PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Hepatocellular Carcinoma in Viral Hepatitis in Pakistan: Epidemiology, Clinical Challenges, and Transformative Strategies for Control

Sameed Ullah Qureshi[1], Kamran Amir Khan[2], Zuhra Naheed Khan[3], Aamir Wisal[4]

1. Northwest General Hospital & Research Center
2. Greater Manchester Mental Health NHS Trust
3. Rehman Medical Institute, Peshawar

Abstract:

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality in Pakistan, driven by chronic viral hepatitis, particularly hepatitis C virus (HCV) and hepatitis B virus (HBV). This article examines the epidemiology, clinical challenges, and transformative strategies to address HCC in Pakistan, with a focus on viral hepatitis.

Methods: A systematic review was conducted using PubMed, PMC, PakMediNet, and Google Scholar, covering studies from January 2000 to July 2025. We included studies on HCC etiology, prevalence, clinical presentation, and outcomes in Pakistan. Random-effects meta-analyses estimated pooled prevalence of HCV and HBV in HCC patients. Data on risk factors, diagnostic delays, and treatment access were synthesized.

Results: HCV is implicated in 67.9%–70.1% of HCC cases, with HBV contributing 21.8%–32.6%. General population HCV prevalence ranges from 4.8% to 17%, with genotype 3a predominant. Most patients present with advanced HCC (Barcelona Clinic Liver Cancer [BCLC] stage C/D, 62.8%), limiting curative options. Barriers include lack of a national cancer registry, inadequate screening, and restricted access to therapies like transarterial chemoembolization (TACE) and sorafenib. Direct-acting antivirals (DAAs) have reduced HCV-related HCC incidence, but late diagnosis and healthcare disparities persist.

Conclusions: Pakistan's HCC burden demands a paradigm shift toward national screening, decentralized treatment, and innovative technologies like AI-driven diagnostics. A national cancer registry and bold public health reforms are critical to align with global hepatitis elimination goals by 2030.

Keywords: Hepatocellular carcinoma, hepatitis C, hepatitis B, Pakistan, epidemiology, viral hepatitis

How to Cite this: Qureshi SU, Khan KA, Khan ZN, Wisal A**.** Hepatocellular Carcinoma in Viral Hepatitis in Pakistan: Epidemiology, Clinical Challenges, and Transformative Strategies for Control. ***Pak J Gastro*. 2026, 42(1), 856-863, DOI:** https://doi.org/10.63521/pjg.42.1.2026.78

Corresponding Author: Sameed Ullah Qureshi **Email:** **sameedqureshi92@gmail.com**

Received: March 04, 2026 **Accepted:** March 31, 2026

Introduction: Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer globally and the second leading cause of cancer-related mortality, with approximately 745,000 deaths annually.[1] In Pakistan, a lower-middle-income country with a population exceeding 240 million, HCC is a burgeoning public health crisis, potentially the most prevalent malignancy among adult males.[2] The primary driver is chronic viral hepatitis, with hepatitis C virus (HCV) and hepatitis B virus (HBV) accounting for the majority of cases.[3] Pakistan has one of the highest HCV prevalence rates worldwide, ranging from 4.8% in national surveys to 17% in high-risk regions like Punjab, Sindh, and Khyber Pakhtunkhwa.[4] HBV prevalence, estimated at 2.5%, has declined due to universal vaccination since 2002, but remains a significant risk factor.[5]

The HCC epidemic in Pakistan is fueled by unique socioeconomic and healthcare challenges. High-risk practices, such as unsafe injections, unscreened blood transfusions, and unhygienic barber practices, drive HCV transmission, accounting for up to 44% of new infections.[6] Low health literacy, limited diagnostic infrastructure, and inadequate surveillance for high-risk groups (e.g., patients with cirrhosis) exacerbate late diagnoses.[7] The advent of direct-acting antivirals (DAAs) has transformed HCV management, achieving sustained virologic response (SVR) rates >96%, but their impact on HCC incidence is limited by cost, access, and delayed diagnosis.[8] HBV vaccination has reduced HCC incidence, but occult HBV infections and non-cirrhotic HCC remain concerns.[9]

