



Original Article



GP73 Level in Patients with Chronic Hepatitis B: Relationship with Liver Biopsy, Levels of ALT, AST and HBV DNA

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ARTICLE INFO

Keywords:

Golgi Protein 73, Chronic Hepatitis B, Liver Diseases, Necro-Inflammations, Ishak Scoring System

How to Cite:

Ramani, R. K., Ashraf, S., Phulpoto, A. H., Pervez, S. A., Memon, A. Q., & Aziz, A. (2025). GP73 Level in Patients with Chronic Hepatitis B: Relationship with Liver Biopsy, Levels of ALT, AST and HBV DNA: GP73 Level with Chronic Hepatitis B: ALT, AST and HBV DNA. *Pakistan Journal of Health Sciences*, 6(6), 139-144. <https://doi.org/10.54393/pjhs.v6i6.2821>

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Received Date: 30th January, 2025

Revised Date: 10th June, 2025

Acceptance Date: 22nd June, 2025

Published Date: 30th June, 2025

ABSTRACT

GP73 is a serum protein that increases with liver disease progression in chronic hepatitis B (CHB) and has been proposed as a marker for liver status monitoring. **Objectives:** To evaluate the correlation between GP73 levels, Histological Activity Index (HAI), and fibrosis stages in CHB patients, assessing its potential as a non-invasive biomarker. **Methods:** A cross-sectional study was conducted over six months (May to October 2024) at the Department of Infectious Diseases, Khairpur Medical College/Civil Hospital Khairpur. A total of 250 CHB patients were enrolled and categorized by fibrosis stages and HAI scores. GP73 concentrations were measured using ELISA. Patients were classified based on fibrosis stage (F0-F4) and HAI scores, determined through liver biopsy, with F0 representing no fibrosis and F4 indicating cirrhosis. Statistical analysis included one-way ANOVA, Kruskal-Wallis test, and correlation analysis. **Results:** GP73 levels increased progressively with fibrosis stages: 5.3 ng/mL in Group 1, 6.1 ng/mL in Group 2, and 7.5 ng/mL in Group 3 ($p=0.001$). GP73 also rose with HAI scores, from 5.0 ng/mL in minimal to 8.0 ng/mL in severe activity groups ($p=0.05$). GP73 showed a moderate correlation with fibrosis stage ($r=0.6$, $p<0.05$) and a strong correlation with HAI ($r=0.75$, $p<0.001$). **Conclusions:** GP73 is a promising non-invasive biomarker for evaluating liver fibrosis and necroinflammation in CHB, warranting further validation in larger studies.

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health concern, affecting over 296 million people worldwide [1, 2]. In 2019, it was responsible for an estimated 331,000 deaths, including 192,000 deaths from HBV-related liver cancer, a significant rise from 2010 figures. Chronic hepatitis B (CHB) prevalence is highest in Sub-Saharan Africa and East Asia, where most infections occur perinatally or in early childhood [3]. Despite the availability of effective vaccines and antiviral therapies, gaps in diagnosis, treatment, and prevention continue to drive the disease burden [4, 5]. CHB results from the immune system's failure to clear the virus, leading to chronic inflammation, necrosis, and progressive liver fibrosis, and

eventually cirrhosis and hepatocellular carcinoma (HCC). Necrosis plays a pivotal role in the pathogenesis of Chronic Hepatitis B (CHB), reflecting ongoing hepatocellular injury and contributing to disease progression, fibrosis, and potential liver failure [6, 7]. Early detection of liver damage is crucial for guiding treatment decisions and preventing complications. While liver biopsy remains the gold standard for assessing fibrosis and necroinflammatory activity, its invasiveness and associated risks limit its routine use [8]. Golgi Protein 73 (GP73) is a promising non-invasive biomarker for liver fibrosis and cirrhosis [9]. Studies suggest GP73 levels increase progressively with disease severity, including in conditions like autoimmune



hepatitis, fatty liver disease, and viral hepatitis [10]. However, commonly used liver enzymes like ALT and AST, though indicative of hepatocellular injury, lack sensitivity and correlation with disease severity [11]. The Histological Activity Index (HAI) measures necroinflammation, while the Ishak scoring system stages liver fibrosis. Both remain essential in CHB management. Although HBV DNA levels reflect viral replication, they do not consistently correlate with liver damage. Hence, additional markers are needed to bridge the gap between virological activity and histological changes [12]. Although GP73 has been associated with fibrosis, its relationship with necroinflammation (HAI) and fibrosis stages in CHB patients is not yet well defined.

