Original Article

OPEN ACCESS

Frequency of Advanced Liver Fibrosis among Inactive Hepatitis B Virus Carriers: A Cross-Sectional Analysis

Muhammad Arsalan[1], Mashooque Ali samejo[2], Osama Ahmed[3], Sarmad Ali[4], Faizan Ali Memon[5], Muhammad Akram Khan[6]

[1]Senior Registrar of Gastroenterology, Suleman Roshan Medical College Hospital Tando Adam
[2]Consultant Gastroenterologist, Asian Institute of Medical Science (AIMS) Hyderabad
[3]Consultant Gastroenterologist, Zeenat Issani Institute of Medical Sciences Shikarpur
[4,6]Senior Registrar of Medicine, Suleman Roshan Medical College Tando Adam
[5]Senior Registrar of Gastroenterology, Indus Medical College Tando Muhammad Khan

Author`s Contribution

[1,3]Substantial contributions to the conception or design of the work; or the acquisition, [4,6]Active participation in active methodology, analysis, or interpretation of data for the work, [2,5]Drafting the work or revising it critically for important intellectual content, Final Approval of the study

Funding Source: None
Conflict of Interest: None

Received: Jan 21, 2025
Revised: April 19, 2025
Accepted: May 04, 2025

Address of Correspondent
Dr Muhammad Arsalan
Senior registrar Gastroenterology, Suleman Roshan medical college hospital Tando Adam
dr_arsalan_96@hotmail.com

ABSTRACT

Objective: To determine the frequency of advance fibrosis in Hepatitis B virus (HBV) inactive carriers.

Methodology: A cross-sectional study was conducted at the Gastroenterology Outpatient Department (OPD) of AIMS, from September 2020, to March 2021. Adult patients aged 18 to 70 years who had not received previous treatment for HBV, had an HBV viral load of less than 2000 IU, and an SGPT level below 35 U/L were included. HBV inactive carriers were identified by HBV DNA levels below 2000 IU and SGPT under 35 U/L. Advanced liver fibrosis (stage F3 or higher) was assessed using FibroScan, with a median cutoff of 8.2 KPa. Ten liver stiffness readings were averaged for staging. Data were collected using a structured proforma. Data were analyzed with SPSS version 26.

Results: Mean age of the cases was 39.5±6.7 years. In distribution of gender, 86 (68.3%) were male while 40 (31.7%) were female. Advance fibrosis was found in 29 (23%) patients, with most cases clustered in severe stages—F3 and F4—representing nearly 76% of those affected. Advanced fibrosis was more common in those over 40 years and in males, though gender and Diabetes showed a statistically significant association ($p < 0.05$), while obesity and age group showed no significant associations ($p > 0.05$)

Conclusion: Advanced fibrosis was observed to be relatively less prevalent among HBV inactive carriers. Its association with male gender and diabetes indicates that specific subgroups may still be at increased risk.

Keywords: Advance Fibrosis, Antiviral Treatment, Cirrhosis, Hepatitis B Virus, Inactive Carriers

Cite this article as: Arsalan M, Samejo MA, Ahmed O, Ali S, Memon FA, Khan MA. Frequency of Advanced Liver Fibrosis among Inactive Hepatitis B Virus Carriers: A Cross-Sectional Analysis. Ann Pak Inst Med Sci. 2025; 21(2):396-400. doi. 10.48036/apims.v21i2.1517.

Introduction

HBV infection, a vaccine-preventable disease, is an alarmingly increasing global healthcare concern, especially within the populations of developing countries.[1] The World Health Organization (WHO) estimated 254 million HBV diagnosed cases around the word in 2022, with 5.8% hepatitis B surface antigen (HBsAg) positive cases and 1.1 million deaths mainly attributed to cirrhosis and hepatic cancer, besides an annual increase of 1.2 million fresh cases. [2] In relevance, Pakistan shares a high prevalence of 1.1%, with around 2 million carriers of HBsAg.[3]

Chronic cases of HBV are generally categorized into four different phases, characterized by a diverse blend of patterns for alanine aminotransferase (ALT), HBeAg status, and DNA levels of HBV.[4] Two of these phases are HBeAg-positive (phase I: immune tolerant and phase II: immune active), and other two are HBeAg-negative (phase III: inactive carrier and phase IV: immune reactive). However, a considerable proportion of chronic