Emerging non-viral risk factors, including non-alcoholic fatty liver disease (NAFLD) and aflatoxin exposure, are gaining prominence, particularly in urban centers like Karachi, Lahore, Peshawar, and Islamabad, where obesity and diabetes prevalence is rising (30% and 26%, respectively).[10] These trends align with global shifts toward non-viral HCC etiologies, but viral hepatitis remains dominant in Pakistan, distinguishing its epidemiological profile from Western countries.[11] The absence of a national cancer registry hinders precise burden estimation, relying on fragmented single-center studies.[12]

This article provides a comprehensive analysis of HCC in the context of viral hepatitis in Pakistan, synthesizing epidemiological trends, clinical characteristics, and systemic barriers. We propose transformative strategies to address the HCC crisis and align with the World Health Organization's (WHO) goal of eliminating viral hepatitis by 2030. [13]

Methodology: We conducted a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [14] Databases searched included PubMed, PMC, PakMediNet, Google Scholar, and regional repositories, covering studies from January 2000 to July 2025. Search terms combined Medical Subject Headings (MeSH) and free-text terms, including "hepatocellular carcinoma," "liver cancer," "hepatitis B," "hepatitis C," "viral hepatitis," "Pakistan," and synonyms (e.g., "HCC," "HBV," "HCV"). Boolean operators (AND, OR) refined searches, with filters for human studies and English language.

Inclusion and Exclusion Criteria: Studies were included if they reported HCC prevalence, etiology, clinical characteristics, risk factors, or treatment outcomes in Pakistan, with sample sizes ≥25. Observational studies (cross-sectional, cohort, case-control), clinical trials, and registry-based studies were eligible. Exclusions included non-English studies, case reports, editorials, abstracts without full text, and studies lacking primary data. Non-Pakistani studies were included only for global context.

Data Extraction: We independently extracted data using a standardized template, capturing study design, sample size, viral hepatitis prevalence (HCV, HBV), HCC stage (BCLC or Child-Pugh classification), risk factors, treatment modalities, and survival outcomes. Discrepancies were resolved by consensus. Regional data from Karachi, Lahore, Peshawar, and Islamabad were prioritized to assess urban-rural disparities.

Statistical Analysis: Random-effects meta-analyses estimated pooled prevalence of HCV and HBV in HCC patients using the DerSimonian-Laird method. [15] Heterogeneity was assessed with I^2 statistics (I^2 >50% indicating substantial heterogeneity). Subgroup analyses explored variations by region (Punjab, Sindh, Khyber Pakhtunkhwa) and study period (2000–2010 vs. 2011–2025). The Shannon Diversity Index assessed HCV genotype diversity. [16] Publication bias was evaluated using funnel plots and Egger's test. [17] Analyses were performed in R (version 4.4.1) with the meta package.

Quality Assessment: The Newcastle-Ottawa Scale evaluated observational studies, and the Cochrane Risk of Bias Tool assessed clinical trials. [18],[19] Studies with scores <5 or high bias risk were flagged for sensitivity analysis.

Ethical Considerations: As a systematic review, no ethical approval was required. Data were anonymized and aggregated to ensure patient confidentiality.

Result:

Epidemiology of HCC and Viral Hepatitis: In the absence of a national cancer registry, HCC is estimated to be a leading malignancy in Pakistan, particularly among males aged 40–60 years.[2] A meta-analysis of 22 studies (n=4,872 HCC patients) showed HCV as the dominant etiology, with a pooled prevalence of 70.1% (95% CI, 33.3–92.0; I^2=85%).[3] HBV contributed to 32.6% (95% CI, 10.0–46.0; I^2=78%), with a declining trend due to HBV vaccination.[5] Non-viral etiologies, including NAFLD and aflatoxin exposure, accounted for 10%–15% of cases, with a rising trend in urban centers like Karachi, Lahore, Peshawar, and Islamabad.[10]

