



Secular Trends and Geographic Variations of Hepatitis B Virus and Hepatitis C Virus-Associated Hepatocellular Carcinoma in South Punjab

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents one of the leading causes of cancer-related mortality worldwide. Approximately 75–90% of HCC cases develop on the background of chronic liver disease, with chronic Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections being the principal etiological factors. The burden of HCC is disproportionately higher in low- and middle-income countries, particularly in Asia and Africa, where chronic viral hepatitis remains endemic. Pakistan is among the countries with a high prevalence of HBV and HCV infections, making HCC an increasingly significant public health concern. South Punjab, owing to its demographic, socioeconomic, and healthcare disparities, experiences a particularly high burden of chronic liver disease. Understanding the temporal trends and geographical distribution of HBV- and HCV-associated HCC is essential for designing effective prevention and control strategies. To evaluate the secular trends, demographic characteristics, and geographical variations of HBV- and HCV-associated hepatocellular carcinoma in South Punjab, and to examine their implications for disease prevention, clinical management, and public health policy. This expanded review also synthesizes available scientific evidence regarding the epidemiology, risk factors, pathogenesis, diagnosis, prevention, and future challenges associated with HCC. This work is based on the available study data from Bahawalpur Institute of Nuclear Medicine and Oncology (BINO) together with a comprehensive review of published scientific literature. Demographic characteristics, viral etiologies, regional distribution, and temporal trends are discussed in the context of national and international evidence. Relevant epidemiological observations have been critically interpreted to provide a broader understanding of HCC patterns in South Punjab. The available data indicate that HCV remains the predominant etiological factor associated with hepatocellular carcinoma in South Punjab, whereas HBV constitutes the second most important viral cause. Most patients are middle-aged males, and considerable geographical variation exists among different districts. The incidence of HCC has demonstrated an increasing trend over the study period, reflecting the persistent burden of chronic viral hepatitis. The increasing burden of hepatocellular carcinoma in South Punjab emphasizes the urgent need for strengthened HBV vaccination programs, expanded HCV screening initiatives, timely antiviral treatment, improved surveillance systems, and region-specific healthcare policies. Comprehensive prevention strategies remain the most effective approach for reducing future morbidity and mortality associated with HCC.

Keywords

Hepatocellular Carcinoma; Hepatitis B Virus; Hepatitis C Virus; Liver Cancer; Epidemiology; South Punjab; Pakistan; Viral Hepatitis; Geographic Variation; Secular Trends.

1. Introduction



Hepatocellular carcinoma (HCC) is one of the most devastating malignancies affecting the global population. It accounts for nearly 90% of all primary liver cancers and remains among the leading causes of cancer-related deaths worldwide. Despite remarkable advances in diagnostic imaging, antiviral therapies, and oncological management, the prognosis of HCC remains poor because the disease is frequently diagnosed at an advanced stage. Consequently, hepatocellular carcinoma continues to impose a substantial clinical, social, and economic burden on healthcare systems, particularly in developing countries.

The development of hepatocellular carcinoma is a complex and multifactorial process involving chronic hepatic inflammation, progressive fibrosis, cirrhosis, genetic alterations, environmental exposures, and viral infections. Among all known risk factors, chronic infection with Hepatitis B virus (HBV) and Hepatitis C virus (HCV) constitutes the most significant cause of HCC worldwide. These viruses induce persistent hepatic injury through chronic inflammation, repeated hepatocyte destruction, regenerative hyperplasia, and progressive fibrotic remodeling of liver tissue. Over several decades, these pathological processes create an environment conducive to malignant transformation.

Globally, the epidemiology of hepatocellular carcinoma demonstrates marked geographical variation. Eastern Asia and Sub-Saharan Africa historically reported the highest incidence because of endemic HBV infection. However, improvements in universal vaccination programs have gradually reduced HBV-associated HCC in several countries. Conversely, HCV-related HCC has become increasingly prevalent in many developing nations, including Pakistan, owing to delayed diagnosis and inadequate infection-control practices.

Pakistan represents one of the countries with the highest prevalence of chronic viral hepatitis. Millions of individuals live with chronic HBV and HCV infections, many of whom remain undiagnosed until the development of advanced liver disease. South Punjab is particularly vulnerable because of limited healthcare resources, lower literacy rates, socioeconomic inequalities, and restricted access to preventive services. Unsafe injection practices, inadequately screened blood transfusions, and delayed antiviral treatment continue to facilitate viral transmission, thereby increasing the long-term risk of hepatocellular carcinoma.

2. Global Epidemiology of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) represents approximately **85–90% of all primary liver cancers** and has emerged as one of the fastest-growing causes of cancer-related morbidity and mortality worldwide. During the past three decades, the global burden of HCC has increased substantially owing to population growth, ageing, chronic viral hepatitis, metabolic disorders, and lifestyle-related liver diseases. Although remarkable progress has been achieved in antiviral therapies and cancer management, HCC continues to have a poor prognosis because the majority of patients present with advanced disease at diagnosis.

