review articles

# Comprehensive Review of Hepatocellular Carcinoma in India: Current Challenges and Future Directions

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abstract

There is not much information on hepatocellular carcinoma (HCC) in India. Here, we review the existing data, available treatment choices, and future directions in HCC management. An extensive search was conducted through PubMed and MEDLINE for studies published between January 2000 and June 2022 on the epidemiology of HCC in India using the following key words: atezolizumab, BCLC staging, hepatocellular carcinoma, immune checkpoint inhibitors, immunotherapy, and programmed cell death ligand-1, with the filters humans and English language. The most frequent risk factors for the development of HCC in India include nonalcoholic fatty liver disease, hepatitis B virus and hepatitis C virus infection, liver cirrhosis, and alcohol intake. On the basis of new findings, the Barcelona Clinic Liver Cancer (BCLC) Staging Criteria need to be revised. As most cases in India are discovered at a later stage, curative treatments such as surgical resection, ablation, or liver transplantation may not be an option. Clinical trials are underway for a number of immune checkpoint drugs that target cytotoxic T-cell lymphocyte-4 and programmed cell death-1/programmed cell death-ligand 1. In India, phase III trials of atezolizumab in combination with other drugs are underway for the treatment of various malignancies. Renin angiotensin system inhibitors, antivirals, primary hepatocyte transplantation, and bioartificial liver devices are among the future options for the management of HCC. In developing countries like India, HCC is often diagnosed at an advanced stage because of a delay in routine testing or screening. Therefore, developing effective treatment regimens for such stages is critical. Immunotherapy is a promising treatment option that has the potential to increase overall response and survival rate.

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## INTRODUCTION

As per the GLOBOCAN 2018 report, liver cancer is the third leading cause of cancer-related deaths worldwide and contributed to 781,631 (8.2%) deaths in 2018.[1] Hepatocellular carcinoma (HCC) accounts for the bulk of liver cancer cases, accounting for 80% of all instances.[2] Chronic hepatitis B virus (HBV) infection was found to be responsible for 44% of all HCC cases worldwide, followed by hepatitis C virus (HCV) infection (21%).[3] HCC has an estimated 5-year survival rate of only 18%, which is partly due to the fact that only 30%-40% of patients are discovered early and thus suitable for curative treatments such as liver resection (LR), ablation, or liver transplantation (LT).[4] Most of them are diagnosed at a later stage with widespread liver disease, vascular invasion, and metastasis.[4,5]

There is a dearth of information about HCC in India, as cancer is not a reportable disease, and the country's cancer registries are primarily urban. According to unpublished data from multiple tertiary care institutes in India, the incidence of HCC is rising.[6] The available data suggest that age-adjusted incidence rates of HCC range from 1 to 7.5 per 100,000 population, 0.7 to 7.5 among men, and 0.2 to 2.2 in women.[7] According to Population-Based Cancer Registry from 2012 to 2014, Sikkim and Arunachal Pradesh have the highest incidence of liver cancer among all cancers in the country.[8] Liver cancer was responsible for 14,000 cancer deaths in India in 2010, with an age-standardized cancer mortality rate of 6.8 (5.4-8.1) per 100,000 cases.[9] In this review, we discuss the available evidence, current treatment options, and future directions in managing HCC, with a special emphasis on atezolizumab-based immunotherapy.

## METHODOLOGY

An extensive search was performed for studies published in the last two decades on the epidemiology of HCC in India through PubMed and MEDLINE using the key words: *atezolizumab, BCLC staging, hepatocellular carcinoma, immune checkpoint inhibitors, immunotherapy, programmed cell death ligand-1*, with

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## CONTEXT

**Key Objective**

In India, there is a scarcity of information on hepatocellular carcinoma (HCC). We review the available evidence, current treatment choices, and future possibilities in the management of HCC in India.

**Knowledge Generated**

Nonalcoholic fatty liver disease is likely to become the most common etiologic factor for the development of HCC in both cirrhotic and noncirrhotic patients in India. Atezolizumab, an immune checkpoint inhibitor that targets programmed cell death-ligand 1 receptor, combined with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

**Relevance**

Surgical resection, ablation, or liver transplantation may not be feasible as most cases of HCC are diagnosed late. Systemic therapy with lenvatinib is now considered an alternative first-line therapy for advanced HCC, because of its noninferiority compared with sorafenib. Immunotherapy is a promising treatment option for HCC, which has the potential to increase overall response and survival rates.

the filters *humans* and *English language*. The start and end dates for the searches were January 2000 and June 2022, respectively. Articles published before the start search date provided conceptual content only.

## RISK FACTORS OF HCC

HBV and HCV infection, cirrhosis of the liver, and alcohol consumption are the most common risk factors involved in the development of HCC in India.[10] Obesity, diabetes mellitus (DM), and nonalcoholic fatty liver disease (NAFLD) are other important risk factors.[11]

The prevalence of hepatitis B surface antigen is 3%-4.2% in India, with more than 40 million HBV carriers.[12] Patients infected with HBV have a 100-fold increased risk of developing HCC.[14] Several studies have reported HBV infection to be the most common cause of HCC in India accounting for 70%-80% of all cases, whereas HCV contributes to about 15% of HCC cases.[5,10,14] Lack of proper education and basic sanitation facilities and poor waste management and drainage systems have been conducive to the spread of HBV infection through the fecal-oral route.[15] In addition, birth-dose immunization against hepatitis B is poor in India. As per the WHO, less than half of newborns (45%) received birth dose of hepatitis B vaccination in 2015.[12] A systematic review and meta-analysis found that the pooled anti-HCV seroprevalence rates were 0.44% and 0.88% among blood donors and pregnant women, respectively, in India. Prevalence rates were higher among persons with HIV infection or sexually transmitted diseases, commercial sex workers, persons who inject drugs, and those undergoing frequent blood transfusions.[16] Factors that increase the risk of needle stick injury and transmission of HBV and HCV include the following: excessive unwarranted usage of injections, unsafe injection practices, insufficient hepatitis B vaccination among health care workers, and improper sharps disposal.[17] The Government of India has launched the National Viral Hepatitis Control Program in 2018 for prevention, detection, and treatment of viral hepatitis in India.[18]

