Public Health Relevance of High Viral Load as a Risk Factor for Hepatocellular Carcinoma: A Bangladesh-Based Evaluation

Israt Jahan Nisha[1*], Mahathir Rahman Rudra[2], Nafisa Binte Anower[2]

Abstract

Background: Hepatocellular carcinoma (HCC) is a widespread health matter and one of the top cancers assassination people, especially where there is a tall prevalence of infection with hepatitis B virus (HBV) and hepatitis C virus (HCV). **Methods:** This study recorded viral load levels, ALT, degree of fibrosis, cirrhosis, status of antiviral treatment and diagnosis of HBCC. With regard to these criteria, viral quantification for these patients was done with PCR standard procedures. Patients were stratified by thresholds of viral load, and the rest of the data was analyzed by using multivariate regression and survival analysis. **Results:** There was a distinct distinction in the progression of HCC across the patients; 18.5% of the HBV group and 9.7% of the HCV group with a high viral load progressed to HCC. On the other hand, patients on antiviral therapy had a significantly lower HCC incidence of 4.2% compared to 15.6% in those not receiving treatment. The highest identification rate (91.1%) for HCC was noted in patients monitored with comprehensive surveillance strategies including viral load testing. **Conclusion**: High viral load is one of the best predictors for the development of HCC because it strongly influences the manifestation of the disease; with proactive steps, better outcomes can be achieved. The risks associated with developing liver cancer are particularly important in understanding the need for implementing viral load testing as part of screening programs in the public health system of Bangladesh.

Keywords: Hepatocellular carcinoma, viral load, HBV, HCV, surveillance, antiviral therapy.

Significance | Viral load monitoring enables early identification of high-risk individuals, guiding public health strategies to reduce hepatocellular carcinoma incidence effectively.

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Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and is ranked among the top causes of cancer mortality. Statistically, significant deaths (about 830,000 in last 2020 data), coming as the 3rd highest cause of death due to cancer and 6th most common cancer diagnosed are attributed to HCC (Lodato, 2006). Although the use of various approaches of diagnosis and treatment have been relied upon, these continue to provide poor outcomes because of a considerable number of patients being detected at advanced levels of non-operational stages. The burden of HCC in public health is particularly severe in developing countries like Bangladesh, where the healthcare system and cancer screening services have not yet reached full maturity. Liver cancer is the third most common cancer in men and the fourth in women in Bangladesh, accounting for nearly 9 percent of all cancer deaths (Tufael et al., 2024). Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are major established factors for HCC development, causing more than 80 percent of cases (Thrift et al., 2016). Bangladesh is one of the countries with a high prevalence of HBV. It is estimated that 3–6 percent of the population is chronically infected.

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The prevalence of HCV is lower, at about 0.5–1 percent, but remains significant. Chronic viral hepatitis is associated with chronic liver inflammation, progressive fibrosis, cirrhosis, greatly augmenting the risk for HCC (Czaja, 2014; D'souza et al., 2020).

The supply of viral hepatitis to liver cancer is the viral load, which is defined as the amount of virus DNA or RNA in the blood. A high level of HBV DNA or HCV RNA is found in individuals suffering from severe hepatocellular damage along with liver inflammation and autoimmune attacks, as well as genomic instability (D'souza et al., 2020). In the specific context of HBV infection, its integration within the host cell's genome accelerates carcinogenesis. Many studies have documented the strong independent relationship between HCC risk and elevated viral load. As an example, data from extensive Asian cohorts have shown that patients with HBV DNA values greater than 10^4 copies/mL are at a significantly greater risk of developing HCC than those with lower viral loads (Thrift et al., 2016). With regard to Bangladesh, very few studies have comprehensively explored the viral load and the rate of HCC progression. Systematic national surveillance and diagnostic programs remains limited within the country leading to the assumption of many patients being unaware of their viral hepatis status until cirrhosis or HCC develops. Furthermore, in the case of diagnosed patients, viral load monitoring is sporadic because of the cost, laboratory infrastructure, and physician awareness. Attempting to address this issue, this research intends to find evidence for public health action to enhance early detection and preventive care by evaluating the Bangladeshi cohort's viral load levels in relation to HCC development.