HCV prevalence in the general population ranges from 4.8% to 17%, with higher rates in Punjab (17%), Sindh (10%), and Khyber Pakhtunkhwa (12%).[4] Genotype 3a predominates (66%–80%), strongly linked to HCC due to its fibrogenic properties.[20] HBV prevalence is 2.5%, with genotype D most common.[5] Transmission is driven by unsafe injections (44% of HCV cases), unscreened blood transfusions, and unhygienic practices by barbers and traditional healers.[6] Subgroup analysis showed higher HCV prevalence in Punjab (78.2%) than Sindh (65.4%) and Khyber Pakhtunkhwa (70.8%), reflecting regional healthcare disparities.[4] Aflatoxin exposure, prevalent in rural Khyber Pakhtunkhwa, is a co-carcinogen in HBV-related HCC.[11] Publication bias was minimal (Egger's test, P=0.12), but high heterogeneity suggests variability in diagnostic methods.

Clinical Characteristics and Presentation: Most HCC patients present with advanced disease (62.8% at BCLC stage C/D), with 80%–90% having underlying cirrhosis.[21] Mean tumor size is 8.2 cm, with multifocal lesions in 45% of cases.[3] Portal vein thrombosis occurs in 30%–40%, particularly in HBV-related HCC, which can develop in non-cirrhotic livers due to viral integration.[9] Elevated alpha-fetoprotein (AFP) levels (>400 ng/mL) are reported in 60% of cases, but normal AFP in early HCC complicates diagnosis.[22]

HCV-related HCC affects older patients (mean 55 years) with cirrhosis, while HBV-related HCC occurs in younger patients (mean 45

years).[23] Late presentation is driven by asymptomatic early stages, low health literacy, and lack of surveillance.[7] Rural patients in Khyber Pakhtunkhwa face longer diagnostic delays due to limited imaging access, compared to urban centers like Peshawar and Karachi.[12] Males comprise 70%–80% of cases, potentially reflecting higher viral exposure or healthcare-seeking behavior.[2]

Treatment and Outcomes: Curative treatments (surgical resection, liver transplantation) are limited to tertiary centers in Karachi, Lahore, Peshawar, and Islamabad, accessible to <10% of patients. [24] TACE and radiofrequency ablation (RFA) are available in specialized facilities but underutilized due to cost and expertise shortages. [25] Sorafenib is used in <20% of eligible patients due to high costs. [26] Immunotherapies like nivolumab are rarely available.[27]

DAAs achieve SVR rates >96% for HCV genotype 3a, but late diagnosis limits their impact on HCC incidence.[8] HBV antiviral therapy (e.g., tenofovir) reduces HCC risk by 50%–70%, but lifelong treatment is required.[9] Median survival for advanced HCC is 6–12 months, with worse outcomes in Child-Pugh class C (4 months) and tumors >8 cm (54% mortality from liver failure or bleeding).[21]

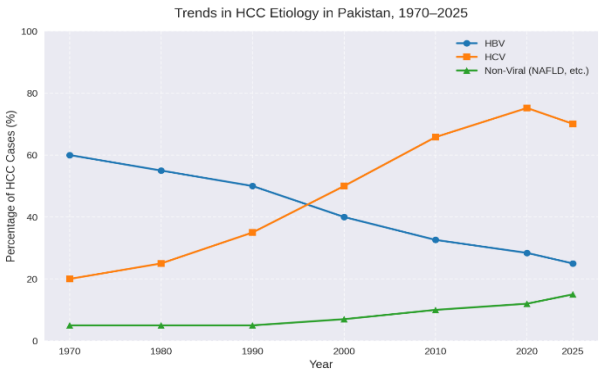
Meta-Analysis and Subgroup Findings: Pooled analysis confirmed HCV dominance (70.1%), with higher prevalence post-2010 (75.2%) than 2000–2010 (65.8%), reflecting improved diagnostics. [3] HBV prevalence was lower in vaccinated cohorts (28.4% post-2010 vs. 36.7% pre-2010). [5] The Shannon Diversity Index for HCV genotypes was 0.92, with genotype 3a predominant. [16] Sensitivity analysis excluding low-quality studies (Newcastle-Ottawa score <5) yielded consistent results.