Risk of HCC is heightened in people with HBV-related or HCV-related chronic liver disease if there is concomitant chronic alcoholism, obesity, DM, HIV, or aflatoxin exposure.[11] Recent reports have confirmed this, wherein viral hepatitis combined with alcohol was the most common risk factor for HCC in India (63.9%).[19] They also reported a changing trend in etiology of HCC. A decrease in HBV infections, stability in HCV infections, and rising incidence of alcohol and nonalcoholic steatohepatitis (NASH) were observed as risk factors for HCC over the past few decades.[19]

NAFLD has become a major risk factor for chronic liver disease, cirrhosis, and HCC in India.[14,20,21] NAFLD seems to have surpassed hepatitis B as the most common cause for HCC. In a 3-year observational study in a tertiary care center in India, most common etiology of HCC was found to be NAFLD/cryptogenic in 51% of the patients, followed by 17.4% for hepatitis B and 5.8% for hepatitis C,[22] It is likely to become the most prevalent etiologic factor in patients with both cirrhotic and noncirrhotic HCC.[22] The risk of having NAFLD is affected by increased consumption of energy-dense foods leading to obesity, type 2 DM, and physical inactivity, all of which are common among Indians.[15] About 3%-15% of obese patients with NASH develop cirrhosis, whereas about 4%-27% of patients with NASH with cirrhosis acquire to HCC.[21] Therefore, diagnosis of HCC in its early stages, even among patients with noncirrhotic NAFLD, is essential.

Patients with cirrhosis caused by HBV or HCV have a higher risk of developing HCC than those with chronic hepatitis or cirrhosis caused by other etiologies.[11] The incidence of HCC in cirrhotic patients in India is 1.6% per year.[6] The prevalence of cirrhosis among patients with HCC is as high as 59% to 86%.[5,10,19] Therefore, cirrhotic patients must undergo surveillance at regular intervals for the early detection of HCC.[14]

 

Chronic exposure to the fungal toxin aflatoxin B1 (AFB1) is strongly linked to the development of HCC.[23] In Southeast Asian countries such as India, stored grains may contain significant amounts of AFB1 in the months after the monsoon.[24] Histopathologic examination of HCC liver biopsies revealed high prevalence of AFB1 in the samples (58.1%).[24]

There is emerging evidence from observational studies that DM is a significant risk factor for HCC.[11] Diabetes-related risk factors include NAFLD, cirrhosis, and excessive fat retention.[13] Mechanisms underlying HCC progression in patients with type 2 DM include aberrant glucose and lipid metabolism, hyperinsulinemia, and insulin resistance; the role of activated platelets; HCC-associated hub gene expression; inflammation and signaling pathways; microRNA; altered gut microbiota, and immunomodulation.[25] Risk of HCC has also been linked to other factors such as frequent consumption of processed meat and processed fish, and there is a protective effect of consumption of fresh fish, milk, and fruits.[8]

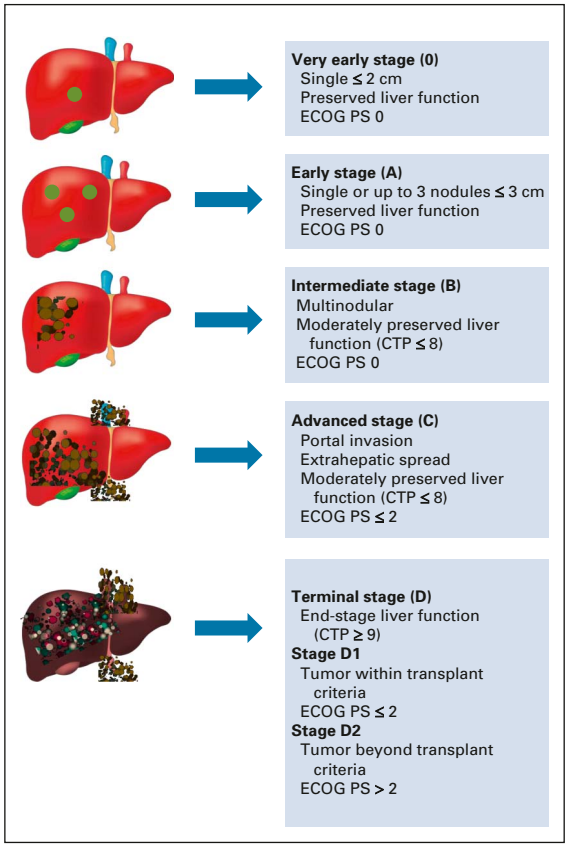


**FIG 1.** INASL-modified BCLC staging of HCC. BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; HCC, Hepatocellular Carcinoma; INASL, Indian National Association for Study of Liver; PS, performance status.

## SURVEILLANCE OF HCC

HCC surveillance helps to identify early tumors that are amenable to treatment. Global associations, including the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and Indian National Association for Study of the Liver (INASL), advocate a 6-monthly abdominal ultrasonogram for HCC surveillance.[11,26-28] The INASL 2019 Consensus recommends the following patients to be subjected to surveillance for HCC: (1) Child's A and B cirrhotic patients of any etiology; (2) Child's C cirrhotic patients of any etiology who are listed for LT; (3) patients with chronic hepatitis B (CHB) who have increased risk for HCC according to risk scores such as Chinese university (CU-HCC) or platelets, age, gender-hepatitis B (PAGE-B); and (4) chronic HCV with advanced fibrosis. They recommend a semiannual abdominal ultrasonogram along with assessment of alpha-fetoprotein levels.[11]