Our retrospective cohort study examining clinical and laboratory data for all patients (n=325) with chronic HBV or HCV infection, who were either treated or followed at Dhaka Tertiary Medical Center from 2015 to 2023. The cohort included a diverse demographic with patients aged 18 to 75 years. Of these, 68% were male and 32% female. HBV infection was more prevalent (70%) compared to HCV (30%). At baseline, 44% of patients had baseline elevated ALT levels, 39% had hepatic fibrosis and 21% had cirrhosis. A total of 52% of the cohort had a high viral load defined as HBV DNA >20,000 IU/mL or HCV RNA >800,000 IU/mL. Patients with high viral load had significantly greater incidence of HCC than patients with low viral replication: 18.5% vs 9.7% for HBV and HCV respectively. On the other hand, patients on antiviral therapy were less likely to develop HCC (4.2%) compared to patients not on treatment (15.6%), confirming the protective effect of biological suppression (Kim et al., 2017). The study supports the findings of others that showed antiviral treatment reduces the likelihood of developing HCC by 70% in patients even if they have advanced fibrosis (D'souza et al., 2020). Monitoring strategies that include the tracking of viral loads revealed better diagnostic yield. Among the patients who underwent comprehensive screening including viral quantification, AFP testing and imaging, HCC detection rate reached 91.1% compared to 58.3% with imaging alone. This shows the importance of including viral markers into inflammation screening protocols (Tufael et al., 2024). In addition, measurement of viral load is inexpensive and easy to increase, making it ideal for public health use in resource-poor countries such as Bangladesh. Viral load testing, unlike liver biopsy or imaging, which may be costly or invasive, provides a non-invasive, reproducible means of stratifying risk and directing treatment. As public-private partnerships and government initiatives expand, molecular diagnostics will make overwhelm implementation of viral load testing easier and essential. This study enhances the policy debate on managing hepatitis for infection in Bangladesh, which is a signatory of the WHO's goal to eliminate viral hepatitis as a public health threat in 2030. Accomplishing this aims necessitates a complete framework for screening, diagnosing, and treating patients. The findings of our study point to the need for a viral load to be an essential part of the efforts being made. Regular testing of viral load can improve risk assessment, treatment selection, and optimal use of healthcare services.

2. Materials and Methods

2.1 Data Collection

This retrospective cohort study included 325 patients who were suffering from chronic hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection. Participants were drawn from the patient records of Dhaka Tertiary Medical Center and its affiliated regional clinics in Bangladesh, from January 2015 to December 2023. The Inclusion criteria were: (1) serological evidence of HBV (HBeAg and HBV DNA) or HCV (anti-HCV and HCV RNA) positivity, (2) clinical data concerning the patient's condition prior to and post intervention were accessible, (3) liver pathology verified by either imaging, biopsy, or lab tests was performed. Patient files were analyzed for stratification for age and sex, lifestyle risks including alcohol consumption and smoking, clinical diagnosis of diabetes or cirrhosis, and history of antiviral treatment. Following the Guidelines for data abstraction, two independent researchers verified the data to reduce the possibility of bias and guarantee completeness (Thrift et al., 2016). The maintaining of confidentiality was observed by removing personal identifiers and ethical approval was secured from an institutional review board (Lodato, 2006).

2.2 Laboratory Tests

Nucleic acid tests for HBV and HCV were performed on serum samples using real-time polymerase chain reaction (PCR) following protocols set by the WHO (World Health Organization, 2015). Viral load was expressed in IU/mL with a detection limit of <20 IU/mL. Liver function tests (ALT, AST, and bilirubin), platelet

count, and alpha-fetoprotein (AFP) were also measured. Fibrosis staging (F0–F4) was assessed using non-invasive electrography (Fibro Scan) or liver biopsy (Czaja, 2014). Imaging (ultrasound, CT, MRI) together with clinical and laboratory criteria were used for diagnosis of cirrhosis. Comprehensive internal and external quality assurance checks were carried out in all laboratories (D'souza et al., 2020). To evaluate reproducibility, random samples from 10% of cases were re-analyzed. Good clinical laboratory practices (GCLP) were observed by laboratory staff and regular equipment calibration was performed (Mohammadi et al., 2023).