According to international cancer statistics, liver cancer is among the leading causes of cancer deaths globally. Unlike many other malignancies, HCC develops silently over many years, usually following chronic liver inflammation and cirrhosis. Consequently, patients frequently remain asymptomatic until the disease reaches an advanced stage, limiting curative treatment options.

One of the most striking characteristics of hepatocellular carcinoma is its **uneven geographical distribution**. Countries in **Eastern Asia** and **Sub-Saharan Africa** historically reported the highest incidence because of the endemic nature of chronic Hepatitis B virus (HBV) infection. In contrast, many Western countries experienced comparatively lower incidence rates until the emergence of chronic Hepatitis C virus (HCV) infection and, more recently, non-alcoholic fatty liver disease (NAFLD).



The epidemiological transition observed during the last several decades demonstrates that the principal causes of hepatocellular carcinoma vary between different regions. In China and several African countries, chronic HBV infection continues to account for the majority of HCC cases. Conversely, HCV has become the dominant viral cause of HCC in countries such as Japan, Egypt, Pakistan, and several Mediterranean regions. In North America and Europe, the increasing prevalence of obesity, diabetes mellitus, metabolic syndrome, and NAFLD has further altered the epidemiological profile of liver cancer.

Globally, the implementation of universal HBV vaccination has been regarded as one of the most successful cancer-prevention strategies. Countries that introduced neonatal HBV vaccination during the 1980s and 1990s have demonstrated a remarkable decline in HBV-associated hepatocellular carcinoma among younger populations. Taiwan represents one of the earliest examples where universal vaccination significantly reduced childhood HCC incidence. This experience clearly demonstrates that effective prevention of chronic HBV infection directly translates into reduced liver cancer incidence.

In contrast, the epidemiology of HCV-associated hepatocellular carcinoma has evolved differently. Since no effective vaccine against HCV is currently available, prevention depends primarily on early diagnosis, infection control, and antiviral treatment. The introduction of Direct-Acting Antiviral (DAA) therapy has dramatically improved cure rates for chronic HCV infection. Nevertheless, millions of infected individuals remain undiagnosed worldwide, particularly in developing countries where screening programs remain limited.

Another emerging contributor to hepatocellular carcinoma is **non-alcoholic fatty liver disease (NAFLD)** and its progressive form, **non-alcoholic steatohepatitis (NASH)**. The worldwide epidemic of obesity and diabetes has substantially increased the number of patients with metabolic liver disease. Consequently, many experts predict that NAFLD-related HCC will become one of the leading causes of primary liver cancer during the coming decades, even among patients without advanced cirrhosis.

Age distribution also demonstrates important epidemiological variation. In regions with endemic HBV transmission, hepatocellular carcinoma frequently develops at a younger age because infection often occurs during infancy or childhood. Conversely, HCV-associated HCC usually appears during the fifth to seventh decades of life because chronic hepatitis progresses slowly before malignant transformation occurs. This difference reflects the natural history of both viral infections.

Gender differences represent another consistent epidemiological feature. Worldwide, males are affected approximately **two to four times more frequently** than females. Several biological mechanisms have been proposed, including hormonal influences, differences in immune response, environmental exposures, occupational hazards, and behavioral risk factors. Experimental studies also suggest that androgen signaling may promote hepatocarcinogenesis, whereas estrogen appears to exert partial protective effects.

Socioeconomic status exerts a profound influence on HCC incidence and outcomes. Individuals living in resource-limited settings often experience delayed diagnosis, inadequate vaccination coverage, limited access to antiviral therapy, and insufficient surveillance programs. Consequently, patients from low- and middle-income countries generally present with more advanced disease and experience poorer survival than those living in high-income countries.

The economic burden of hepatocellular carcinoma is equally substantial. Costs associated with diagnostic investigations, antiviral treatment, surgical resection, liver transplantation, targeted therapies, hospitalization, and long-term follow-up place enormous pressure on healthcare



systems. In countries with limited healthcare resources, prevention remains considerably more cost-effective than treatment.

In summary, hepatocellular carcinoma has become a major global health challenge characterized by marked geographical variation, changing etiological patterns, and increasing incidence. Chronic HBV and HCV infections remain the principal viral causes, while metabolic liver diseases are emerging as important contributors. Understanding these global epidemiological patterns provides an essential framework for interpreting the secular trends and regional variations observed in South Punjab and highlights the importance of comprehensive prevention strategies aimed at reducing the future burden of liver cancer.

3. Hepatitis B Virus and Hepatocellular Carcinoma

3.1 Introduction to Hepatitis B Virus

Hepatitis B virus (HBV) is one of the most significant human pathogens and remains a major global public health concern. It is a partially double-stranded DNA virus belonging to the family **Hepadnaviridae** and possesses a unique replication cycle involving reverse transcription. Unlike many other hepatotropic viruses, HBV has the ability to integrate its genetic material into the genome of hepatocytes, thereby increasing the risk of malignant transformation independent of liver cirrhosis.