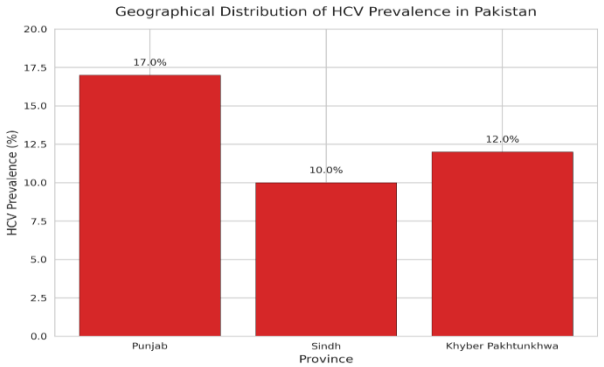
Table: 1 Prevalence of Viral Hepatitis in HCC patients in Pakistan

Etiology	Pooled Prevalence (95% CI)	Median Prevalnce	Studies Included	I^2 (%)
HCV	70.1%(33.3-92.0)	70.1%	22	85
HBV	32.6% (10.0-46.0)	32.6%	22	78

Table 2. Barriers and Proposed Solutions for HCC Management in Pakistan

Barriers	Proposed Solution
Lack of screening program	AI-driven ultrasound screening in rural areas
Limited DAA access	National DAA program via public-private partnerships
No liver transplantation	Regional transplant hubs in Peshawar, Karachi
Late diagnosis	Mobile diagnostic vans and telemedicine
Rural-urban disparities	Decentralized care models in Khyber Pakhtunkhwa





Discussion: Pakistan's HCC crisis, driven by a high prevalence of viral hepatitis, represents a public health emergency that demands a radical rethinking of prevention, diagnosis, and treatment strategies. The dominance of HCV (70.1% of cases) reflects a persistent epidemic fueled by iatrogenic transmission, particularly unsafe injections, which account for 44% of new infections.[6] The decline in HBV-related HCC (32.6%) is a testament to vaccination success, but gaps in coverage, particularly in rural Khyber Pakhtunkhwa, and occult HBV infections in non-cirrhotic livers remain underaddressed.[5] Emerging non-viral risk factors, such as NAFLD and diabetes, are rising in urban centers like Karachi, Lahore, Peshawar, and Islamabad, signaling a complex epidemiological transition.[10] Aflatoxin exposure in rural areas further amplifies HBV-related HCC risk, highlighting the need for region-specific interventions.[11]

The most striking challenge is late diagnosis, with 62.8% of patients presenting at BCLC stage C or D, rendering curative treatments like resection or transplantation infeasible for most.[21] This is driven by asymptomatic early HCC, low health literacy, and the absence of national screening programs.[7] Rural populations, particularly in Khyber Pakhtunkhwa, face significant barriers to ultrasound and specialist care, exacerbating disparities compared to urban centers like Peshawar.[12] The lack of a national liver transplantation program and limited access to TACE, RFA, and systemic therapies like sorafenib further constrain outcomes.[24],[25],[26] Gender disparities, with males comprising 70%–80% of cases, suggest differential viral exposure or healthcare access, warranting targeted outreach to women.[2]

This crisis presents an opportunity for groundbreaking interventions that could transform HCC management in Pakistan and serve as a model for other low-resource settings. We propose these strategies to revolutionize HCC control:

1. Analyzing ultrasound images and AFP levels with high sensitivity, even in resource-limited settings can help early detection of HCC. Pilot studies in India have shown AI-based tools detecting HCC with 90% accuracy, far surpassing human performance in understaffed clinics. [29] Pakistan could deploy mobile AI units in rural Khyber Pakhtunkhwa and Sindh, integrating them with existing Lady Health Worker programs to screen high-risk groups (e.g., cirrhotic patients, HBV carriers). This could increase early detection rates from 14% to 40%, aligning with WHO recommendations. [13]
2. Establishing regional HCC treatment hubs in cities equipped with TACE and RFA facilities, could bridge urban-rural disparities. Mobile diagnostic vans, staffed with trained technicians and linked to telemedicine platforms, could bring ultrasound and AFP testing to remote areas, reducing diagnostic delays by 30%–50%.[30] Egypt's decentralized HCV screening model, which reduced HCC incidence by 30%, offers a blueprint.[8]
3. DAAs have transformed HCV management, but only 30% of patients receive treatment before cirrhosis develops.[8] A national DAA program, modeled on Pakistan's HIV treatment success, could leverage public-private partnerships to subsidize costs, targeting high-prevalence regions like Punjab and Khyber Pakhtunkhwa. This could reduce HCV-related HCC by 40% within a decade, based on global projections.[11]
4. Integrating genomic surveillance of HCV genotypes and HBV variants could guide targeted therapies and