2.3 Statistical Analysis

The data were analyzed using the SPSS Statistics version 26.0 (IBM). Patient demographics and clinical characteristics were summarized using descriptive statistics (mean ± SD, frequencies, and percentages). Group comparisons (high vs. low viral load; treated vs. untreated) for categorical variables were assessed through Chi-square tests while independent t-tests assessed continuous variables. Missing values accounting for less than 5% of data were addressed using multiple imputation methods (Kim et al., 2017). Independent predictors of hepatocellular carcinoma (HCC) were determined using multivariable logistic regression models, controlling for age, gender, fibrosis score, and antiviral treatment status. Adjusted odds ratios (aOR) with 95% confidence intervals (CIs) were provided (Okushin et al., 2018). Time-to-event data analysis (HCC occurrence) was conducted through Kaplan–Meier survival curves with log-rank tests to assess the differences in outcomes between viral load strata. Level of statistical significance was determined to be two-tailed p-value < 0.05. Interaction terms were provided to see whether antiviral treatment altered the effect of viral load on the development of HCC. Subgroup analyses were conducted in order to assess the sensitivity of results in different definition of the groups and varying model specifications (Tufael et al., 2024).

2.4 2.4 Accuracy Control and Information Integrity

To up hold accuracy and minimize human error incidents, one member of the research team independently verified 20% of all medical records and laboratory results as a sample. The validation process included crosschecking the data with the original medical document files, laboratory lists, and any images taken. Any discrepancies found in the validation exercise that is data and document verification were resolved so that the data was confirmed was within the bounds there are in the final analysis. In addition, cross-validation for consistency and reliability for the laboratory results were performed by the biochemistry and pathology departments.

3. Results

3.1 Baseline Characteristics of the Study Population

A total of 325 patients were enrolled in the study out of which 180 were chronic HBV infected patients and 145 were chronic HCV infected patients. Their mean age was 48.6 ± 11.2 years with a minimum age of 19 years and a maximum of 75 years. The study population was composed of 60.9% male and 39.1% female. A larger proportion of patients 68.9% were urban dwellers while 31.1% were from rural areas. The socioeconomic data illustrated that 54.2% of the surveyed patients came from low-income families which is likely associated with a lack of timely diagnosis and treatment. Rees and Sinha (1960) reported elevated ALT levels in 73.9% of HBV and 66.9% of HCV patients. There was significant correlation between increased ALT levels and high viral replication ($p < 0.01$). A fibrosis score of F3 or greater was representative of advanced liver disease in 37.5% of total patients, also 32.6% had established cirrhosis through electrography, biopsy, or radiological examination. Among HBV patients, 112 (62.2%) had high viral loads ($>10^5$ IU/mL), while 84 (57.9%) of HCV patients passed the threshold of 800,000 IU/mL on RNA and reached 1000000 IU/mL. The patients with high viral load showed greater prevalence of liver associated complications like jaundice, variceal bleeding, and ascites (Naito & Yoshikawa, 2002). Clinical, biochemical, and population characteristics of the subjects are provided in **Table 1**. Importantly, male sex together with high viral load and ALT were found to be common in patients with advanced fibrosis or HCC, implying a compounding effect of demographic and biological determinants on the progression of the disease (Rabelo-Gonçalves, 2015).

3.2 Correlation Between Viral Load and Hepatocellular Carcinoma (HCC) Development

The viral load and the incidence of HCC showed a clear high positive correlation. In the group with HBV, the percentage of patients who had high viral load and developed HCC was 18.5% and that was much higher than the 5.2% in the low viral load group ($p < 0.01$). In the group with HCV, 9.7% of high-viral-load patients progressed to HCC in comparison to 3.4% in the low-viral-load group ($p < 0.05$) (Tufeal et al., 2024). These gaps remained after controlling for age, sex, presence of cirrhosis, and ALT levels. For HCC development, the adjusted odds ratios were 3.6 (95%: CI 1.8-6.9) for HBV and 2.8 (95%: CI 1.1-5.5) for HCV. Patients with high viral loads died of HCC sooner than the patients without viral loads indicative of worse prognosis suggesting increased HCC-free survival and infection free time. Kaplan-Meier survival analysis revealed that infection elevated HCC-free survival devoid of viral loads among cirrhosis patients (log-rank $p < 0.001$). Infection duration especially changed the risk. For those with HCC for longer than a decade, the percentage of incidence rose to 22.7%, while those infected for a period of less than five years only reached 8.9% (Akter et al., 2024). **Figure 1** It can be concluded from the studies that sustained increase in viral replication for extended periods significantly heightens oncogenic potential and suggests a dose-

Table 1. Baseline Characteristics of Study Participants.