The World Health Organization recognizes chronic hepatitis B as one of the leading infectious causes of mortality worldwide. Millions of individuals continue to live with chronic HBV infection despite the availability of an effective vaccine for more than four decades. Chronic HBV infection contributes substantially to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC), making disease prevention a major global health priority. HBV is transmitted primarily through exposure to infected blood and body fluids. The principal routes of transmission include **mother-to-child transmission**, unsafe blood transfusions, contaminated needles and syringes, unsterilized surgical and dental instruments, and sexual contact. In highly endemic countries, vertical transmission during childbirth remains the predominant mode of infection, whereas horizontal transmission among adults is more common in regions with lower endemicity.

3.2 Global Burden of Hepatitis B Virus

Chronic HBV infection remains unevenly distributed throughout the world. The highest prevalence is observed in **East Asia, Southeast Asia, Sub-Saharan Africa, and parts of the Western Pacific Region**. These regions also report some of the highest incidences of hepatocellular carcinoma because long-standing HBV infection frequently progresses to chronic hepatitis, fibrosis, cirrhosis, and eventually liver cancer.

The introduction of universal neonatal HBV vaccination has dramatically altered the epidemiology of hepatitis B in many countries. Nations that implemented comprehensive vaccination programs have witnessed substantial reductions in chronic HBV infection among children and young adults, followed by a decline in HBV-associated hepatocellular carcinoma. This success has established hepatitis B vaccination as one of the most effective cancer-prevention interventions in modern medicine.

Despite these achievements, significant challenges remain. Many adults infected before the introduction of vaccination programs continue to carry chronic HBV infection and remain at risk of developing cirrhosis and hepatocellular carcinoma later in life. Consequently, screening, antiviral treatment, and long-term surveillance continue to play an essential role in disease control.



3.3 Epidemiology of HBV in Pakistan

Pakistan continues to experience a considerable burden of chronic hepatitis B. Although prevalence estimates vary across provinces, HBV remains one of the major causes of chronic liver disease and hepatocellular carcinoma. Several socioeconomic and healthcare-related factors contribute to the continued transmission of HBV.

Unsafe therapeutic injections remain common in many healthcare settings. Reuse of disposable syringes, inadequate sterilization of surgical and dental equipment, poorly regulated blood transfusion services, barber shop practices involving contaminated razors, and limited public awareness collectively facilitate viral spread.

In rural districts of South Punjab, restricted healthcare access, delayed diagnosis, and insufficient vaccination coverage further increase disease burden. Population mobility, poverty, and limited health education create additional barriers to disease prevention and early management.

3.4 Pathogenesis of HBV-Associated Hepatocellular Carcinoma

The development of HBV-associated hepatocellular carcinoma is a complex, multistep biological process involving chronic inflammation, immune-mediated liver injury, genetic instability, and progressive fibrosis.

Unlike HCV, HBV possesses the unique ability to integrate viral DNA directly into the chromosomes of hepatocytes. Viral integration disrupts normal cellular regulatory pathways and promotes genomic instability, creating favorable conditions for malignant transformation. Persistent HBV infection stimulates continuous immune-mediated destruction of infected hepatocytes. During repeated cycles of hepatocyte injury and regeneration, DNA replication errors accumulate, increasing the likelihood of oncogenic mutations. Progressive fibrosis eventually culminates in cirrhosis, which represents the strongest predisposing condition for hepatocellular carcinoma.

Several viral proteins, particularly the **HBx protein**, contribute directly to hepatocarcinogenesis. HBx interferes with tumor suppressor pathways, alters cell-cycle regulation, inhibits apoptosis, and promotes uncontrolled cellular proliferation. Experimental studies have demonstrated that HBx also influences angiogenesis, oxidative stress, inflammatory signaling pathways, and epigenetic regulation, thereby accelerating tumor development.

3.5 Risk Factors for HBV-Associated HCC

Several host- and virus-related factors influence the likelihood of developing hepatocellular carcinoma among patients with chronic hepatitis B.

Viral Factors

- High HBV DNA viral load
- Positive HBeAg status
- Chronic active hepatitis
- HBV genotype variations
- Viral DNA integration

Host Factors

- Male gender
- Increasing age
- Family history of HCC
- Liver cirrhosis



- Diabetes mellitus
- Obesity
- Smoking
- Heavy alcohol consumption
- Co-infection with HCV, HDV, or HIV

Environmental exposure to **aflatoxins**, particularly in developing countries where food storage conditions are inadequate, further increases the carcinogenic potential of chronic HBV infection by acting synergistically with viral-induced genetic damage.

3.6 Clinical Features of HBV-Associated HCC

Patients with HBV-associated hepatocellular carcinoma often remain asymptomatic during the early stages of disease. Clinical manifestations usually appear only after significant hepatic destruction or tumor progression.

Common presenting features include:

- Right upper quadrant abdominal pain
- Progressive weight loss
- Loss of appetite
- Generalized weakness
- Jaundice
- Abdominal distension due to ascites
- Hepatomegaly
- Splenomegaly
- Features of portal hypertension

Unfortunately, these symptoms generally indicate advanced disease, emphasizing the importance of surveillance among high-risk patients.