## STAGING OF HCC

HCC staging is required for guiding treatment decisions, prognosis, and standardization of research protocols. Several staging systems for HCC have been proposed over the past few decades. There is, however, lack of an internationally acknowledged staging system that allows for the comparison of current management regimens among diverse populations.[11] The Barcelona Clinic Liver Cancer (BCLC) Staging System is a commonly used tool for guiding HCC treatment strategies both in clinical practice and in clinical trials.[29] Nonetheless, limitations of this staging system include similar treatment recommendation for individuals with heterogeneous disease since they are classified as the same stage.[30] Surgery is not recommended for patients with intermediate-stage HCC, and they are referred to palliative treatment as per BCLC staging. However, availability of new evidence suggests the need for BCLC criteria to be refined or possibly changed.[30-33] Recent advances in surgical techniques have widened the scope for LR as a treatment modality for HCC by reducing the risk of postoperative complications and improving the resectability of liver tumors that were previously considered unresectable.[32] Current findings demonstrate that LR can provide good survival benefit in patients with large and multinodular HCC or Child-Pugh B cirrhosis.[34] Fukami et al[35] compared the survival benefits of LR with those of transarterial chemoembolization (TACE) in patients with multiple HCCs and reported that the overall survival (OS) rate of patients who underwent LR was 60% at 5 years compared with 41.6% with TACE ($P < .001$). Similar findings were noted in a meta-analysis of 18 high-quality studies comparing primary hepatectomy with TACE in patients with intermediate- to advanced-stage HCC. They found significantly better OS and 5-year survival rates for primary hepatectomy compared with TACE.[36]

INASL has proposed a modified version of the BCLC staging system[11] (Fig 1). They proposed that patients with end-stage liver cirrhosis and heavily impaired liver functions (Child-Pugh class C) but tumor size within Milan criteria showing a performance score (PS) ≤ 2 should be considered for LT. In addition, expanded criteria were recommended for LT. A detailed assessment of extrahepatic dissemination is required for accurate staging of HCC, which may be performed through positron emission tomography-computed tomography (PET CT) scan. A CT scan of the abdomen and chest and a bone scan may also be used.[11] In patients who do not respond to the treatment option that corresponds to their BCLC stage, the treatment stage migration concept is followed, which refers to patients who, because of a coexisting comorbidity, technical issue, treatment failure, or disease progression, but still within the original stage, are unable to be treated with the initial suggested treatment. These individuals are referred to the appropriate treatment for the next stage.[11,37]

## TREATMENT MODALITIES FOR HCC

Because of its diversified nature, the management of HCC is complex, requiring a multidisciplinary team approach to attain the best possible outcome.[38] A standard oncologic approach consisting of systemic chemotherapy, external radiation, or plain surgery does not work for HCC because of the frequent presence of concomitant cirrhosis and portal hypertension.[39] Over the past 10 years, there have been substantial advancements in HCC treatment. The available treatment interventions can be broadly divided into curative and noncurative therapies. Curative therapies include LR, thermal ablation, and LT, whereas noncurative therapies include TACE, transarterial radioembolization (TARE), stereotactic body radiation therapy, and systemic chemotherapy, which aim to improve survival by delaying the growth of the tumor.[40] Figure 2 presents the treatment algorithm for HCC.

### Curative Therapies

***Resection.*** Surgical resection is a treatment that has the potential to be curative. It is recommended in patients with resectable disease who do not have clinically significant portal hypertension.[41] The number and location of tumors, hepatic reserve, the expected volume of resection, and the underlying liver function are the factors that need to be considered to determine if a lesion is resectable.[40]

In the absence of cirrhosis, LR is the treatment of choice if there is an adequate amount of liver remaining.[11] According to the BCLC staging system, most of the patients with large size HCC (> 10 cm) do not meet the criteria for LR. Wagle et al studied the surgical outcome in such cases and found that large HCC is not a contraindication for surgery. Only if vascular invasion is evident, it has a negative impact on survival. Therefore, a higher chance of survival with minimal morbidity can be achieved through proper case selection, such as a single tumor with no gross vascular invasion, good PS, liver remnant augmentation by sequential TACE with portal vein embolization, good preoperative planning, and adherence to hepatic surgery principles.[42] The INASL suggests that LR needs to be considered in experienced centers, particularly for solitary tumors (≤ 5 cm) located in favorable regions, using laparoscopic/minimally invasive techniques using a wide surgical margin (≥ 1 cm) for better prognosis.[11]

However, there is a high risk of recurrence after resection.[26,43] In such cases, postoperative adjuvant therapy is to be considered. An international expert consensus on the

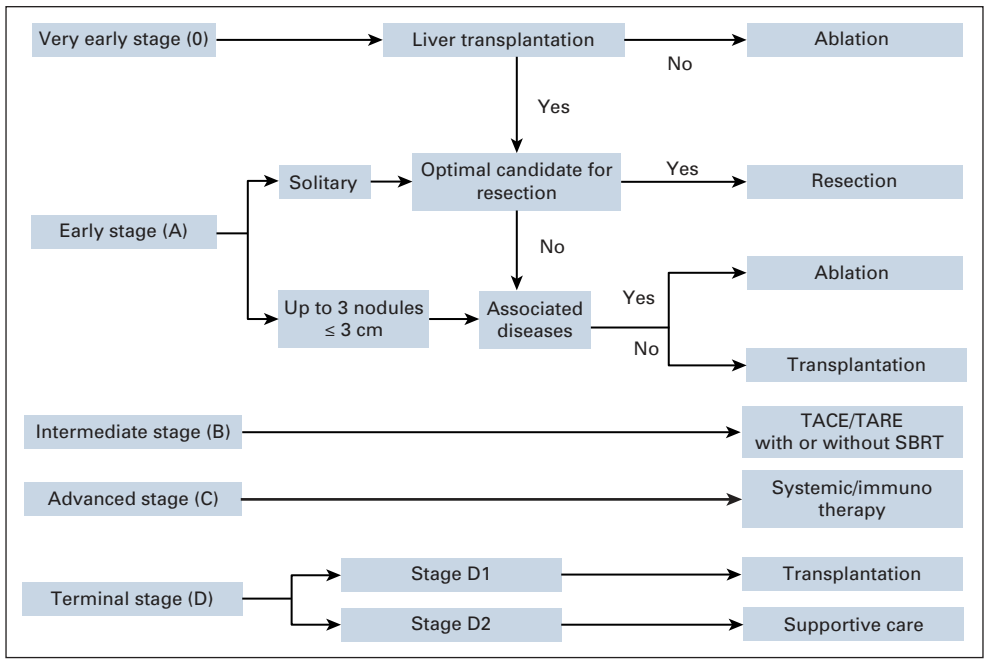


**FIG 2.** Treatment algorithm for hepatocellular carcinoma. SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

 

management of recurrent and metastatic HCC after LR recommends that follow-up should be performed once in every 3-4 months within the first 2 years after LR. The follow-up interval could be increased to 6 months if all the evaluated factors remain within normal range for 5 years.[43]