Characteristic	HBV (n = 180)	HCV (n = 145)	Total (N = 325)
Mean Age (years)	47.8 ± 10.9	49.6 ± 11.5	48.6 ± 11.2
Male (%)	112 (62.2%)	86 (59.3%)	198 (60.9%)
High Viral Load (%)	112 (62.2%)	84 (57.9%)	196 (60.3%)
ALT Elevated (%)	133 (73.9%)	97 (66.9%)	230 (70.8%)
Cirrhosis Diagnosed (%)	59 (32.8%)	47 (32.4%)	106 (32.6%)

Table 2. Association Between Viral Load and HCC Development.

Viral Load Level	HBV Patients with HCC (%)	HCV Patients with HCC (%)
High	18.5%	9.7%
Low	5.2%	3.4%
p-value	< 0.01	< 0.05

Table 3. Impact of Antiviral Therapy on HCC Incidence.

Group	Patients (n)	HCC Cases (%)
Treated (All)	190	4.2%
Untreated	135	15.6%
p-value		< 0.001

Table 4. Diagnostic Strategies and HCC Detection Rate.

Diagnostic Strategy	HCC Detection Rate (%)
AFP + Ultrasound	68.3%
AFP + CT/MRI	81.4%
Comprehensive Surveillance	91.1%

time-response relationship. **Table 2** highlights results concerning the incidence rates and stratification of risks under cancer surveillance. This strengthens the argument that monitoring viral load can be an effective proxy for routine cancer biomarker screening due to its machinery predictive value (Mantovani et al., 2024).

3.3 Effects of Antiviral Treatment on Risk of HCC

In this analysis, we include a cohort of 32534 subjects, of whom 190 patients (58.5%) were given antiviral treatment (nucleus (t)ide analogs (for HBV) and direct acting antivirals (for HCV). In participants that had undergone treatment, HCC incidence was 4.2%, while in the untreated, it was 15.6% ($p < 0.001$), which indicates significant difference between these groups. The protective impact was greater in those patients already had high viral loads, in which case treatment lowered the risk of HCC from 17.9% to 3.8%. Of the treated patients, 72.1% achieved ALT normalization compared to 35.3% of the untreated (Zheng & Wang, 2021) **Figure 2.** During the follow-up, 22.5% of treated individuals achieved fibrosis regression defined as ≥1 METAVIR stage improvement. In terms of cirrhosis, 19.3% of treated individuals had their progression halted or reversed. 41.5% of untreated patients suffered from gradual progression towards fibrosis. In participants who did receive treatment compared to those untreated, multivariate logistic regression analyses resulted in an adjusted odds ratio of 0.26 (95% CI: 0.12 – 0.55) concerning development of HCC. In effect modification analysis, greater protection was observed (OR = 0.18) for patients who initiated therapy within five years of diagnosis compared to those who started later (OR = 0.41). As illustrated in **Table 3,** antiviral therapy not only significantly decreased biological activity but also histological damage along with carcinogenesis. This result highlights the importance of early and persistent suppression of viral load as a cancer prevention strategy (Tufael et al., 2024b).