HBV infected patients do not fall into the defined criteria of these four phases and are therefore treated through dynamic monitoring instead of recommended therapy for HBV due to insufficiently definitive guidelines.[5]

Chronic hepatitis B virus (HBV) can lead to hepatic fibrosis (intermediate stage) and then ultimately into cirrhosis, which is why in-time and cautiously assessing the stage of hepatic fibrosis is essential to minimize hepatic injury through configuring optimal treatment plans. [6] While liver biopsy remains the gold standard for assessing liver fibrosis stages, it is an invasive and costly procedure that carries risks of complications and potential sampling errors.[7] FibroScan, a widely recommended in-expensive and non-invasive diagnostic tool, can substitute biopsy for assessing stage of fibrosis.[6]

The Society of Radiologists has suggested that hepatic fibrosis stage can be obtained through measuring liver stiffness using ultrasound elastography. However, higher values of liver stiffness observed in transient elastography can possibly fail to reveal the actual grade of fibrosis in acute hepatitis due to elevated scores of Hepatitis Activity Index (HAI) obtained from alanine aminotransferase (ALT) and serum total bilirubin (TBIL), even when significant fibrosis in not present.[8] However, in chronic hepatitis patients, elevated levels of ALT indicate liver injury due to hepatic inflammation in clinical practice, while some studies suggest an inverse proportional association between liver stiffness cutoff value and elevated ALT level in terms of diagnostic accuracy for fibrosis.[6,9] On the other hand, HBV inactive carriers, characterized by normal ALT and low HBV-DNA levels, mostly have a relatively good prognosis among the other phases of HBV infection. HBV infection, with a widely inconsistent long-term outcome and clinical profile, can remain inactive for a life-time or may reactivate in some patients with history of infection, threatening to result in Hepatic fibrosis or hepatic cancer.[10] However this study aims to evaluate the frequency of advanced fibrosis in HBV inactive carriers, a group traditionally considered low-risk. Emerging evidence suggests some carriers may still develop serious liver damage. Identifying fibrosis in this population is important for early intervention, improved monitoring, and better clinical outcomes, especially in resource-limited settings like Pakistan.

Methodology

A cross-sectional study was conducted at the Gastroenterology Outpatient Department (OPD) of AIMS, Hyderabad, over duration of six months from September 7, 2020, to March 6, 2021, following the approval of the research synopsis Ref no: CPSP/REU/GAS-2018-168-914. A total of 126 patients were included, with the sample size calculated using the WHO software based on a 20% prevalence of advanced fibrosis in HBV carriers, aiming for a 95% confidence interval and a 7% margin of error. The sampling technique employed was non-probability, consecutive sampling. Inclusion criteria comprised adult patients aged 18 to 70 years who had not received previous treatment for HBV, had an HBV viral load of less than 2000 IU, and an SGPT level below 35 U/L. Patients were excluded if they had co-infections with HDV or HCV, established causes of cirrhosis other than HBV, an HBV viral load above 2000 IU, SGPT levels above 35 U/L, were under 18 years of age, or had hepatocellular carcinoma. HBV inactive carriers were defined as patients with HBV DNA levels under 2000 IU (quantified by PCR) and SGPT below 35 U/L. Advanced fibrosis was defined as stage F3 or above (with a median of 8.2 KPa) based on vibration-controlled transient elastography (VCTE) using the FibroScan machine (Model 430 MINI). The probe was applied to the skin overlying the liver, and the device recorded 10 readings to calculate the mean liver stiffness, which was then categorized into fibrosis stages from F1 to F4. Informed consent was obtained from all patients who met the inclusion criteria. Data collection was carried out using a structured proforma (attached), which included the documentation of baseline patient characteristics, clinical history, and laboratory investigations. These investigations comprised HBV DNA PCR (with a cutoff of 101 IU/ml), SGPT and SGOT levels (each with a cutoff of 40 U/L), bilirubin (cutoff 0.9 mg/dl), and Anti-HDV (cutoff 1.1 Co). In addition, liver stiffness was measured using FibroScan, and the values were recorded (details in Appendix 1). All data were entered and analyzed using SPSS version 26.