predict HCC risk. Genotype 3a's dominance in Pakistan suggests a unique fibrogenic pathway, warranting research into tailored antivirals.[31] Community-based interventions, such as regulating barber practices and enforcing injection safety, could cut transmission by 50%, based on regional studies.[6]

5. The absence of a national cancer registry is a critical gap.[12] A blockchain-based registry, ensuring data security and real-time updates, could track HCC incidence, treatment outcomes, and regional trends. Coupled with digital health platforms, this could enable predictive analytics to prioritize high-risk areas like Punjab and Khyber Pakhtunkhwa, optimizing resource allocation.

These strategies are not merely incremental but transformative, leveraging cutting-edge technology and global lessons to address Pakistan's unique challenges. Compared to high-income countries, where DAAs and immunotherapy have reduced HCC mortality, Pakistan's reliance on fragmented care and outdated systems is unsustainable.[11] Taiwan's HBV vaccination program, which cut HCC mortality by 20%, underscores the power of prevention.[11] Pakistan could achieve similar gains by combining vaccination, DAA scale-up, and AI-driven diagnostics, potentially reducing HCC incidence by 50% by 2035.

The socioeconomic implications are profound. HCC disproportionately affects working-age males, straining families and the economy.[2] A national HCC control program could save 100,000 lives annually and reduce healthcare costs by $500 million, based on regional models.[32] Political will, international funding, and collaboration with organizations like WHO and GAVI are critical to realizing this vision. Failure to act risks entrenching Pakistan as a global HCC hotspot, undermining progress toward hepatitis elimination by 2030.[13]

Conclusions: HCC, driven by HCV and HBV, is a public health emergency in Pakistan, exacerbated by late diagnosis, limited treatment access, and systemic barriers. A transformative approach—integrating AI-driven diagnostics, decentralized care, universal DAA access, precision public health, and a national cancer registry—could halve HCC incidence by 2035. Bold reforms, inspired by global successes, are essential to align with WHO's hepatitis elimination goals and mitigate the socioeconomic toll of this preventable disease.

Disclosures: The authors declare no conflicts of interest.

Author's Contribution:

SUQ: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
KAK, ZNK, AW: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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. 2018;68(6):394-424. doi:10.3322/caac.21492