Despite advances in the management of chronic hepatitis B (CHB), there remains a lack of reliable non-invasive markers that accurately reflect both necroinflammatory activity and fibrosis severity, as commonly used parameters like ALT, AST, and HBV DNA show limited correlation with histological changes. While Golgi Protein 73 (GP73) has shown promise as a marker of liver fibrosis, its relationship with necroinflammation (Histological Activity Index) and fibrosis stages in CHB patients is not well established. Therefore, this study aims to evaluate the association of GP73 levels with HAI and fibrosis stages to assess its potential as a comprehensive non-invasive biomarker in CHB.

METHODS

This cross-sectional study was conducted for six months from May 2024 to October 2024 at the Department of Infectious Diseases, Khairpur Medical College. Written informed consent was obtained from all patients included in the study. The study was conducted by the principles of the Declaration of Helsinki, and ethical approval was obtained from the Institutional Review Board (IRB) of Khairpur Medical College, Khairpur (KMC/RERC/112). A total of $n=250$ participants in fibrosis stages and HAI scores are categorized into groups. The participants were divided into two groups: HBeAg-positive ($n=120$) and HBeAg-negative ($n=130$). The age range was 20–65 years. Fibrosis stages (F0–F4) were determined using liver biopsy, while HAI scores were categorized as mild, moderate, or severe based on histopathological assessment. The sample size was calculated to detect a minimum correlation of $r = 0.18$ between GP73 levels and fibrosis stages at a 95% confidence level and 80% power using the following formula: $n = (Z_{\alpha/2} + Z_{\beta})^2 (0.5 \times \ln(1+r) - r)^2 = 1.96 Z_{\alpha/2} = 1.96$ (for a significance level of 5%), $Z_{\beta} = 0.84$ (for 80% power), and $r = 0.18$ (the minimum detectable correlation based on conservative estimates). The calculated minimum sample size was approximately 250 participants. HAI grades liver activity from 0–22 based on periportal necrosis (0–10), lobular degeneration (0–4), and portal inflammation (0–4), while the Ishak system provides an inflammation grade (0–18) and fibrosis stage (0–6), offering more detailed

assessment [13]. Inclusion criteria: Positivity for HBsAg for more than 6 months, abnormal ALT level, or normal ALT level, or the presence of advanced liver disease. Physicals, liver function tests (AST, ALT), CBC, and prothrombin time were basic evaluations. Patients were included if they had a history of HBV DNA $\geq 2,000$ IU/mL within the past three months. Minor variations below this threshold at the time of sampling were accepted to account for natural viral fluctuations. By ultrasound and AFP testing, liver cancer was excluded. Exclusion criteria were HDV, HCV, and/or HIV co-infections. Other causes of chronic diseases of the liver. Patients with a history of liver cancer or those having conditions that make it difficult to accurately assess CHB. Biochemical Parameters were ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, albumin, full blood count, and prothrombin time. HBV DNA: Quantified by PCR. GP73 Levels were measured by ELISA using the RayBio® Human G0LM1/GP-73 ELISA kit. The normal reference range for ALT (Alanine Aminotransferase) is 7–56 U/L, and for AST (Aspartate Aminotransferase) is 10–40 U/L, with values exceeding these ranges considered elevated. For HBV DNA levels, a viral load of $\geq 2,000$ IU/mL was used as the clinically significant cutoff, by established international guidelines for chronic hepatitis B management. GP73 levels, measured using an ELISA kit, were interpreted based on previously published studies and manufacturer recommendations, with levels above 70 ng/mL considered elevated and indicative of significant liver pathology. HBeAg status was determined using ELISA testing. GP73 is a valuable biomarker with growing clinical relevance in liver diseases. It has shown higher sensitivity and specificity than AFP in diagnosing hepatocellular carcinoma (HCC), with cutoff levels typically ranging from 8.5 to 10 ng/mL. GP73 levels also correlate with liver fibrosis severity, making it useful in staging chronic liver disease. Liver biopsy was performed using the Menghini technique with 16-gauge Hepafix® needles. Histological grading and staging were conducted using the Ishak scoring system, which classifies fibrosis on a scale from 0 (no fibrosis) to 6 (cirrhosis). Based on this system, patients were categorized into three groups: Group 1 (fibrosis stages 0–1), Group 2 (stages 2–4), and Group 3 (stages 5–6). This classification allowed us to stratify patients by the severity of fibrosis for analytical purposes. The use of the Metavir system, which ranges only from F0 to F4. The use of the Ishak system was now explicitly stated and justified within the scientific context. The scored specimens were graded for necro-inflammatory activity and fibrosis using the Ishak system. Patients were grouped by fibrosis stages: Stage 0–1: Group 1; Stage 2–4: Group 2; Stage 5–6: Group 3. The data were analyzed using SPSS version 21.0. Spearman's rank correlation was used to make a correlation between GP73 and other variables. Normality was tested using the Shapiro-Wilk test, and since the data were non-normally distributed, for non-parametric tests (Kruskal-Wallis and Mann-Whitney U) for appropriate group comparisons,