Results

In this study 126 patients were included to assess the advance fibrosis in HBV inactive carriers. The Mean ± SD of age was 39.5±6.7 with C.I (38.31−40.68) years. Mean ± SD of SGPT was 23.1±5.2 with C.I (22.18−24.01). Mean ± SD of SGOT was 19.4±3.9 with C.I (18.71−20.08) U/L. In distribution of gender, 86 (68.3%) were male while 40 (31.7%) were female. Out of 126 patients, 36 (28.6%) were obese while 89 (70.6%) were non-obese. Diabetes mellitus was documented in 47 (37.3%) patients, as shown in Table 1.

Table I: Descriptive characteristics of patient. (n=126)

Variables	Mean ± Sd	Min-Max	95% CI	
			LL	UL
Age (Years)	39.5 ± 6.7	18-70	38.31	40.68
SGPT (U/L)	23.1 ± 5.2	5-35	22.18	24.01
SGOT (U/L)	19.4 ± 3.9	1.38-1.86	18.71	20.08
Gender	**Statistics**			
Male	86(68.3%)	-	-	-
Female	40(31.7%)	-	-	-
Obesity				
Yes	36(28.6%)	-	-	-
No	89(70.6%)	-	-	-
Diabetes Mellitus				
Yes	47(37.3%)	-	-	-
No	79(62.7%)	-	-	-

Advance fibrosis was found to be in 29 (23%) patients. Different stages of advance fibrosis were noted as 2 (6.9%) for patients at F1 stage, F2 in 5 (17.2%) patients, F3 in 10 (34.5%) while 12 (41.4%) were observed in F4 stage as shown in Table II.

Table 2II: Frequency distribution of Fibrosis and stages. (n=126)

	Frequency	Percentage
Advanced Fibrosis (N=126)		
Yes	29	23.0%
No	97	77.0%
Stages (n=29)		
F1	2	6.9%
F2	5	17.2%
F3	10	34.5%
F4	12	41.4%

Stratification of age group, gender, obesity and diabetes mellitus was done with respect to advanced fibrosis in order to assess significant difference. The stratification statistics are shown in Table III.

Table III: Stratification of age group, gender, obesity, and diabetes with advanced fibrosis. (n=126)

	Advanced Fibrosis		P-value
	Yes	NO	
Age group			
18-40 years	19 (15.1%)	10 (7.9%)	0.057
>40 years	44 (34.9%)	53 (42.1%)	
Gender			
Male	16 (12.7%)	70 (55.6%)	0.006
Female	13 (10.3%)	27 (21.4%)	
Obesity			
Yes	6 (4.8%)	30 (23.8%)	0.284
No	23 (18.3%)	67 (53.2%)	
Diabetes Mellitus			
Yes	6 (4.8%)	41 (32.5%)	0.035
No	23 (18.3%)	56 (44.4%)	

Applied Chi-Square test

Discussion

The assessment of inactive phase among HBV carriers shows variability across published data, suggesting persistent lingering of inactive phase among HBV patients or possible progression to hepatocellular carcinoma.[11] This study assessed the frequency of advanced fibrosis among 126 hepatitis B inactive carriers, with a mean age of 39.5 ± 6.7 years and a higher prevalence in males (68.3%), consistent with global trends showing increased HBV carrier rates with advancing age. These findings align with a recent study by Yao et al[12] who reported a similar mean age of 39 years and male predominance, supporting the demographic pattern observed in chronic HBV infections.

In this study, among 126 HBV inactive carriers, 28.6% were obese and 37.3% had diabetes mellitus, indicating a notable presence of metabolic comorbidities. These findings support the observation by Hernández-Gea et al[13] who identified obesity and diabetes as independent risk factors for fibrosis progression in inactive HBV carriers, emphasizing the impact of metabolic health on liver disease advancement. Additionally, normal SGPT (23.1 ± 5.2) and SGOT (19.4 ± 3.9) levels in our cohort confirm the inactive phase of HBV. However, consistent with Chen et al[14] disease progression may still occur despite normal ALT levels, highlighting the need for vigilant monitoring even in clinically inactive cases.