***Ablation.*** Ablative treatment is a potentially curative alternative that has increased substantially in popularity during the past decade. Radiofrequency ablation (RFA) is the preferred treatment modality for HCC, and it has now surpassed percutaneous ethanol injection as the most commonly used ablative therapy.[11]

The EASL and European Organisation for Research and Treatment of Cancer (EORTC) recommend the use of RFA in tumors $< 5$ cm and ethanol injections in cases where RFA is not technically feasible. However, both the techniques have demonstrated complete resolution in $> 90\%$ of cases, when the tumors are $< 2$cm in size with BCLC 0.[44] The INASLD guidelines also recommend use of RFA, in patients with solitary HCC $< 3$ cm, as the first-line treatment, if the tumor is in a favorable location, and RFA + TACE is offered if the tumor size is between 3 and 5 cm.[11]

***LT.*** In general, patients requiring LT present late to the hospitals in India, majority of them having developed some form of decompensation.[45] According to the National Organ and Tissue Transplant Organization of India, 1,780 liver transplants were performed in 2020; of them, 1,487 were living liver transplants and only 291 were deceased liver transplants.[46] Hence, deceased donor LT should be prioritized and encouraged. Furthermore, present organ-sharing regulations that are based on waiting time or institutional rotation must be replaced with a severity-based system.[15] The INASL considers LT in patients within Milan criteria with cirrhosis and HCC as a gold standard procedure.[11] In addition, in patients beyond Milan criteria, LT may be considered if the patient can be successfully downstaged into the Milan criteria using locoregional therapy. Feasibility of LR must be checked if LT is not an option in these patients.[11]

### Noncurative Therapies

***TACE.*** TACE is widely used in patients with HCC who are not candidates for curative treatments. According to AASLD guidelines, TACE is a standard palliative treatment in the management of intermediate-stage HCC.[40] Paul SB and colleagues evaluated the outcome of TACE therapy in patients with unresectable HCC in India. They concluded that TACE is safe and well tolerated. Postprocedure complications were mild with 13.6% showing postembolization syndrome, which included pain abdomen, fever, nausea, and vomiting.[47] Agarwal et al evaluated the factors influencing the outcome of TACE in Indians and proposed that it is an effective and safe treatment in Child A and early Child B patients. Factors such as Child class B, larger tumor size, presence of portal vein thrombosis, metastasis, and high baseline alpha-fetoprotein levels have a negative effect on survival.[48]

***TARE.*** TARE is a form of radiation therapy that involves embolization with a radiotherapy agent injected into the arteries supplying the HCC.[11] Yttrium-90 based microspheres are widely used in TACE. The INASL recommends the use of TARE in patients with advanced HCC, such as patients with portal vein thrombosis with good liver function (Child A), and contraindicated in BCLC-D, Child C, patient with contraindications to angiography, prior external beam radiotherapy, significant hepatopulmonary shunt ($> 20\%$), and extrahepatic metastases.[11] Numerous studies have validated its safer toxicity profile when compared with TACE. It also has longer time-to-progression and greater ability to downsize and/or bridge patients to LT. Emerging evidence has demonstrated that TARE may well be a viable alternative to the first-line systemic drug sorafenib.[49] The INASL recommends the use of TARE in patients with advanced HCC, such as patients with portal vein thrombosis with good liver function (Child A) and contraindicated in BCLC-D, Child C, patient with contraindications to angiography, prior external beam radiotherapy, significant hepatopulmonary shunt ($>$ 20%) and extrahepatic metastases.[11]

***Systemic chemotherapy.*** Systemic therapy includes tyrosine kinase inhibitors (TKIs): sorafenib, lenvatinib, regorafenib, and cabozantinib; monoclonal antibodies: ramucirumab and bevacizumab; and immune checkpoint inhibitors (ICI): nivolumab, pembrolizumab, and atezolizumab. Since the introduction of molecular targeted agent sorafenib in 2007, systemic therapy for HCC has changed remarkably. Sorafenib is the current first-line treatment for advanced HCC (BCLC C) and intermediate-stage HCC (BCLC-B) with preserved liver function (child A; selected child B), not suitable for or progressing despite locoregional therapy as per the INASL.[11] But because of its adverse effects, often there is a need for dose reductions or cessation of the drug, and therefore, sorafenib should be started at a lower dose.[11] In a prospective real-world study of sorafenib, a higher incidence of liver dysfunction and hand-foot syndrome-rash was reported among Indians compared with published data from other countries.[50] In a phase I dose de-escalation study aimed to assess the safety and efficacy of sequentially decreasing doses of sorafenib in combination with atorvastatin (10 mg once daily) and metformin (500 mg twice daily), there was a marked reduction in sorafenib-related side effects.[51] Both these drugs show an inhibitory effect against chronic hepatitis and liver cirrhosis and also resensitize HCC cells to the action of sorafenib.