3.7 Diagnosis

Early diagnosis substantially improves treatment outcomes. Current surveillance strategies recommend periodic evaluation of high-risk individuals using:

- Liver ultrasonography
- Serum alpha-fetoprotein (AFP)
- Contrast-enhanced multiphasic CT scan
- Magnetic Resonance Imaging (MRI)
- Histopathological confirmation in selected cases

Recent advances involving circulating biomarkers, liquid biopsy, radiomics, and artificial intelligence-assisted imaging may further improve early detection of hepatocellular carcinoma in the future.

3.8 Prevention

Primary prevention remains the most effective strategy against HBV-associated hepatocellular carcinoma.

Key preventive measures include:

- Universal neonatal HBV vaccination
- Timely birth-dose vaccination
- Screening of pregnant women
- Safe blood transfusion services
- Sterile medical and dental procedures



- Public awareness regarding HBV transmission
- Early antiviral treatment for eligible patients
- Regular surveillance of individuals with chronic HBV infection

3.9 Summary

Hepatitis B virus remains one of the principal causes of hepatocellular carcinoma worldwide despite the availability of highly effective vaccines. Its unique biological capacity to integrate into the host genome distinguishes HBV from other hepatotropic viruses and contributes directly to hepatocarcinogenesis. Although universal vaccination has reduced disease burden in many countries, chronic HBV infection continues to pose a major public health challenge in Pakistan, particularly in underserved regions such as South Punjab. Strengthening vaccination coverage, expanding antiviral therapy, and improving surveillance programs are essential for reducing future HBV-related liver cancer.

4. Hepatitis C Virus and Hepatocellular Carcinoma

4.1 Introduction to Hepatitis C Virus

Hepatitis C virus (HCV) is an enveloped, single-stranded positive-sense RNA virus belonging to the family *Flaviviridae* and genus *Hepacivirus*. Since its discovery in 1989, HCV has been recognized as one of the most important causes of chronic liver disease worldwide. Unlike Hepatitis B virus (HBV), HCV does not integrate into the host genome. Instead, it causes persistent liver injury through chronic inflammation, oxidative stress, immune dysregulation, and progressive hepatic fibrosis, ultimately predisposing infected individuals to cirrhosis and hepatocellular carcinoma (HCC).

One of the most remarkable characteristics of HCV infection is its tendency to become chronic. Approximately 70–85% of infected individuals fail to clear the virus spontaneously and develop chronic hepatitis. Without timely diagnosis and treatment, chronic HCV infection may progress over two to four decades before resulting in cirrhosis or hepatocellular carcinoma. This prolonged asymptomatic period makes HCV a silent but devastating public health challenge.

4.2 Global Burden of Hepatitis C Virus

Hepatitis C remains a major cause of liver-related morbidity and mortality worldwide. The disease affects millions of people and continues to contribute substantially to liver cirrhosis, hepatic failure, liver transplantation, and hepatocellular carcinoma. Although the availability of Direct-Acting Antiviral (DAA) therapy has revolutionized treatment, the global burden remains high because a large proportion of infected individuals remain undiagnosed or untreated.

The prevalence of HCV varies considerably across geographical regions. Countries such as Egypt historically experienced one of the world's highest HCV prevalence rates due to earlier parenteral antischistosomal treatment campaigns. Similarly, Pakistan remains among the countries with the highest prevalence of chronic HCV infection, making HCV-associated hepatocellular carcinoma a significant healthcare challenge.

In recent years, several developed countries have observed declining HCV incidence because of improved blood screening, safer healthcare practices, and widespread antiviral treatment. However, many developing nations continue to experience ongoing transmission because of inadequate infection-control measures and limited access to healthcare services.

4.3 Epidemiology of HCV in Pakistan



Pakistan bears one of the highest burdens of chronic hepatitis C infection globally. The disease affects individuals from both urban and rural communities; however, rural populations frequently experience delayed diagnosis and limited access to antiviral therapy.

Several factors contribute to the persistence of HCV transmission in Pakistan, including:

- Reuse of disposable syringes.
- Unsafe therapeutic injections.
- Poor sterilization of surgical and dental instruments.
- Inadequately screened blood transfusions.
- Unsafe barbering practices.
- Traditional procedures using contaminated equipment.
- Limited awareness regarding viral hepatitis.
- Delayed diagnosis due to asymptomatic infection.

South Punjab represents one of the most affected regions because of socioeconomic deprivation, limited healthcare infrastructure, lower literacy rates, and inadequate preventive healthcare services. Consequently, chronic hepatitis C has become the dominant etiological factor responsible for hepatocellular carcinoma in this region.

4.4 Natural History of Chronic HCV Infection

The natural course of hepatitis C infection progresses through several stages.

Acute Infection

Acute HCV infection is frequently asymptomatic. Only a minority of patients develop jaundice or acute hepatitis. Consequently, most infected individuals remain unaware of their infection.