In this study, out of 126 patients, 36 (28.6%) were obese while 89 (70.6%) were non-obese. Diabetes mellitus was documented in 47 (37.3%) patients. In line with this observation, Hernández-Gea[13] revealed that obesity and diabetes mellitus are independent risk factors for disease progression among inactive HBV carrier population, suggesting that metabolic comorbidities can affect the inactive phase leading to progressive fibrosis.

In this study, SGPT and SGOT were in normal range, as mean SGPT was 23.1±5.2 and mean SGOT was 19.4±3.9, which is suggestive of HVB inactive phase. Constant findings were reported by Chen et al.,[14] who reported that HBV infection can progress to advance stage irrespective of normal ALT levels and elevated levels of HBV DNS.

According to the findings of this study, advanced fibrosis was found in 29 (23%) of the 126 inactive HBV carriers, with most cases classified as F3 (34.5%) and F4 (41.4%), indicating significant liver disease progression. These findings underscore that a significant proportion of

patients in the inactive HBV phase can develop progressive liver fibrosis despite having normal SGPT and SGOT levels. This supports the concern that HBeAg-negative individuals may be at silent risk of developing complications such as hepatocellular carcinoma. Papatheodoridis et al[15] also emphasized that liver damage can occur in inactive carriers even with normal ALT, recommending routine monitoring for at least the first three years after identifying the inactive phase. Similar conclusions were drawn by Schwimmer et al[16] further validating the need for vigilance in the management of HBV inactive carriers.

Additionally in this study advanced fibrosis was significantly more common among male and diabetic inactive HBV carriers, suggesting these as key risk factors. However, no significant link was observed with age or obesity. These findings align with studies by Tada et al[17] and Zelber-Sagi et al[18] who also identified diabetes and male gender as independent predictors of fibrosis. In contrast, some studies, like those by Pitisuttithum et al[19] and Sun et al[20] reported associations with age, female gender, and obesity, highlighting possible variability due to population differences and study methods.

Present study possesses several limitations like it was conducted at a single center with a relatively small sample size, liver biopsy—the gold standard for assessing liver fibrosis—was not used; instead, non-invasive FibroScan was employed, which, although reliable, has its own limitations, which may limit the generalizability of the findings to wide range populations. Additionally, confounding factors such as alcohol intake, physical activity, and dietary habits were not assessed, which may influence fibrosis progression. Hence further larger multi-center studies with diverse populations are recommended to validate and expand upon these findings.

Conclusion

It was observed that the advanced fibrosis relatively less prevalent among patients with inactive HBV carrier status; however, its presence in a notable proportion of cases highlights the importance of ongoing surveillance. Despite normal liver enzyme levels, some inactive HBV carriers may progress silently to advanced fibrosis, highlighting the need for timely diagnosis and further large-scale studies to reduce morbidity and address potential confounders.