p<0.050 was considered significant.

RESULTS

HBeAg-positive patients had a significantly lower mean age than HBeAg-negative patients (p=0.020). Male were predominated in the HBeAg-positive group (p=0.001), while female was more common in the HBeAg-negative group (p=0.001). ALT (p=0.030), AST (p=0.040), and HBV DNA levels (p=0.001) were significantly higher in HBeAg-positive patients, indicating greater liver activity and viral load. No BMI difference was noted (p=0.150). GP73 levels were slightly lower in HBeAg-positive cases (p=0.045). HAI scores were higher in HBeAg-negative patients (p=0.038), while fibrosis stages were greater in HBeAg-positive patients (p=0.045) (Table 1).

Table 1: Patients' Characteristics by HBeAg Status (n=250)

Variables	Total (n=250)	HBeAg (+) (n=120)	HBeAg (-) (n=130)	p-value
Age (Years, Mean ± SD)	40.5 ± 12.3	38.2 ± 10.5	42.7 ± 13.2	0.020*
Gender (Male, n (%))	160 (64%)	90 (75%)	70 (54%)	0.001**
Gender (Female, n (%))	90 (36%)	30 (25%)	60 (46%)	0.001**
ALT (U/L, Median [IQR])	55 [45-68]	60 [50-72]	50 [40-65]	0.030*
AST (U/L, Median [IQR])	47 [38-59]	50 [40-63]	45 [35-55]	0.040*
BMI (kg/m ² , Mean ± SD)	25.8 ± 3.2	26.1 ± 3.4	25.5 ± 3.1	0.150
HBV DNA (IU/mL, Median [IQR])	8000 [2000-20,000]	12,000 [5000-30,000]	4000 [1000-10,000]	0.001**
GP73 (ng/mL)				
Mean ± SD	6.2 ± 2.4	5.8 ± 2.3	6.5 ± 2.5	0.045
Median	5.8	5.6	6.0	
HAI Score (mean)	8.5 ± 4.2	7.9 ± 4.5	9.0 ± 3.8	0.038
Fibrosis Stage (mean)	6.5 ± 3.2	7.2 ± 3.0	5.9 ± 3.4	0.045

On the basis of the Histological Activity Index (HAI) scores in 250 chronic hepatitis B patients, most were considered to be in moderate (34%) and severe (14%) activity group, suggesting a high prevalence rate of advanced liver disease. Fewer patients were in the minimal (24%), mild (28%), moderate (34%), and severe (14%) activity categories (Figure 1).

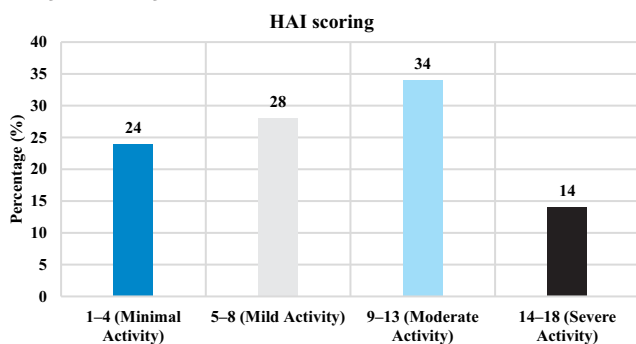


Figure 1: HAI Scoring Analysis

A distribution of fibrosis stage with more patients in Group 2 (2-4) than in Group 1 (0-1) and Group 3 (5-6). There is a statistically significant difference on these stages (Figure 2).