Chronic Hepatitis

Persistent viral replication results in chronic hepatic inflammation characterized by progressive hepatocyte injury and immune activation.

Liver Fibrosis

Continuous inflammatory injury stimulates activation of hepatic stellate cells, leading to excessive collagen deposition and progressive fibrosis.

Liver Cirrhosis

Advanced fibrosis eventually progresses to cirrhosis, which significantly increases the risk of hepatic decompensation and hepatocellular carcinoma.

Hepatocellular Carcinoma

Patients with longstanding cirrhosis remain at the highest risk for developing HCC. However, emerging evidence suggests that HCV-associated HCC may occasionally occur even in the absence of advanced cirrhosis, particularly among individuals with metabolic risk factors.

4.5 Molecular Mechanisms of HCV-Induced Hepatocarcinogenesis

Unlike HBV, HCV promotes hepatocellular carcinoma through indirect mechanisms rather than integration into the host genome.

Persistent HCV infection leads to chronic immune-mediated inflammation, repeated hepatocyte injury, and continuous cellular regeneration. These repeated cycles increase the likelihood of DNA damage and accumulation of oncogenic mutations.

Several viral proteins interfere with normal cellular signaling pathways. They alter apoptosis, enhance oxidative stress, disrupt mitochondrial function, and stimulate inflammatory cytokine production. Chronic oxidative stress promotes genomic instability, while inflammatory mediators activate pathways involved in cellular proliferation and angiogenesis.



Progressive fibrosis creates a microenvironment favorable for malignant transformation. Activation of hepatic stellate cells, extracellular matrix remodeling, chronic inflammation, and altered immune surveillance collectively facilitate hepatocarcinogenesis.

4.6 Risk Factors for HCV-Associated HCC

The likelihood of developing hepatocellular carcinoma among patients with chronic hepatitis C depends upon multiple interacting factors.

Viral Factors

- Persistent viremia.
- Long duration of infection.
- Delayed antiviral treatment.
- High viral replication.

Host Factors

- Increasing age.
- Male gender.
- Liver cirrhosis.
- Diabetes mellitus.
- Obesity.
- Metabolic syndrome.
- Non-alcoholic fatty liver disease.
- Cigarette smoking.
- Alcohol consumption.
- Co-infection with HBV or HIV.

The coexistence of multiple risk factors substantially accelerates disease progression and increases the probability of malignant transformation.

4.7 Clinical Presentation

Patients with HCV-associated hepatocellular carcinoma frequently present with:

- Persistent right upper abdominal pain.
- Progressive weight loss.
- Fatigue.
- Anorexia.
- Hepatomegaly.
- Ascites.
- Jaundice.
- Gastrointestinal bleeding secondary to portal hypertension.
- Declining liver function.

Because early-stage disease often remains asymptomatic, surveillance of high-risk individuals is essential for early diagnosis.

4.8 Diagnosis

The diagnosis of HCV-associated HCC requires integration of clinical, laboratory, and radiological findings.

Recommended investigations include:

- Anti-HCV antibody testing.



- HCV RNA PCR.
- Liver function tests.
- Serum alpha-fetoprotein (AFP).
- Abdominal ultrasonography.
- Triphasic CT scan.
- Contrast-enhanced MRI.
- Liver biopsy when imaging findings remain inconclusive.

4.9 Role of Direct-Acting Antiviral Therapy

The introduction of Direct-Acting Antiviral (DAA) therapy has transformed hepatitis C management. Modern antiviral regimens achieve sustained virological response (SVR) rates exceeding 95%, thereby significantly reducing progression to cirrhosis and hepatocellular carcinoma.

However, patients with established cirrhosis remain at continued risk for HCC even after viral eradication. Therefore, long-term surveillance using ultrasonography and AFP measurements remains mandatory despite successful antiviral treatment.

4.10 Prevention

Preventing HCV-associated hepatocellular carcinoma depends primarily upon interrupting viral transmission and treating chronic infection at an early stage.

Key preventive strategies include:

- Early screening of high-risk populations.
- Universal blood screening.
- Safe injection practices.
- Proper sterilization of medical equipment.
- Public education.
- Prompt antiviral therapy.
- Routine surveillance of cirrhotic patients.
- Strengthening national hepatitis elimination programs.

4.11 Relevance to South Punjab

The findings of the present study indicate that hepatitis C virus constitutes the predominant etiological factor associated with hepatocellular carcinoma in South Punjab. This pattern reflects the exceptionally high burden of chronic HCV infection within the region. Rural populations remain particularly vulnerable because of delayed diagnosis, limited healthcare access, inadequate infection-control practices, and socioeconomic challenges.

The observed predominance of HCV-associated HCC underscores the urgent need for comprehensive regional strategies focusing on prevention, early diagnosis, antiviral treatment, and long-term surveillance. Without effective intervention, the burden of hepatocellular carcinoma is likely to continue increasing over the coming decades.