Lenvatinib, a TKI, has demonstrated its immunomodulatory activity, which enhances its antitumor activity.[52] An open-labeled, phase III, multicentric, noninferiority trial was conducted in Asia-Pacific, European, and North American regions. It reported that the median survival time for

lenvatinib of 13.6 months (95% CI, 12.1 to 14.9) was noninferior to that of sorafenib (12.3 months, 10.4-13.9; hazard ratio, 0.92; 95% CI, 0.79 to 1.06) in patients with unresectable HCC.[53] In another study, only 32.2% of patients on lenvatinib required dose reduction because of side effects in comparison with patients taking sorafenib. These findings have changed the treatment of HCC in India, and lenvatinib is now considered an alternative first-line therapy for advanced HCC.[11,54]

***Immunotherapy.*** Immunotherapy is a promising therapeutic approach in the management of HCC because of its immune-rich milieu. When combined with other treatment modalities such as local treatment, monoclonal antibodies, or TKIs, immunotherapy has the potential to improve the overall response rate and survival.[55]

Development of ICIs has revolutionized the practice of medical oncology. ICIs reinvigorate antitumor immune responses by disrupting coinhibitory T-cell signaling.[56] Various ICIs that target cytotoxic T-cell lymphocyte-4–associated protein and programmed cell death-ligand 1 (PD-1/PD-L1) are now available that are increasingly being tested in clinical trials and are gaining approval for a variety of indications.[57] Single-agent PD-1/PD-L1 ICIs, such as atezolizumab, nivolumab, and pembrolizumab, have demonstrated clinical effectiveness in the treatment of HCC in phase Ib studies.[58-60] Nivolumab and pembrolizumab are approved as second-line agents.[61] However, major drawbacks of single-agent ICIs are the presence of primary resistance and emergence of acquired resistance.[57,62]

Combination drug trials have revealed better outcomes compared with monotherapy. Atezolizumab + bevacizumab combination led to higher OS.[61] In a phase Ib trial, patients with advanced HCC were offered a combination of lenvatinib and pembrolizumab. The objective response rate was 46%, which was higher than objective response rates of 24% and 17% for single-agent lenvatinib and pembrolizumab, respectively. The median progression-free survival was 9.3 months, whereas the OS was 22 months. This combination produced no new safety signals.[63]

## ROLE OF ATEZOLIZUMAB IN THE MANAGEMENT OF HCC

Atezolizumab is a fully humanized, engineered monoclonal antibody of IgG1 isotype that selectively targets PD-L1. In the year 2016, atezolizumab (TECENTRIQ, Genentech Oncology) became the first PD-L1 inhibitor to be approved by the US Food and Drug Administration for treatment of urothelial carcinoma and non–small-cell lung cancer (Table 1).[64] Currently, it is approved in the treatment of small-cell lung cancer, HCC, and melanoma.[65] Atezolizumab phase III trials are currently underway in India for breast cancer (CTRI/2017/10/010010, CTRI/2020/05/025040, and CTRI/2021/08/035911), urothelial or non-urothelial carcinoma of the urinary tract (CTRI/2017/08/009196), non–small-cell lung cancer (CTRI/2017/11/010690), and squamous cell carcinoma of the head and neck (CTRI/2018/05/014028).[66]

### Safety of Atezolizumab

The IMBrave150 trial has revealed an OS of 67.2% at 12 months with combination of atezolizumab and bevacizumab and a median progression-free survival of 6.8 months. Both revealed a better safety profile when compared with sorafenib. Grade 3 or 4 HTN occurred in 15.2% in the atezolizumab + bevacizumab group. Atezolizumab + bevacizumab also reduced risk of deterioration on all EORTC QLQ-C30 generic cancer symptom scales that were prespecified for analysis (appetite loss, diarrhea, fatigue, and pain) and two of three EORTC QLQ-HCC18 disease-specific symptom scales that were prespecified for analysis (fatigue and pain, but not jaundice).[67]

### Combination Therapy Trials

Atezolizumab, when combined with bevacizumab, is indicated for the treatment of unresectable or metastatic HCC who have not received prior systemic therapy.[65] Bevacizumab inhibits the vascular endothelial growth factor pathway. Vascular endothelial growth factor promotes immunosuppressive cells such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages inside the tumor microenvironment, resulting in immunosuppression. It also suppresses antigen-presenting cells and cytotoxic T-cell lymphocyte. Therefore, bevacizumab not only inhibits tumor growth by reducing angiogenesis but also enhances the immune agonistic effects of atezolizumab.[68] This explains the combined use of atezolizumab and bevacizumab in cancer therapy. Dosage recommendation of atezolizumab is 840 mg once every 2 weeks for breast cancer. Bevacizumab is administered at 15 mg/kg once every 3 weeks.[65] Several trials are now underway to determine the efficacy of atezolizumab in combination with other drugs in the treatment of various malignancies. Table 1 shows the studies conducted to date on the use of atezolizumab in HCC.[58,67,69,70]

## CURRENT TREATMENTS AND FUTURE STRATEGIES

### Renin Angiotensin System Inhibitors

Antihypertensive medicines such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are a group of drugs, which may potentially help patients with cancer. Pinter et al investigated the effect of renin angiotensin system inhibitors (RASi) treatment on the survival of patients with HCC and found that patients treated with sorafenib + RASi had better median OS (19.5 months) compared with those treated with either sorafenib (10.9 months) or RASi (9.7 months) alone ($P = .043$). Possible mechanisms for improved survival in RASi-treated patients include reduced tumor desmoplasia and liver fibrosis, improved antitumor immunity, decreased portal pressure, and suppression of angiogenesis.[71]

 