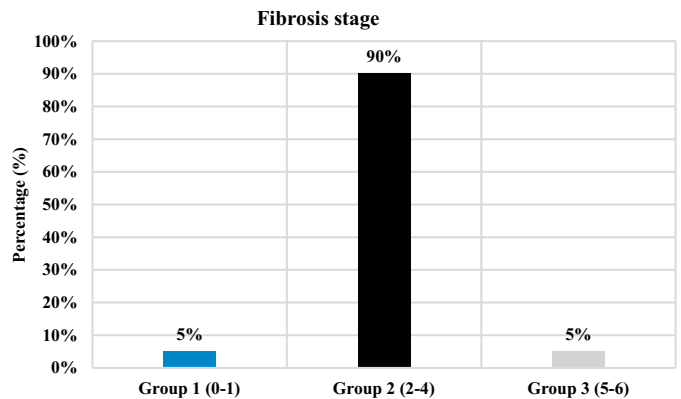


Figure 2: Fibrosis Stage Distribution

GP73 levels showed significant variation across different HAI scores and fibrosis stages. As disease activity worsened, GP73 levels increased, with minimal activity (HAI 1-4) averaging 5.0 ng/mL and severe activity (HAI 14-18) reaching 8.0 ng/mL (Kruskal-Wallis, p = 0.050). Similarly, GP73 rose with fibrosis severity: 5.3 ng/mL in stage 0-1, 6.1 ng/mL in stage 2-4, and 7.5 ng/mL in stage 5-6 (One-way ANOVA, p=0.001) (Table 2).

Table 2: Correlation Between Golgi Protein 73 Levels and Liver Fibrosis Staging Using the Ishak Scoring System

Groups	n	Mean Gp73 (ng/mL)	Median	Min	Max	p-value
HAI Score Range						
Minimal Activity (1-4)	50	5.0 ± 1.9	4.8	1.0	7.2	0.050
Mild Activity (5-8)	100	6.0 ± 2.0	6.0	2.0	8.5	0.050
Moderate Activity (9-13)	75	6.8 ± 2.5	6.5	3.0	9.5	0.050
Severe Activity (14-18)	25	8.0 ± 3.0	8.2	5.5±	12.0	0.050
Fibrosis Stage						
Group 1 (0-1)	25	5.3 ± 2.1	5.0	1.0	8.5	0.001
Group 2 (2-4)	40	7.5 ± 2.3	6.0	1.5	9.0	0.001
Group 3 (5-6)	185	6.4 ± 2.0	7.5	5.5	10.0	0.001

GP73 levels were significantly associated with higher fibrosis stages and HAI scores (p<0.050) (Figure 3).