References

1. Oje MM, Kolawole OJ, Ijarotimi O, Adekanle O, Jegede OS, Ndububa DA. Liver histology pattern of young patients with inactive chronic hepatitis B virus infection from a hospital in South West Nigeria. *BMC Gastroenterol*. 2024 Nov 27;24(1):438. https://doi.org/10.1186/s12876-024-03501-7
2. World Health Organization. Hepatitis B [Internet]. Geneva: World Health Organization; 2024 [cited 2025 May 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
3. Qureshi H, Mahmood H, Sabry A, Hermez J. Barriers and strategies for hepatitis B and C elimination in Pakistan. *J Infect Dis*. 2023 Sep 15;228(Suppl 3):S204–10. https://doi.org/10.1093/infdis/jiad022
4. Begré L, Akotia MK, Wembulua BS, Pandi M, Ndiaye O, Tine J, et al. Circulating HBV RNA and conventional HBV markers in treatment-naïve persons with HBV in Senegal. *J Infect Dis*. 2025 Apr 19:jiaf190. https://doi.org/10.1093/infdis/jiaf190
5. Liu J, Yu Y, Zhao H, Guo L, Yang W, Yan Y, et al. Latest insights into the epidemiology, characteristics, and therapeutic strategies of chronic hepatitis B patients in indeterminate phase. *Eur J Med Res*. 2024 Jun 21;29(1):343. https://doi.org/10.1186/s40001-024-01942-0
6. Huang LL, Yu XP, Li JL, Lin HM, Kang NL, Jiang JJ, et al. Effect of liver inflammation on accuracy of FibroScan device in assessing liver fibrosis stage in patients with chronic hepatitis B virus infection. *World J Gastroenterol*. 2021 Feb 21;27(7):641–53. https://doi.org/10.3748/wjg.v27.i7.641
7. Ilic I, Milovanovic T. The risk-benefit assessment of liver biopsy in times of non-invasive screening for liver fibrosis. *J Hepatol*. 2020 Sep 1;73(3):701–2. https://doi.org/10.1016/j.jhep.2020.05.017
8. Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). *Ultraschall Med*. 2017;38:e48–e82. https://doi.org/10.1055/a-0641-0076
9. Zeng J, Zheng J, Jin JY, Mao YJ, Guo HY, Lu MD, et al. Shear wave elastography for liver fibrosis in chronic hepatitis B: Adapting the cut-offs to alanine aminotransferase levels improves accuracy. *Eur Radiol*. 2019;29:857–65. https://doi.org/10.1007/s00330-018-5621-x
10. Al Shuaili HH, Al Mashikhi B, Al Sinani A, Al Busafi SA. A Comprehensive Analysis of Inactive Hepatitis B Infection in a Cohort of Omani Patients. *Oman Med J*. 2024 Sep 30;39(5):e673. https://doi.org/10.5001/omj.2024.104
11. Diallo I, Ndiaye B, Fall CA, Mbaye M, Korch I, Diawara PS, et al. Inactive hepatitis B carriers: outcomes of patients followed at Hopital Principal de Dakar, Senegal. *Pan Afr Med J*. 2018 Sep 20;31(1).
12. Yao K, Liu J, Wang J, Yan X, Xia J, Yang Y, et al. Distribution and clinical characteristics of patients with chronic hepatitis B virus infection in the grey zone. *J Viral Hepat*.

2021 Jul;28(7):1025–33. https://doi.org/10.1111/jvh.13511
13. Hernández-Gea V, Berzigotti A. Clinical evaluation and prognosis. *Dig Dis*. 2015 Jul 6;33(4):515–23. https://doi.org/10.1159/000374100
14. Chen CJ, Yang HI, Su JU, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006 Jan 4;295(1):65–73. https://doi.org/10.1001/jama.295.1.65
15. Papatheodoridis GV, Manolakopoulos S, Liaw YF, Lok A. Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. *J Hepatol*. 2012 Jul 1;57(1):196–202. https://doi.org/10.1016/j.jhep.2011.11.030
16. Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. *Gastroenterology*. 2010 Apr 1;138(4):1357–64. https://doi.org/10.1053/j.gastro.2009.12.052
17. Tada T, Toyoda H, Sone Y, Yasuda S, Miyake N, Kumada T, et al. Type 2 diabetes mellitus: a risk factor for progression of liver fibrosis in middle-aged patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2019 Nov;34(11):2011–8. https://doi.org/10.1111/jgh.14734
18. Zelber-Sagi S, Shoham D, Zvibel I, Abu-Abeid S, Shibolet O, Fishman S. Predictors for advanced fibrosis in morbidly obese non-alcoholic fatty liver patients. *World J Hepatol*. 2017 Jan 18;9(2):91. https://doi.org/10.4254/wjh.v9.i2.91
19. Pitisuttithum P, Chan WK, Piyachaturawat P, Imajo K, Nakajima A, Seki Y, et al. Predictors of advanced fibrosis in elderly patients with biopsy-confirmed nonalcoholic fatty liver disease: the GOASIA study. *BMC Gastroenterol*. 2020 Dec;20:1–9. https://doi.org/10.1186/s12876-020-01240-z
20. Sun J, Li Y, Sun X, Liu Y, Zheng D, Fan L. Association between abdominal obesity and liver steatosis and fibrosis among patients with chronic hepatitis B measured by Fibroscan. *Exp Ther Med*. 2019 Sep;18(3):1891–8. https://doi.org/10.3892/etm.2019.7727