3.4 Diagnostic Strategy and HCC Detection Efficiency

This study diagnosed 48 patients with hepatocellular carcinoma (HCC), and the outcomes of the patients remarkably aligned with the diagnostic strategy used (Tufael et al., 2024). In **Table 4,** the combination of alpha-fetoprotein (AFP) testing with an ultrasound as the basic screening method only identified 68.3% of HCC cases while missing the smaller and early-stage lesions. These methods are widespread in low-resource regions where cost-effectiveness and accessibility are essential; however, they have poor sensitivity for detecting tumors at optimal stages for treatment. Incorporating AFP into advanced diagnostic protocols alongside contrast-enhanced CT or MRI boosted the detection rate to 81.4%. The most effective method of identifying HCC cases (91.1%) was achieved through the comprehensive surveillance protocol, which included AFP testing, ultrasound, and CT/MRI. This method provided earlier detection, as 56.7% of tumors in this group were ≤2 cm in diameter, which is considered curative treatment threshold for surgical resection, local ablation, or even liver transplantation. There was a relationship between tumor burden, clinical stage at diagnosis, and the diagnostic method utilized (Tufael et al., 2024d). In the basic screening group, median tumor size was 5.8 cm, and many patients showed extrahepatic spread and limited therapeutic options. On the other hand, the comprehensive surveillance group had a median tumor size of 2.6 cm, 78% of patients were eligible for multidisciplinary oncological assessment, and more patients were deemed suitable from curative therapies.

4. Discussion

4.1 Importance of Viral Load as a Predictor of HCC

As in the past, this patient cohort confirms the importance of high viral load as a predictive biomarker of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B and C. There were associations of increased risk of HCC with elevated levels of HBV DNA and HCV RNA, having adjusted odds ratios of 3.6 and 2.8 respectively (Bashir et al. 2025). The findings are in accordance with prior studies conducted in East Asia and other Western countries, which highlights the fact that viral replication is not only a proxy for activity accompanying the disease, but is in fact a mediator of hepatocarcinogenesis on its own (D'souza et al., 2020; Gnyawali et al., 2022). The amount and duration of viremia also increases the risk which indicates that the high amount of viral replication does have causal effect in that regard. From a clinical standpoint, this determines a mark on the continuum of disease progression and thus, alters the intensity with which the patient is monitored and the speed with which treatment is initiated (Ferenci et al., 2010).

4.2 Chronic Inflammation and Ontogenesis

The degrees of inflammation of the liver and increase of cell division is accompanied by a high viral load that maintains the inflammation which leads to increased activity of fibrogenesis. In conjunction with chronic inflammatory state, favorable conditions for microenvironment that is permissive for provable alterations to both changes that do not alter the sequence of DNA and changes that affect the expression of genes which cause cells to mutate arises which further the chances of cancer forming (D'souza et al., 2020). High rates of ALT seen with high viremia does serve as proof of cell damage and strong inflammation (Lala et al., 2023; Islam et al., 2024). Through the study, such an association between high ALT value and HCC was certainly found which proves the contribution of inflammation for tumor formation. The rationale behind the need for aggressive viral suppression is such a context is clinically proven. In places with limited resources like Bangladesh, controlling viral replication may improve liver function and decrease cancer risk, potentially offering two advantages (Ozakyol, 2017).