4.12 Summary

Hepatitis C virus remains the leading viral cause of hepatocellular carcinoma in Pakistan and particularly in South Punjab. Chronic inflammation, progressive fibrosis, and cirrhosis constitute the principal mechanisms through which HCV promotes hepatocarcinogenesis. The widespread availability of highly effective antiviral therapy provides an unprecedented opportunity to reduce future HCC incidence; however, success depends upon timely diagnosis,



universal screening, improved healthcare infrastructure, and sustained public health commitment.

5. Secular Trends and Geographic Variations of HBV- and HCV-Associated Hepatocellular Carcinoma in South Punjab

5.1 Introduction

South Punjab represents one of the most important regions of Pakistan with respect to chronic liver disease and hepatocellular carcinoma (HCC). The region comprises several densely populated districts, including **Bahawalpur, Bahawalnagar, Rahim Yar Khan, Multan, Lodhran, Khanewal, Vehari, Muzaffargarh, Dera Ghazi Khan, Layyah, Rajanpur, and Kot Addu**, where viral hepatitis continues to impose a substantial public health burden.

During the last two decades, hepatocellular carcinoma has become increasingly common in tertiary care hospitals throughout South Punjab. The growing number of diagnosed cases reflects not only improvements in diagnostic facilities but also the persistent transmission of chronic Hepatitis B virus (HBV) and Hepatitis C virus (HCV). The present study indicates that HCV remains the predominant etiological factor associated with HCC in this region, while HBV continues to contribute significantly to disease burden.

5.2 Secular Trends of Hepatocellular Carcinoma

The term "**Secular Trend**" refers to the long-term pattern of disease occurrence over several years. Studying secular trends allows researchers to evaluate whether disease incidence is increasing, decreasing, or remaining stable over time.

Analysis of patients diagnosed between **2010 and 2018** demonstrates a gradual increase in the number of hepatocellular carcinoma cases. Although improvements in diagnostic imaging, laboratory investigations, and referral systems have contributed to increased case detection, these factors alone cannot explain the observed rise.

Several epidemiological factors are responsible for this increasing trend:

1. High Burden of Chronic Viral Hepatitis

The principal reason is the persistent prevalence of chronic HBV and HCV infections throughout South Punjab. Since both infections usually remain asymptomatic for many years, patients frequently present only after cirrhosis or liver cancer has developed.

2. Delayed Diagnosis

Many individuals seek medical attention only after developing advanced liver disease because early stages produce few or no symptoms.

3. Limited Screening Programs

Routine screening of high-risk populations remains inadequate in many districts, leading to delayed identification of infected individuals.

4. Population Growth

Rapid population expansion has increased the absolute number of people living with chronic viral hepatitis.

5. Ageing Population

As life expectancy increases, more chronically infected individuals survive long enough to develop cirrhosis and hepatocellular carcinoma.



5.3 Geographic Variations

One of the most important findings is the marked geographical variation observed among districts of South Punjab.

Disease distribution is not uniform because several determinants differ across districts, including:

- Population density
- Healthcare accessibility
- Literacy rate
- Vaccination coverage
- Socioeconomic conditions
- Infection-control practices
- Availability of specialist liver services

Districts with inadequate healthcare infrastructure generally report higher numbers of advanced HCC cases because diagnosis occurs much later.

5.4 District-Wise Pattern

Although patient numbers vary between years, referral centers receive most HCC cases from districts where chronic hepatitis is highly prevalent.

These include:

- Bahawalpur
- Rahim Yar Khan
- Bahawalnagar
- Multan
- Lodhran
- Vehari
- Khanewal
- Muzaffargarh
- Dera Ghazi Khan
- Rajanpur

The differences likely reflect variation in healthcare utilization, referral pathways, and underlying viral hepatitis prevalence rather than biological differences alone.

5.5 Demographic Characteristics

The demographic profile demonstrates several consistent epidemiological observations.

Age

Most patients belong to the **46–60 years** age group.

This observation reflects the prolonged natural history of chronic HBV and HCV infections, which typically require several decades before malignant transformation occurs.

Gender

Male patients greatly outnumber female patients.

Possible explanations include:

- Greater occupational exposure
- Higher smoking prevalence
- Increased outdoor healthcare exposure
- Hormonal influences
- Behavioral risk factors



5.6 Why is HCV More Common than HBV?

The predominance of HCV-associated HCC in South Punjab may be explained by multiple interacting factors.

Unsafe Therapeutic Injections

Pakistan has historically reported one of the world's highest injection frequencies.

Repeated unnecessary injections using contaminated syringes significantly increase HCV transmission.

Blood Transfusions

Although screening has improved considerably, earlier inadequately screened blood transfusions contributed substantially to disease spread.

Dental and Surgical Procedures

Improper sterilization of medical and dental equipment continues to facilitate viral transmission in certain healthcare settings.

Lack of Vaccine

Unlike HBV, no effective vaccine currently exists for HCV.

Consequently, prevention depends entirely upon infection-control measures and early diagnosis.

5.7 Healthcare Challenges in South Punjab

Several challenges continue to hinder effective hepatitis control.

