mo	11.77	19.79	20.94	8.58
(95% CI), mo	(7.8–15.74)	(7.3–32.28)	(10.93–30.96)	(0.0–22.64)
HR (95% CI)	1.014 (0.79–1.31)			
P-value (2-sided)	P=0.918			

Notes: *Others (lenvatinib =4, ramucirumab =4, atezolizumab =2, pembrolizumab =1).
Abbreviations: OS, Overall Survival; N, number; Mo, Month; CI, confidence interval; HR, Hazard ratio.

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to note that the Wang study did not include patients treated with systemic therapy, and the meta-analysis showed heterogeneity in the use of systemic therapy among the studies. Our study showed NLR significance in multivariate regression and makes this study, to our knowledge, the first to assess NLR association in a cohort using systemic therapy in the Middle East. In addition, sarcopenia has been established as a strong predictor of cirrhosis, and when it comes to HCC, a meta-analysis of 57 studies showed a strong association between sarcopenia and poor prognosis, including tumor recurrence, mortality, and drug-adverse events.[29]

Local analysis of hepatocellular carcinoma (HCC) is important given its increasing prevalence and incidence, particularly in regions such as Saudi Arabia, where detailed reporting is still undermined. This study investigated the treatment landscape and prognostic factors influencing survival, and provided crucial insights into the management of this malignancy. Our retrospective analysis at King Abdulaziz Medical City in Riyadh revealed significant findings regarding treatment patterns and outcomes among patients with HCC. With 130 patients undergoing first-line systemic therapy, we report sorafenib as the most commonly utilized treatment, followed by the nivolumab and a Atezo+Bev combination. Notably, the Atezo+Bev arm exhibited the highest proportion of patients with ALBI Grade 3, highlighting the severity of liver dysfunction in this subgroup. Multivariate regression analysis revealed that an elevated NLR was a predictor of poor survival. The efficacy of atezolizumab-bevacizumab observed in our cohort aligns with findings from pivotal trials, emphasizing the global applicability of this regimen despite variations in patient demographics and disease characteristics. Similarly, the median OS reported for various regimens illustrates the importance of exploring immunotherapeutic options as first-line treatments, particularly in populations demonstrating heightened efficacy. Although our study provides valuable insights, it is important to acknowledge its limitations, including its retrospective nature and inherent bias. Robust prospective trials are needed to validate these findings. The limited sample size in some systemic therapy arms restricts the generalizability of subgroup outcomes and raises the possibility of selection bias, particularly for less commonly used regimens.

Conclusion

In conclusion, this study provides crucial insights into the survival outcomes and prognostic factors for advanced hepatocellular carcinoma (HCC) within Saudi Arabia, addressing significant gaps in regional data. The retrospective review encompassed 130 patients undergoing first-line systemic therapies, underscoring the potential of the atezolizumab-bevacizumab (Atezo+Bev) combination, which showed the longest median overall survival (OS) among various treatments. Although no statistically significant differences in survival were noted across treatments, the trend toward better outcomes with Atezo+Bev highlights its potential, especially in patients with severe liver dysfunction.

The research affirmed the neutrophil-to-lymphocyte ratio (NLR) as a significant prognostic marker, predicting poorer survival outcomes. It also pointed to other influential factors such as elevated alpha-fetoprotein (AFP) levels and sarcopenia, which, while not statistically significant, are recognized as important in HCC prognosis.

This investigation substantially enriches the local Saudi data on HCC, laying a foundation for more customized treatment approaches and a deeper understanding of disease dynamics in the region. It emphasizes the necessity for prospective studies to confirm these findings and refine treatment strategies for the Saudi population. Furthermore, it highlights the importance of regional studies in global oncology, where local variations in disease presentation and treatment responses are prominent. This study not only bridges a critical data void but also sets the stage for future research and enhanced management strategies in hepatocellular carcinoma in Saudi Arabia and potentially other similar regions.

Data Sharing Statement

De-identified raw Excel data can be obtained within reasonable request by contacting the corresponding senior author Dr. Kanan Alshammari.

Ethics Statement

The study obtained all required approvals from the IRB committee of King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia (Ref IRB approval/

SP21R-376-07). This study complied with all applicable national and international ethical guidelines for researching human participants, including following the Code of Ethics of the World Medical Association (Declaration of Helsinki). The IRB protocol of KAIMRC waived patient individual consent due to the retrospective nature of the study. All patient data were anonymised and de-identified prior to analysis to ensure confidentiality. No personal identifiers were collected or reported in this study following institutional and international ethical standards.

Disclosure

All authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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