**TABLE 1.** Various Studies Showing the Efficacy and Safety of Atezolizumab in HCC

| Name of the Study | Type of Study | Study Participants | Study Groups | Primary and Secondary End Points | Study Findings |
|---|---|---|---|---|---|
| GO30140 (NCT02715531) | Open-label, multicentric, multiarm, phase Ib study | Age ≥ 18 years with histologically, cytologically, or clinically confirmed unresectable HCC not amenable to curative treatment; no previous systemic treatment; and ECOG PS of 0 or 1 | Group A: ATEZO (1,200 mg) + BEV (15 mg/kg) IV once every 3 weeks (n = 104)<br>Group F: ATEZO (1,200 mg) + BEV<br>(15 mg/kg) IV once every 3 weeks<br>(n = 60) or ATEZO monotherapy (n = 59) | Group A: Confirmed objective response rate in all patients who received the combination treatment<br>Group F: PFS in the ITT population<br>Safety data were assessed in both the groups | Group A: About 37 (36%) of 104 patients had a confirmed objective response<br>Most common grade 3-4 treatment–related AEs were HTN (13%) and proteinuria (7%)<br>Treatment-related SAE—24%<br>Treatment-related deaths—3%<br>Group F: The median PFS was 5.6 months for ATEZO + BEV *v* 3.4 months for ATEZO monotherapy ($P = 0.011$)<br>Most common grade 3-4 treatment–related AEs were HTN (5%) for ATEZO + BEV; none for monotherapy and proteinuria (3%) for ATEZO + BEV; none for monotherapy<br>Treatment-related SAE—12% in the ATEZO + BEV group and 3% patients in the ATEZO monotherapy group<br>Treatment-related deaths—none |
| IMBrave 150 (NCT03434379) | Open-label, multicentric, phase III trial | Age ≥ 18 years with systemic, treatment-naive, histologically, cytologically, or clinically confirmed unresectable HCC not amenable to curative, surgical, or locoregional treatment and ECOG-PS of 0 or 1 | ATEZO (1,200 mg) + BEV (15 mg/kg) IV once every 3 weeks (n = 336) or SOR (400 mg) twice daily (n = 165) | OS and PFS in the ITT population, as assessed at an IRF according to RECIST 1.1 and HCC-modified RECIST (mRECIST)<br>QoL questionnaire for cancer (QLQ-30)<br>QLQ for HCC (QLQ-HCC18) | Hazard ratio for death (ATEZO + BEV/SOR)—0.58 ($P < .001$)<br>OS at 12 months—67.2% with ATEZP + BEV and 54.6% with SOR<br>Median PFS—6.8 months (ATEZO + BEV) and 4.3 months (SOR)<br>Hazard ratio for disease progression or death, 0.59 ($P < .001$)<br>Grade 3 or 4 AE—56.5% (ATEZO + BEV) and 55.1% (SOR)<br>Grade 3 or 4 HTN occurred in 15.2% in the ATEZO + BEV group.<br>Compared with SOR, ATEZO + BEV reduced the risk of deterioration on all EORTC QLQ-C30 generic cancer symptom scales that were prespecified for analysis (appetite loss, diarrhea, fatigue, and pain) and two of three EORTC QLQ-HCC18 disease-specific symptom scales that were prespecified for analysis (fatigue and pain, but not jaundice)<br>At day 1 of treatment cycle five, the mean EORTC QLQ-C30 score changes from baseline in the ATEZO + BEV *v* SOR groups were –3.29 (SD 17.56) *v* –5.83 (20.63) for QoL, –4.02 (19.42) *v* –9.76 (21.33) for role functioning, and –3.77 (12.82) *v* –7.60 (15.54) for physical functioning<br>The median TTR was 2.8 months per RECIST 1.1 and mRECIST with ATEZO/BEV<br>Patients receiving ATEZO/BEV had a greater DpR, per both criteria, across baseline liver lesion sizes<br>Characteristics of complete responders were similar to those of the ITT population<br>In complete responders receiving ATEZO/BEV per mRECIST *v* RECIST 1.1, respectively, median TTCR was shorter (5.5 *v* 7.0 months), mean baseline sum of lesion diameter was longer (5.0 [SD, 5.1] *v* 2.6 [SD, 1.4] cm), and the mean largest liver lesion size was larger (4.8 [SD, 4.2] *v* 2.3 [SD, 1.0] cm) |

Abbreviations: AE, adverse effects; ATEZO, atezolizumab; BEV, bevacizumab; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; HCC, hepatocellular carcinoma; HTN, hypertension; IRF, Independent Review Facility; ITT, intention to treat; IV, intravenous; OS, overall survival; PFS, progression-free survival; PS, performance status; QLQ, Quality of life questionnaire; QoL, quality of life; SAE, serious adverse events; SD, standard Deviation; SOR, sorafenib; TTCR, time to complete response; TTR, time to response.

### Cell Therapies

Cell-based therapies have emerged as alternatives to LT, which include primary hepatocyte transplantation and bioartificial liver devices. Primary hepatocyte transplantation makes use of hepatocytes encapsulated in alginate beads or mesenchymal stem cells, which has resulted in greater engraftment, cell survival, and a reduced host immunological response. However, challenges such as the availability of good quality hepatocytes, cell function monitoring, cryopreservation, and the immediate blood-mediated immune response leading to cell loss remain.[72] Another type of cell-based therapy is the use of BALs, which are extracorporeal devices integrating hepatic cells and tissues. Although several prototypes have been tested in clinical trials, BALs are not in use in clinical settings or commercially available.[73] The use of liver micro-organs as the biologic component for BAL devices is intriguing because they harbor all hepatic cellular types and microarchitecture and can easily be obtained.[73] As a result, further research is warranted in these areas.

### Antiviral Prophylaxis

Because of widespread availability of antiviral medication, the long-term clinical results in patients with CHB have improved considerably in recent decades.[74] Antiviral therapy in patients with BCLC-D may improve liver function, expanding the therapeutic window for tumor-specific medicines.[11] Immunomodulators (conventional interferon alpha and pegylated interferon alpha) and nucleoside/nucleotide analog (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) have shown short-term efficacy in the treatment of CHB.[75] Long-term studies using lamivudine and adefovir reveal a consistent decrease in development of HCC in both cirrhotic and noncirrhotic patients.[75] Another class of antivirals currently in clinical trials for treatment of HCV-related HCC is direct-acting antivirals, which have improved the cure rate to $>$ 90%. Yet, because of high costs and underdiagnosis in certain subpopulations, access to these drugs is limited.[76]

## CONCLUSION

In conclusion, management strategies for HCC remain a challenge. Presentation of HCC in advanced stage is frequently encountered in developing countries like India, which could be attributed to the delay in routine test or screening. Thus, it is imperative to develop effective therapeutic regimens for such stages. In addition, focus should be diverted to understanding of molecular carcinogenesis, to derive effective treatment options. Finally, preventive strategies including hepatitis B vaccination, lifestyle modification, reduced alcohol consumption, and surveillance for HCC may help in part to reduce the incidence of HCC in India.