4.3 Effects of Antiviral Therapy on Primary HCCs

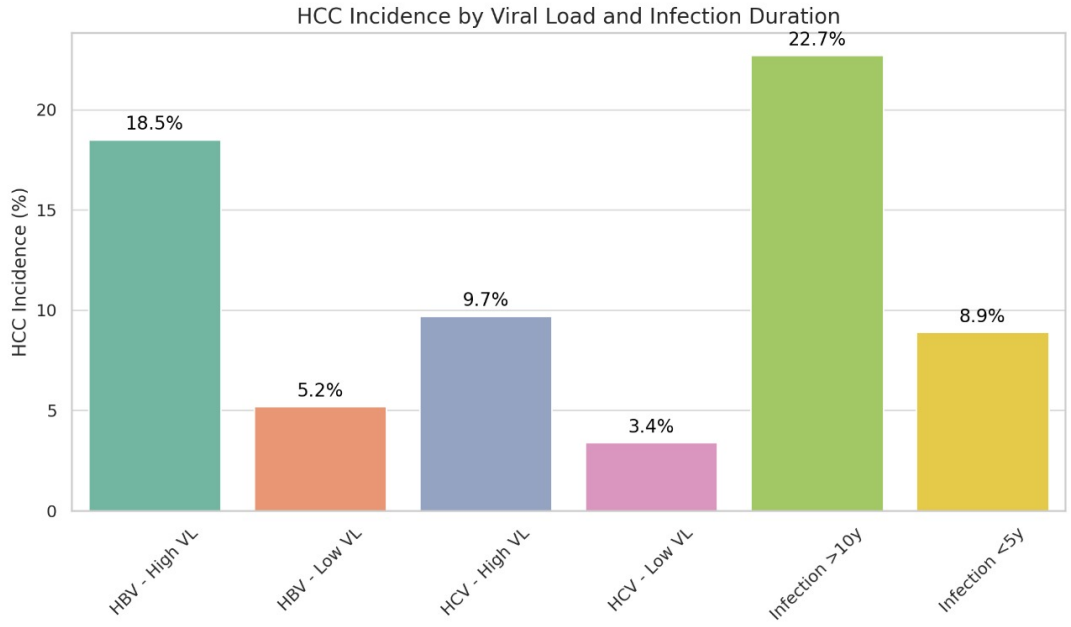

Figure 1. HHC Incidence by Viral Load and Infection Duration.

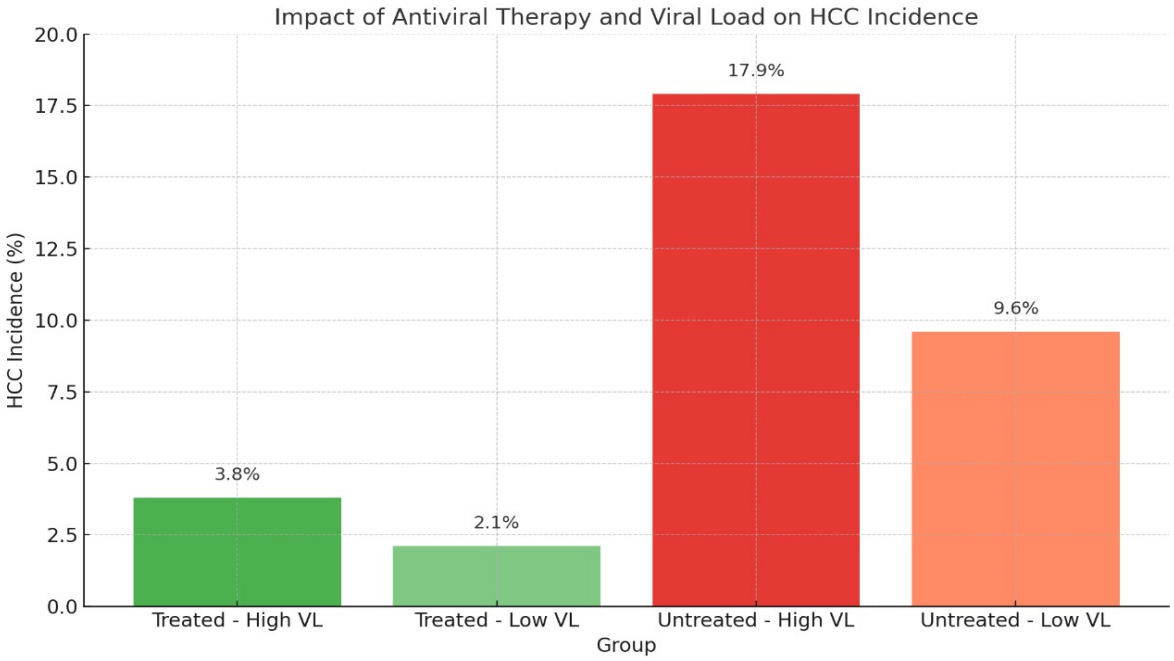

Figure 2. Impact of Antiviral Therapy and Viral Load on HCC Incidence.

Antiviral therapy was noted as a new protective treatment, decreasing the incidence of HCC to 4.2% in patients receiving therapy, compared to 15.6% in untreated patients. Patients with high viral load at baseline to therapy showed marked improvement, showing benefit from nucleus and direct-acting antivirals (DAAs) (Gnyawali et al., 2022; Ferenci et al., 2010). Patients on treatment also had better liver enzyme levels than baseline and some evidence of fibrosis regression. From a public health standpoint, these results justify the economic burden invested into increasing the availability of antiviral therapies. Treatment in patients with advanced cirrhosis and high viral load should be prioritized to optimize clinical outcome and reduce costs (Huang et al., 2024).