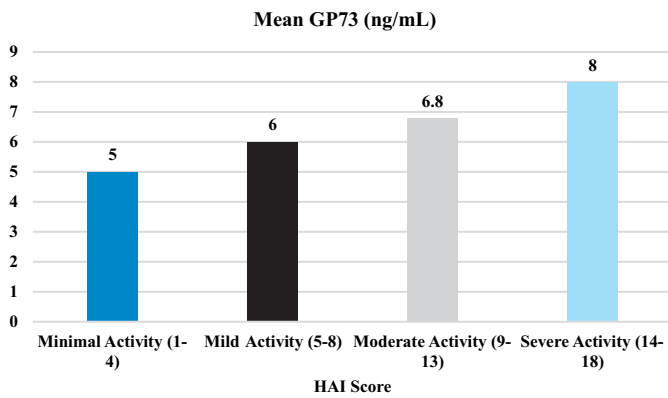


Figure 3: Compare GP73 with Different Activities of HAI Score

DISCUSSION

Chronic hepatitis B virus (HBV) infection increases the risk of cirrhosis and hepatocellular carcinoma (HCC) due to both host and viral factors. The primary goal of treatment is to halt disease progression, thereby improving survival and quality of life. Accurately determining the severity of liver damage is crucial for guiding treatment decisions [14]. When routine blood tests and HBV markers are insufficient, non-invasive tools or liver biopsies are often required. This highlights the need for reliable blood-based biomarkers to reduce reliance on invasive procedures. In this context, we evaluated clinical and biochemical differences between HBeAg-positive and HBeAg-negative patients, identifying GP73, a glycoprotein produced by hepatocytes, as a potential marker for liver disease severity in chronic hepatitis B (CHB). HBeAg status was a secondary analysis and not the primary focus of the study [15]. Our study demonstrated a significant difference in age distribution, with younger patients being predominantly HBeAg-positive ($p=0.020$). This aligns with Wang *et al.*, and Duan *et al.*, who noted that HBeAg positivity is more common in younger CHB patients due to the natural course of the disease, where seroconversion often occurs with age, marking a transition from the immune-tolerant to the immune-active phase [16, 17]. Additionally, male were more frequently HBeAg-positive (75%) compared to female (46%, $p=0.001$), consistent with previous research indicating male are at higher risk of severe disease progression due to the effects of sex hormones on immune regulation and viral replication dynamics [18]. Moreover, HBeAg-positive patients exhibited significantly higher ALT and AST levels ($p=0.030$ and 0.040), reflecting greater liver inflammation. This finding supports earlier studies reporting that higher viral replication in HBeAg-positive patients contributes to more active immune-mediated hepatocyte damage [19]. Elevated ALT and AST levels result from viral replication within hepatocytes, accumulation of viral proteins, and subsequent immune-induced cytopathic effects leading to membrane

disruption and enzyme leakage into the bloodstream [20]. High HBV DNA levels increase with HBeAg positivity and correlate strongly with liver inflammation in this test group. Persistent hepatocyte injury is a result of active, continuing viral replication and perpetuation of immune system activation. Immune recognition of viral proteins, HBeAg, HBcAg, and HBsAg, presented on the hepatocyte surface, adds to primary immune-mediated damage. ALT is localized mainly in the cytoplasm of hepatocytes, where it acts as a specific marker of acute liver damage; in contrast, AST, which exists in the cytoplasm and mitochondria, is increased in response to more severe or protracted hepatocyte injury (deeper cell damage). Patients with HBeAg positivity are in the immune clearance phase of HBV infection, accompanied by ongoing immunological targeting of HBV-infected cells [21]. The consequence is peak liver inflammation at the time when immune cells infiltrate the liver and leading to dramatically increased ALT and AST levels. There are generally lower levels of these enzymes in HBeAg-negative patients compared to HBeAg-positive patients, reflecting reduced viral replication and consequently, less pronounced immune-mediated hepatocyte destruction. In HBeAg-negative patients, there could, however, be ongoing low-level viral activity or residual immune responses that cause chronic liver inflammation as well [22]. In current study, GP73 levels were significantly higher in the HBeAg-negative group to the HBeAg-positive group; there was a trend of lower HBV DNA in HBeAg-negative patients (mean 5 ± 2.5 ng/mL). The previous study reported that the higher GP73 in HBeAg-positive patients; lower GP73 levels were found in HBeAg-positive patients. On the other hand, the higher levels of GP73 in the HBeAg negative individuals in our series could reflect a more advanced stage of disease since their HAI scores and fibrosis stage were also greater. Additionally, correlation analysis showed that GP73 levels had a positive correlation with HAI scores and fibrosis stages, which progressed as liver disease worsens. Mean GP73 levels were, for example, 5.0 ng/mL in minimal activity (HAI 1-4) and 8.0 ng/mL in severe activity (HAI 14-18, $p=0.050$). Similarly, increasing GP73 levels were correlated with fibrosis stage progression ($p=0.001$) from stage 0-1 to stage 5-6. It showed the use of GP73 as a reliable noninvasive biomarker for the assessment of liver fibrosis and inflammation [23]. Fibrosis stage analysis revealed that HBeAg-positive patients had more advanced fibrosis. However, compared with HBeAg-negative patients, the mean stage was 5.9 ± 3.4 ($p=0.045$), which is significantly lower than that of HBeAg-positive patients (mean stage: 2 ± 3.0). These findings are consistent with the previous study in which HBeAg positivity was associated with fibrotic progression through prolonged viral activity and