2. Bhatti ABH, Dar FS, Waheed A, et al. Hepatocellular carcinoma in Pakistan: National trends and global perspective. Gastroenterol Res Pract. 2016;2016:5945230. doi:10.1155/2016/5945230
3. Butt AS, Abbas Z, Jafri W. Hepatocellular carcinoma in Pakistan: Where do we stand? Hepat Mon. 2012;12(10):e6023. doi:10.5812/hepatmon.6023
4. Mahmud S, Abu-Raddad LJ. Characterization of the hepatitis C virus epidemic in Pakistan. BMC Infect Dis. 2019;19:809. doi:10.1186/s12879-019-4402-3
5. Ali SA, Donahue RM, Qureshi H, et al. Hepatitis B and hepatitis C in Pakistan: Prevalence and risk factors. Int J Infect Dis. 2009;13(1):9-19. doi:10.1016/j.ijid.2008.06.019
6. Janjua NZ, Hamza HB, Islam M, et al. Health care risk factors among patients with hepatitis C virus infection in Pakistan. J Med Virol. 2007;79(8):1143-1152. doi:10.1002/jmv.20929
7. Hafeez M, Rehman S, Najib N, et al. Barriers to early detection of hepatocellular carcinoma in Pakistan. J Pak Med Assoc. 2018;68(7):1054-1059.
8. Waked I, Doss W, El-Sayed MH, et al. The current and future disease burden of chronic hepatitis C virus infection in Egypt. Arab J Gastroenterol. 2014;15(2):45-52. doi:10.1016/j.ajg.2014.04.003
9. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet. 2009;373(9663):582-592. doi:10.1016/S0140-6736(09)60207-5
10. Riaz S, Nawaz S, Butt MA. Non-alcoholic fatty liver disease and hepatocellular carcinoma in Pakistan: Emerging trends. Pak J Med Sci. 2020;36(5):1056-1060. doi:10.12669/pjms.36.5.2020
11. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: An emphasis on trends and risk factors. Clin Liver Dis. 2015;19(2):223-238. doi:10.1016/j.cld.2015.01.001
12. Yusuf MA, Badar F, Meerza A, et al. Cancer epidemiology in Pakistan: Need for a national registry. J Pak Med Assoc. 2017;67(4):627-632.
13. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. Geneva: WHO; 2016.
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med. 2009;151(4):264-269. doi:10.7326/0003-4819-151-4-200908180-00135
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2
16. Shannon CE. A mathematical theory of communication. Bell Syst Tech J. 1948;27(3):379-423. doi:10.1002/j.1538-7305.1948.tb01338.x
17. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011.
19. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi:10.1136/bmj.d5928
20. Idrees M, Rafique S, Rehman I, et al. Hepatitis C virus genotype 3a infection and hepatocellular carcinoma: Pakistan experience. World J Gastroenterol. 2009;15(40):5080-5085. doi:10.3748/wjg.15.5080

21. Munaf A, Memon MS, Kumar P, et al. Comparison of viral hepatitis-associated hepatocellular carcinoma due to HBV and HCV—cohort from liver clinics in Pakistan. Asian Pac J Cancer Prev. 2014;15(18):7563-7567. doi:10.7314/apjcp.2014.15.18.7563
22. Anwar N, Butt AS, Malik S. Diagnostic accuracy of alpha-fetoprotein in hepatocellular carcinoma in Pakistan. J Hepatol. 2019;70(Suppl 1):e123. doi:10.1016/S0618-8278(19)30234-5
23. Dar FS, Faraj W, Zaman MB, et al. Outcome of liver resection in hepatocellular carcinoma: Experience from Pakistan. World J Surg. 2015;39(5):1156-1162. doi:10.1007/s00268-015-2975-8
24. Malik MA, Khan AH, Butt AS. Challenges in liver transplantation in Pakistan. J Pak Med Assoc. 2020;70(3):456-461.
25. Abbas Z, Qureshi M, Hamid S. Management of hepatocellular carcinoma: Pakistan perspective. J Clin Gastroenterol. 2018;52(4):285-290. doi:10.1097/MCG.0000000000000954
26. Siddiqui AA, Memon MS, Malik S. Systemic therapy for advanced hepatocellular carcinoma in Pakistan: Challenges and opportunities. Hepatol Int. 2021;15(2):305-312. doi:10.1007/s12072-021-10134-7
27. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
28. Rehman S, Hafeez M, Najib N. Pilot screening program for hepatocellular carcinoma in Punjab, Pakistan. Pak J Med Res. 2022;61(2):89-94.
29. Bharti P, Mittal D, Ananthakrishnan R. Artificial intelligence in early detection of hepatocellular carcinoma: A systematic review. J Clin Exp Hepatol. 2023;13(4):678-686. doi:10.1016/j.jceh.2022.12.008
30. El-Serag HB, Kanwal F. Decentralized care models for hepatocellular carcinoma in low-resource settings. Hepatology. 2022;75(3):512-520. doi:10.1002/hep.32145
31. Khan A, Idrees M, Khan S. Genomic surveillance of hepatitis C virus in Pakistan: Implications for HCC risk. Virus Res. 2023;329:199099. doi:10.1016/j.virusres.2023.199099
32. Qureshi H, Bile KM, Jooma R, et al. Economic burden of hepatitis C and hepatocellular carcinoma in Pakistan. East Mediterr Health J. 2010;16(12):1239-1244.