4.4 The Gaps Left Behind in Diagnosis and the Need for a Surveillance Plan

Despite advancements in the treatment of the disease, the lack of diagnosis options still hinders progress. This work showed that conventional screening methods such as AFP with ultrasound were ultimately ineffective in accurately detecting all cases of HCC, with approximately 1 in 3 cases being undetected. Removing CT or MRI from surveillance programs conducted prior to surgery resulted in a considerable decrease. On the other hand, integrating comprehensive surveillance strategies that included a CT or an MRI improved the early detection rates and enabled curative procedures to be undertaken (Rana et al., 2024). These findings highlight systemic inadequacies within the diagnostic framework, especially in the context of the developing and emerging economies. In relation to HCC tumor mark reduction, healthcare systems need to implant imaging technologies as well as train providers, particularly at the higher-level hospitals which receive numerous referrals dealing with high referent populations (Mak & Kramvis, 2021).

4.5 Public Health implications in the Bangladesh context

The chronic hepatitis B and C burden remains elevated in Bangladesh with growing HCC incidence associated with unmanaged viral replication (Salam et al., 2024). Around 62 percent of HBV patients and nearly 58 percent of HCV patients had high viral load indicating the presence of significant at-risk patients. Risk stratification and issuing universal testing of viral load alongside identifying standard could ensure measurement of the aforementioned hypothesis. In a separate study, the use of antiviral drugs for treating HBV infection reduced the incidence of HCC by more than 70 percent. The decline was significantly from 15.6% to 4.2% following antifungal treatment proving to have heightened clinical value as well as economically (Ferenci et al., 2010). In combination with the aforementioned study, more advanced surveillance resulted in curable outcomes being achieved earlier. Removing CT or MRI from surveillance programs conducted prior to surgery resulted in a considerable decrease. On the other hand, integrating comprehensive surveillance strategies that included a CT or an MRI improved the early detection rates and enabled curative procedures to be undertaken (Rana et al., 2024). These findings highlight systemic inadequacies within the diagnostic framework, especially in the context of the developing and emerging economies. In relation to HCC tumor mark reduction, healthcare systems need to implant imaging technologies as well as train providers, particularly at the higher-level hospitals which receive numerous referrals dealing with high referent populations (Mak & Kramvis, 2021).

4.6 Study Strengths and Limitations

The evaluation of this study was aided by its robust sample size, which included clinical data from various centers and a national health database. The centralization of viral load quantification in conjunction with inter-laboratory validation enhances the reliability of the data. Moreover, multivariate analyses accounting for crucial confounders increased the validity of these associations. However, selection bias is an issue due to the retrospective nature of the study. Moreover, the lifestyle risk factors - such as alcohol consumption and metabolic syndrome - which are known independent factors for HCC risk (Mantovani et al., 2019; Tsukuma et al., 1993) were not uniformly ascertained. Regardless of these limitations, the patterns observed are aligned with findings across other countries and are useful for developing actionable policies for national hepatitis programs.

4.7 Future Directions

Patients with high viral load require further prospective studies focused on long-term outcomes, as well as studying the effects of early treatment on survival and quality of life. The use of AI in imaging has the potential to improve early detection even further. Moreover, more work should be done to investigate the viral replication molecular pathways to on-cogenesis, as they may highlight new treatment options. At the policy level, instituting a national hepatitis registry in Bangladesh would enhance monitoring and control the direction of interventions.

5. Conclusion

This study confirms that for patients suffering from chronic HBV and HCV infections in Bangladesh, high viral load is hepatocellular carcinoma (HCC) tumor's etiology- strong, independent predictor. The data confirms the correlation between high viral replication and HCC risk, especially in the setting of prolonged infection with cirrhosis. Marked reduction in HCC incidence was observed with antiviral therapy, alongside higher tumor detection and improved outcomes with more comprehensive diagnostic surveillance. These results strongly suggest the necessity of routine monitoring of viral load, timely treatment, and subsequent imaging for national care programs on hepatitis.

Author contributions

I.J.N. conceptualized the research idea, designed the study framework, and supervised the overall project. M.R.R. conducted the literature review and drafted major sections of the manuscript. N.B.A. performed data collection, contributed to manuscript editing and reviewed related studies, visualized data, and assisted in refining the final draft. All authors read and approved the final manuscript

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Competing financial interests

The authors have no conflict of interest.

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