liver damage. In our study, GP73 levels correlate positively with both HAI scores and fibrosis stages, supporting GP73 as a biomarker for liver disease progression. GP73 can be used to diagnose stages of fibrosis and cirrhosis. GP73 is a better biomarker for subclinical liver damage compared to traditional markers such as ALT and AST. In our study, GP73 levels dichotomized patients according to mild to severe disease activity ($p=0.050$), and early vs late fibrosis stages ($p=0.001$). It was found that these findings support the notion of GP73 as a potential adjunct to current diagnostic tools for monitoring disease progression in CHB patients, because GP73 measurement can be done noninvasively [24]. Current findings suggest personalized management strategies for chronic HBV patients according to their HBeAg status, GP73 levels, and histological activity. Aggressive antiviral treatment might be considered in HBeAg-positive patients to prevent fibrosis. HBeAg-negative patients with elevated GP73 levels and HAI scores should be followed closely for cirrhotic and HCC risk.

This study was limited by its relatively small sample size and single-center design, which may limit the generalizability of the findings. Additionally, the cross-sectional nature of the study and lack of longitudinal follow-up restricted assessment of GP73 dynamics and long-term disease progression. Further studies are needed to assess GP73 as a dynamic predictive biomarker in response to antiviral therapy. Adding GP73 to routine tests (HBV DNA and liver enzymes) for an expanded risk stratification of HBV patients is warranted.

CONCLUSIONS

It was concluded that GP73 levels are increased with higher HAI scores and more advanced fibrosis stages, suggesting that it is a noninvasive biomarker in liver disease progression. These results have an important contribution toward the body of literature supporting the use of GP73 as a useful clinical tool for the management of chronic hepatitis B infection, which may help improve patient care moving forward.

Authors' Contribution

Conceptualization: RKR

Methodology: SA, AHP, SAP

Formal analysis: SA, AA

Writing and Drafting: AHP, SAP, AQM

Review and Editing: RKR, SA, AHP, SAP, AQM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

- [1] Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. *Nature reviews Gastroenterology and Hepatology*. 2023 Aug; 20(8): 524-37. doi: 10.1038/s41575-023-00760-9.
- [2] Alsulaimany FA. Overview of Hepatitis B virus (HBV) Infection. *Journal of King Abdulaziz University: Science*. 2023 Jan; 33(1).
- [3] World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. *World Health Organization*. 2024 Mar.
- [4] Iannacone M, Andreato F, Guidotti LG. Immunological insights in the treatment of chronic hepatitis B. *Current Opinion in Immunology*. 2022 Aug; 77: 102207. doi: 10.1016/j.coi.2022.102207.
- [5] Meng Z, Chen Y, Lu M. Advances in targeting the innate and adaptive immune systems to cure chronic hepatitis B virus infection. *Frontiers in Immunology*. 2020 Feb; 10: 3127. doi: 10.3389/fimmu.2019.03127.
- [6] Khanam A, Chua JV, Kottlilil S. Immunopathology of chronic hepatitis B infection: role of innate and adaptive immune response in disease progression. *International Journal of Molecular Sciences*. 2021 May; 22(11): 5497. doi: 10.3390/ijms22115497.
- [7] Akbar SM, Yoshida O, Hiasa Y. Immune therapies against chronic hepatitis B. *Journal of Gastroenterology*. 2022 Aug; 57(8): 517-28. doi: 10.1007/s00535-022-01890-8.
- [8] Kaur N, Goyal G, Garg R, Tapasvi C, Chawla S, Kaur R. Potential role of noninvasive biomarkers during liver fibrosis. *World Journal of Hepatology*. 2021 Dec; 13(12): 1919. doi: 10.4254/wjh.v13.i12.1919.
- [9] Szternel Ł, Sobucki B, Wieprzycka L, Krintus M, Panteghini M. Golgi protein 73 in liver fibrosis. *Clinica Chimica Acta*. 2024 Oct; 119999. doi: 10.1016/j.cca.2024.119999.
- [10] Gao Y, Wang M, Liu XN. Noninvasive serum markers for predicting significant liver histopathology in HBeAg-negative chronic HBV-infected patients with normal alanine aminotransferase. *Microbiology Spectrum*. 2024 Apr; 12(4): e03941-23. doi: 10.1128/spectrum.03941-23.
- [11] Zoulim F, Chen PJ, Dandri M, Kennedy PT, Seeger C. Hepatitis B Virus DNA integration: Implications for diagnostics, therapy, and outcome. *Journal of Hepatology*. 2024 Jul. doi: 10.1016/j.jhep.2024.06.037.