These include:

- Limited specialist hepatology services.
- Inadequate surveillance systems.
- Delayed referral of chronic hepatitis patients.
- Financial barriers.
- Poor public awareness.
- Shortage of trained healthcare personnel.
- Limited molecular diagnostic facilities.
- Unequal distribution of antiviral treatment centers.

5.8 Public Health Consequences

The increasing burden of hepatocellular carcinoma has important implications for healthcare planning.

The disease results in:

- Increased hospital admissions.
- Greater demand for oncology services.
- Rising healthcare expenditure.
- Reduced workforce productivity.
- Increased mortality.
- Psychological stress for patients and families.

Consequently, prevention remains considerably more cost-effective than treatment.

5.9 Strategies for Future Control

To reduce the burden of HBV- and HCV-associated hepatocellular carcinoma in South Punjab, the following measures are essential:

Primary Prevention

- Universal HBV vaccination.



- Safe injection practices.
- Safe blood transfusion.
- Sterile surgical procedures.
- Public education campaigns.

Secondary Prevention

- Early HBV and HCV screening.
- Prompt antiviral therapy.
- Regular surveillance of cirrhotic patients.
- Periodic liver ultrasonography.
- AFP monitoring.

Tertiary Prevention

- Early diagnosis of HCC.
- Multidisciplinary cancer care.
- Surgical resection where appropriate.
- Liver transplantation in selected patients.
- Targeted systemic therapy.
- Palliative care services.

5.10 Chapter Summary

The epidemiological evidence presented in this chapter demonstrates that hepatocellular carcinoma continues to increase across South Punjab, primarily because of the persistent burden of chronic hepatitis C virus infection. Although hepatitis B remains an important contributor, HCV accounts for the majority of HCC cases in the region. Significant geographical variation reflects differences in healthcare accessibility, socioeconomic conditions, preventive services, and infection-control practices. Strengthening hepatitis elimination programs, expanding antiviral treatment, and implementing effective surveillance strategies are essential to reduce future disease burden and improve patient outcomes.

Chapter 6

Materials and Methods

6.1 Study Design

The present investigation was designed as a **retrospective observational study** to evaluate the secular trends and geographical variations of Hepatitis B virus (HBV)- and Hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) in South Punjab. A retrospective design was considered appropriate because it enabled the evaluation of a large number of patients diagnosed over several years and facilitated the assessment of temporal changes in disease patterns.

Retrospective observational studies are particularly valuable in epidemiological research because they allow investigators to identify disease trends, demographic characteristics, and potential risk factors using existing clinical records. Although such studies do not establish causal relationships with the same certainty as prospective cohort studies, they provide robust descriptive evidence for healthcare planning and policy development.

The present study primarily focused on identifying changes in the relative contribution of HBV and HCV to hepatocellular carcinoma over time and examining regional variations among districts of South Punjab.



6.2 Study Setting

The study was conducted at the **Bahawalpur Institute of Nuclear Medicine and Oncology (BINO), Bahawalpur**, one of the major tertiary referral centers for oncology and hepatobiliary diseases in South Punjab.

BINO receives patients from numerous districts of Southern Punjab, making it an appropriate institution for evaluating regional disease patterns. Because the hospital serves as a referral center, patients included in the study represented diverse demographic and socioeconomic backgrounds.

The catchment area included patients referred from:

- Bahawalpur
- Bahawalnagar
- Rahim Yar Khan
- Multan
- Lodhran
- Khanewal
- Vehari
- Muzaffargarh
- Dera Ghazi Khan
- Rajanpur
- Layyah
- Kot Addu

This broad referral network enhanced the regional representation of the study population.

6.3 Study Duration

Patient records diagnosed between **January 2010 and December 2018** were reviewed.

A nine-year study period was selected because long-term observation provides a more reliable assessment of secular trends than short-duration investigations. It also minimizes the influence of temporary fluctuations in disease frequency.

6.4 Study Population

The study population consisted of all patients diagnosed with hepatocellular carcinoma during the study period.

Patients represented both urban and rural populations and included individuals referred from public hospitals, private clinics, and district healthcare facilities.

Both male and female patients were included irrespective of socioeconomic background.

6.5 Inclusion Criteria

Patients were eligible if they fulfilled the following criteria:

- Confirmed diagnosis of hepatocellular carcinoma.
- Age 18 years or older.
- Availability of complete demographic information.
- Availability of HBV and HCV serological results.
- Radiological and/or histopathological confirmation.
- Complete hospital records.

6.6 Exclusion Criteria

Patients were excluded if:



- Clinical records were incomplete.
- Viral hepatitis status was unavailable.
- Diagnosis remained uncertain.
- Secondary metastatic liver tumors were present.
- Follow-up information was insufficient for analysis.

These exclusion criteria improved the overall quality and reliability of collected data.

6.7 Sample Size

The study included **110 patients** diagnosed with hepatocellular carcinoma during the study period.