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## REFERENCES


1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Rumgay H, Ferlay J, Martel Cde, et al. Global, regional and national burden of primary liver cancer by subtype. 2021;161:108–118
3. Baecker A, Liu X, La Vecchia C, Zhang ZF: Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. Eur J Cancer Prev 27:205-212, 2018


 

4. Yarchoan M, Agarwal P, Villanueva A, et al: Recent developments and therapeutic strategies against hepatocellular carcinoma. Cancer Res 79:4326-4330, 2019
5. Kumar R, Saraswat MK, Sharma BC, et al: Characteristics of hepatocellular carcinoma in India: A retrospective analysis of 191 cases. Qjm 101:479-485, 2008
6. Acharya SK: Epidemiology of hepatocellular carcinoma in India. J Clin Exp Hepatol 4:S27-S33, 2014
7. Siddiqui MA, Siddiqui HH, Mishra A, Usmani A: Epidemiology of hepatocellular carcinoma. Int J Pharm Sci Res 9:5050-5059, 2018
8. Phukan RK, Borkakoty BJ, Phukan SK, et al: Association of processed food, synergistic effect of alcohol and HBV with Hepatocellular Carcinoma in a high incidence region of India. Cancer Epidemiol 53:35-41, 2018
9. Dikshit R, Gupta PC, Ramasundarahettige C, et al: Cancer mortality in India: A nationally representative survey. Lancet 379:1807-1816, 2012
10. Sarin SK, Thakur V, Guptan RC, et al: Profile of hepatocellular carcinoma in India: An insight into the possible etiologic associations. J Gastroenterol Hepatol 16:666-673, 2001
11. Kumar A, Acharya SK, Singh SP, et al: 2019 Update of Indian National Association for Study of the Liver Consensus on Prevention, Diagnosis, And Management of Hepatocellular Carcinoma in India: The Puri II recommendations. J Clin Exp Hepatol 10:43-80, 2020
12. WHO: Hepatitis B. World Hepatitis Day 2016, 2016. http://www.searo.who.int/india/topics/hepatitis/factsheet_b__hepatitisday2016.pdf?ua=1
13. Kar P: Risk factors for hepatocellular carcinoma in India. J Clin Exp Hepatol 4:S34-S42, 2014
14. Chavda HJ: Hepatocellular carcinoma in India. Indian J Surg 83:959-966, 2021
15. Sarin SK, Kumar M, Eslam M, et al: Liver diseases in the Asia-Pacific region: A Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 5:167-228, 2020
16. Goel A, Seguy N, Aggarwal R: Burden of hepatitis C virus infection in India: A systematic review and meta-analysis. J Gastroenterol Hepatol 34:321-329, 2019
17. Rajasekaran M, Sivagnanam G, Thirumalaikolundusubramainan P, et al: Injection practices in Southern part of India. Public Health 117:208-213, 2003
18. Ministry of Health and Family Welfare: National Viral Hepatitis Control Program (NVHCP). National Health Portal India, 2019. https://www.nhp.gov.in/national-viral-hepatitis-control-program-(nvhcp)_pg
19. Tohra S, Duseja A, Taneja S, et al: Experience with changing etiology and nontransplant curative treatment modalities for hepatocellular carcinoma in a real-life setting—A retrospective descriptive analysis. J Clin Exp Hepatol 11:682-690, 2021
20. De A, Duseja A: Nonalcoholic fatty liver disease: Indian Perspective. Clin Liver Dis 18:158-163, 2021
21. Bhadoria AS, Pathak V: Non-alcoholic fatty liver disease (NAFLD) in India: Challenges and the ways forward. J Indian Med Assoc 120:52-55, 2022
22. Musunuri B, Shetty S, Bhat G, et al: Profile of patients with hepatocellular carcinoma: An experience from a tertiary care center in India. Indian J Gastroenterol 41:127-134, 2022
23. Mungamuri SK, Mavuduru VA: Role of epigenetic alterations in aflatoxin-induced hepatocellular carcinoma. Liver Cancer Int 1:41-50, 2020
24. Murugavel KG, Naranatt PP, Shankar EM, et al: Prevalence of aflatoxin B1 in liver biopsies of proven hepatocellular carcinoma in India determined by an in-house immunoperoxidase test. J Med Microbiol 56:1455-1459, 2007
25. Shi T, Kobara H, Oura K, Masaki T: Mechanisms underlying hepatocellular carcinoma progression in patients with type 2 diabetes. J Hepatocell Carcinoma 8:45-55, 2021
26. Galle PR, Forner A, Llovet JM, et al: EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 69:182-236, 2018
27. Heimbach JK, Kulik LM, Finn RS, et al: AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 67:358-380, 2018
28. Omata M, Lesmana LA, Tateishi R, et al: Asian pacific association for the study of the liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 4:439-474, 2010
29. Mak L, Cruz-ramón V, Chinchilla-lópez P, et al: Global epidemiology, prevention , and management of global epidemiology of HBV. Am Soc Clin Oncol 38:262-279, 2019
30. Moris D: A farewell to Barcelona Clinic Liver Cancer (BCLC) classification for hepatocellular carcinoma. J BUON 26:298-302, 2021
31. Tellapuri S, Sutphin PD, Beg MS, et al: Staging systems of hepatocellular carcinoma: A review. Indian J Gastroenterol 37:481-491, 2018
32. Moris D, Vernadakis S, Papalampros A, et al: The effect of Guidelines in surgical decision making: The paradigm of hepatocellular carcinoma. J BUON 21:1332-1336, 2016
33. Demetrios M, Evangelos F: Ignore reality but not the consequences of its ignorance: Broaden guidelines in surgery of hepatocellular carcinoma. Hepatology 65:1772-1773, 2017
34. Romano F, Chiarelli M, Garancini M, et al: Rethinking the Barcelona clinic liver cancer guidelines: Intermediate stage and Child-Pugh B patients are suitable for surgery? World J Gastroenterol 27:2784-2794, 2021
35. Fukami Y, Kaneoka Y, Maeda A, et al: Liver resection for multiple hepatocellular carcinomas: A Japanese nationwide survey. Ann Surg 272:145-154, 2020
36. Hyun MH, Lee YS, Kim JH, et al: Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. Hepatology 68:977-993, 2018
37. Reig M, Darnell A, Forner A, et al: Systemic therapy for hepatocellular carcinoma: The issue of treatment stage migration and registration of progression using the BCLC-refined RECIST. Semin Liver Dis 34:444-455, 2014
38. Sinn DH, Choi GS, Park HC, et al: Multidisciplinary approach is associated with improved survival of hepatocellular carcinoma patients. PLoS One 14:1-13, 2019
39. Anand AC, Acharya SK: New developments in the treatment of hepatocellular carcinoma: The concept of adjuvant and neoadjuvant chemotherapy. J Clin Exp Hepatol 11:284-287, 2021
40. Marrero JA, Kulik LM, Sirlin CB, et al: Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 68:723-750, 2018
41. Yang JD, Hainaut P, Gores GJ, et al: A global view of hepatocellular carcinoma: Trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 16:589-604, 2019
42. Wagle P, Narkhede R, Desai G, et al: Surgical management of large hepatocellular carcinoma: The first single-center study from western India. Arq Bras Cir Dig 33:1-7, 2020
43. Wen T, Jin C, Facciorusso A, et al: Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: An international expert consensus. Hepatobiliary Surg Nutr 7:353-371, 2018
44. Llovet JM, Ducreux M, Lencioni R, et al: EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 56:908-943, 2012
45. Pamecha V, Sinha PK, Rajendran V, et al: Living donor liver transplantation for hepatocellular carcinoma in Indian patients— Is the scenario different? Indian J Gastroenterol 40:295-302, 2021