- [12] Althubaiti A. Sample size determination: A practical guide for health researchers. *Journal of General and Family Medicine*.2023Mar;24(2):72-8.doi:10.1002/jgf2.600.
- [13] Campbell C, Wang T, McNaughton AL, Barnes E, Matthews PC. Risk factors for the development of hepatocellular carcinoma(HCC)in chronic hepatitis B virus (HBV) infection: a systematic review and meta-analysis. *Journal of Viral Hepatitis*.2021Mar; 28(3): 493-507. doi: 10.1111/jvh.13452.
- [14] Bousali M, Papatheodoridis G, Paraskevis D, Karamitros T. Hepatitis B virus DNA integration, chronic infections and hepatocellular carcinoma. *Microorganisms*.2021Aug;9(8):1787.doi:10.3390/microorganisms9081787.
- [15] Li Y, Zhu Y, Gao D, Pan Y, Wang J, Zhang S *et al.* HBeAg-positive CHB patients with indeterminate phase associated with a high risk of significant fibrosis. *Virology Journal*.2024Nov;21(1):287.doi:10.1186/s12985-024-02561-1.
- [16] Lee HA, Lee HW, Park Y, Kim HS, Seo YS. Hepatitis B core-related antigen is useful for predicting phase and prognosis of hepatitis B e antigen-positive patients. *Journal of Clinical Medicine*.2022Mar;11(6): 1729. doi: 10.3390/jcm11061729.
- [17] Wang N, Zheng J, Huang Y, Pu X, Jiang L, Yang J. A Predictive Model to Evaluate the HbeAg Positivity of Chronic Hepatitis B Virus Patients in Clinics: A Cross-Sectional Study. *Medicina*.2022 Sep; 58(9): 1279. doi: 10.3390/medicina58091279.
- [18] Duan M, Chi X, Xiao H, Liu X, Zhuang H. High-normal alanine aminotransferase is an indicator for liver histopathology in HBeAg-negative chronic hepatitis B. *Hepatology International*. 2021 Apr; 15: 318-27. doi: 10.1007/s12072-021-10153-2.
- [19] Xu C, Zhao Y, Chen H, Ren W, Yang X, Zheng W *et al.* Risk factors for significant histological changes in both HBeAg-positive and negative treatment-naive chronic hepatitis B with persistently normal alanine aminotransferase level. *BioMed Central Infectious Diseases*.2024Oct;24(1):1120.doi:10.1186/s12879-024-10015-w.
- [20] Yao K, Wang J, Wang L, Xia J, Yan X, Wu W *et al.* Association of anti-HBc and liver inflammation in HBeAg-negative chronic hepatitis B virus-infected patients with normal ALT and detectable HBV DNA. *Journal of Medical Virology*. 2022 Feb; 94(2): 659-66. doi: 10.1002/jmv.27327.
- [21] Pan S, Yu Y, Wang S, Tu B, Shen Y, Qiu Q *et al.* Correlation of HBV DNA and hepatitis B surface antigen levels with tumor response, liver function and immunological indicators in liver cancer patients with HBV infection undergoing PD-1 inhibition combinational therapy.*Frontiers in Immunology*. 2022May;13:892618.doi:10.3389/fimmu.2022.892618.
- [22] Zhang ZQ, Shi BS, Lu W, Liu DP, Huang D, Feng YL. Quantitative HBcrAg and HBcAb versus HBsAg and HBV DNA in predicting liver fibrosis levels of chronic hepatitis B patients. *Gastroenterología y Hepatología (English Edition)*.2020Nov;43(9):526-36.doi: 10.1016/j.gastre.2020.03.005.
- [23] Gatselis NK, Tornai T, Shums Z, Zachou K, Saitis A, Gabeta S *et al.* Golgi protein-73: A biomarker for assessing cirrhosis and prognosis of liver disease patients. *World Journal of Gastroenterology*.2020 Sep; 26(34): 5130. doi: 10.3748/wjg.v26.i34.5130.
- [24] Li Y, Yang Y, Li Y, Zhang P, Ge G, Jin J *et al.* Use of GP73 in the diagnosis of non-alcoholic steatohepatitis and the staging of hepatic fibrosis.*Journal of International Medical Research*.2021Nov;49(11):0300605211055378.doi:10.1177/03000605211055378.