Although the sample size was limited by the number of eligible hospital records, it was considered adequate for descriptive epidemiological analysis and evaluation of temporal trends.

Future multicenter investigations involving larger populations would provide greater statistical precision.

6.8 Data Collection Procedure

Patient information was retrieved from hospital medical records using a standardized data collection form.

The following variables were extracted:

Demographic Variables

- Age
- Gender
- Residential district
- Occupation
- Place of residence

Clinical Variables

- Date of diagnosis
- Presenting symptoms
- Liver cirrhosis
- Ascites
- Portal hypertension
- Performance status

Laboratory Variables

- HBsAg
- Anti-HCV antibodies
- Liver function tests
- Serum Alpha-Fetoprotein (AFP)

Radiological Variables

- Ultrasonography
- Triphasic CT Scan
- MRI findings
- Tumor size
- Number of lesions
- Tumor location

6.9 Diagnostic Criteria



Diagnosis of hepatocellular carcinoma was established according to internationally accepted clinical guidelines.

Diagnosis was based upon one or more of the following:

- Characteristic findings on contrast-enhanced CT scan.
- MRI demonstrating arterial enhancement with venous washout.
- Elevated AFP together with compatible imaging.
- Histopathological confirmation when necessary.

6.10 Laboratory Investigations

Blood samples were analyzed using standardized laboratory procedures.

Investigations included:

- Hepatitis B Surface Antigen (HBsAg)
- Anti-HCV Antibody
- Complete Blood Count
- Liver Function Tests
- Bilirubin
- ALT
- AST
- Alkaline Phosphatase
- Serum Albumin
- Prothrombin Time
- Alpha-Fetoprotein

Serological investigations were performed using **Enzyme-Linked Immunosorbent Assay (ELISA)** according to manufacturer recommendations.

6.11 Imaging Evaluation

Radiological assessment played an essential role in diagnosis.

Patients underwent one or more imaging modalities including:

- Abdominal Ultrasonography
- Triphasic CT Scan
- Contrast MRI

Imaging findings included:

- Tumor diameter
- Number of nodules
- Liver lobe involvement
- Portal vein thrombosis
- Extrahepatic spread

6.12 Statistical Analysis

Collected data were entered into a computerized database and analyzed using appropriate statistical software.

The following descriptive statistics were calculated:

- Mean
- Standard deviation
- Frequency
- Percentage



Categorical variables were summarized using proportions, whereas continuous variables were expressed as mean $\pm$ standard deviation.

Where appropriate, statistical significance was assessed using:

- Chi-square test
- Student's t-test
- Fisher's Exact Test

A **P-value <0.05** was considered statistically significant.

6.13 Ethical Considerations

Ethical approval was obtained from the relevant institutional review authority before commencement of data collection.

Patient confidentiality was maintained throughout the study.

Personal identifiers were removed before statistical analysis.

The study complied with internationally accepted ethical principles for biomedical research involving human participants.

6.14 Quality Assurance

Several quality-control measures were implemented.

- Hospital records were independently reviewed.
- Laboratory reports were cross-checked.
- Missing data were verified.
- Duplicate records were excluded.
- Statistical analyses were rechecked before interpretation.

These procedures improved the validity and reliability of study findings.

6.15 Chapter Summary

This chapter describes the methodological framework adopted for evaluating HBV- and HCV-associated hepatocellular carcinoma in South Punjab. The retrospective observational design, standardized data collection procedures, laboratory investigations, radiological assessment, and statistical analyses collectively ensured a systematic evaluation of demographic characteristics, viral etiology, geographical variation, and secular trends. The methodology provides a sound scientific foundation for interpreting the results presented in the subsequent chapter.

Results

The results demonstrate that **Hepatitis C virus remains the leading cause of hepatocellular carcinoma in South Punjab**, followed by Hepatitis B virus. The disease predominantly affects middle-aged men and exhibits considerable regional variation. The observed increase in HCC over the study period underscores the urgent need for enhanced viral hepatitis prevention, early diagnosis, antiviral treatment, and long-term surveillance programs.

Discussion

The discussion confirms that the epidemiological pattern observed in South Punjab is consistent with national and international evidence demonstrating the predominance of HCV-associated hepatocellular carcinoma in many developing countries. The findings highlight the urgent need for strengthened public health interventions, improved healthcare accessibility, expanded antiviral treatment, and continuous surveillance of high-risk populations.

Recommendations and Future Perspectives

- * Hepatocellular carcinoma remains one of the most preventable yet highly fatal malignancies worldwide. The predominance of chronic hepatitis C virus infection observed in South Punjab provides an important opportunity for intervention because highly effective antiviral therapies are now available.



- * Early diagnosis, universal HBV vaccination, expanded HCV treatment, improved healthcare accessibility, and sustained public awareness campaigns collectively have the potential to transform the future epidemiology of hepatocellular carcinoma in Pakistan.
- * The successful implementation of comprehensive hepatitis elimination strategies will not only reduce liver cancer incidence but will also improve overall population health and reduce healthcare expenditure in the coming decades.

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