46. National Organ and Tissue Transplant Organisation: WHO-GODT Data Summary, 2020. http://www.transplant-observatory.org/summary/
47. Paul SB, Gamanagatti S, Sreenivas V, et al: Trans-arterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma: Experience from a Tertiary Care Centre in India. Indian J Radiol Imaging 21:113-120, 2011
48. Agarwal A, Yadav AK, Kumar A, et al: Transarterial chemoembolization in unresectable hepatocellular carcinoma—assessing the factors affecting the survival: An audit from a tertiary care center in northern India. Indian J Gastroenterol 34:117-126, 2015
49. Kallini JR, Gabr A, Salem R, Lewandowski RJ: Transarterial radioembolization with Yttrium-90 for the treatment of hepatocellular carcinoma. Adv Ther 33:699-714, 2016
50. Ostwal V, Gupta T, Chopra S, et al: Tolerance and adverse event profile with sorafenib in Indian patients with advanced hepatocellular carcinoma. South Asian J Cancer 6:144-146, 2017
51. Ostwal V, Ramaswamy A, Gota V, et al: Phase I study evaluating dose de-escalation of sorafenib with metformin and atorvastatin in hepatocellular carcinoma (SMASH). Oncologist 27:165-e222, 2022
52. Kimura T, Kato Y, Ozawa Y, et al: Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci 109:3993-4002, 2018
53. 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 391:1163-1173, 2018
54. Rauthan A, Somashekhar SP, Patil P, Zaveri S: Real-world experience with lenvatinib in the management of hepatocellular carcinoma: A single-center Indian experience. J Clin Oncol 38, 2020 (suppl 15; abstr e16596)
55. Weinmann A, Galle PR: Role of immunotherapy in the management of hepatocellular carcinoma: Current standards and future directions. Curr Oncol 27:S152-S164, 2020
56. Jenkins RW, Barbie DA, Flaherty KT: Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer 118:9-16, 2018
57. Syn NL, Teng MWL, Mok TSK, Soo RA: De-novo and acquired resistance to immune checkpoint targeting. Lancet Oncol 18:e731-e741, 2017
58. Lee MS, Ryoo BY, Hsu CH, et al: Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): An open-label, multicentre, phase 1b study. Lancet Oncol 21:808-820, 2020
59. El-Khoueiry AB, Sangro B, Yau T, et al: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389:2492-2502, 2017
60. 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 19:940-952, 2018
61. Kudo M: Recent advances in systemic therapy for hepatocellular carcinoma in an aging Society: 2020 update. Liver Cancer 9:640-662, 2020
62. Perrier A, Didelot A, Laurent-Puig P, et al: Epigenetic mechanisms of resistance to immune checkpoint inhibitors. Biomolecules 10:1-30, 2020
63. Finn RS, Ikeda M, Zhu AX, et al: Phase ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 38:2960-2970, 2020
64. FDA approves new, targeted treatment for bladder cancer. 2016. www.fda.com
65. Genentech: TECENTRIQ (Atezolizumab), Prescribing Information. https://www.gene.com/download/pdf/tecentriq_prescribing.pdf
66. Clinical Trials Registry - India: http://ctri.nic.in/Clinicaltrials/advsearch.php
67. Finn RS, Qin S, Ikeda M, et al: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382:1894-1905, 2020
68. Jain A, Chitturi S, Peters G, Yip D: Atezolizumab and bevacizumab as first line therapy in advanced hepatocellular carcinoma: Practical considerations in routine clinical practice. World J Hepatol 13:1132-1142, 2021
69. Galle PR, Finn RS, Qin S, et al: Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): An open-label, randomised, phase 3 trial. Lancet Oncol 22:991-1001, 2021
70. Salem R, Li D, Sommer N, et al: Characterization of response to atezolizumab + bevacizumab versus sorafenib for hepatocellular carcinoma: Results from the IMbrave150 trial. Cancer Med 10:5437-5447, 2021
71. Pinter M, Weinmann A, Wörns MA, et al: Use of inhibitors of the renin–angiotensin system is associated with longer survival in patients with hepatocellular carcinoma. United Eur Gastroenterol J 5:987-996, 2017
72. Dhawan A: Clinical human hepatocyte transplantation: Current Status and challenges. Liver Transplant 21:S39-S44, 2015
73. Pizarro MD, Mamprin ME, Daurelio LD, et al: Experimental bio-artificial liver: Importance of the architectural design on ammonia detoxification performance. World J Hepatol 10:719-730, 2018
74. Choi J, Lim YS: Secondary prevention of hepatitis B virus-related hepatocellular carcinoma with current antiviral therapies. Kaohsiung J Med Sci 37:262-267, 2021
75. Lai CL, Yuen MF: Prevention of hepatitis B virus-related hepatocellular carcinoma with antiviral therapy. Hepatology 57:399-408, 2013
76. Baumert TF, Jühling F, Ono A, Hoshida Y: Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. BMC Med 15:1-10, 2017