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Original Article

Low adherence of guideline-based monitoring among chronic hepatitis B patients: a mixed quantitative and qualitative study

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Abstract

Introduction: Adherence to guideline-based monitoring (GBM) for chronic hepatitis B (CHB) in China remains understudied. This mixed-methods study assessed GBM adherence and explored patient-reported barriers.

Methodology: A mixed study was conducted at the Zhongshan Hospital (Xiamen), Fudan University, China. Patients visiting the outpatient department of the hospital between January 2018 and December 2018 were included for the quantitative component. Clinical and biochemical data were retrieved from the hospital's electronic medical record system. Adherence to GBM was defined as regular monitoring of alanine aminotransferase (ALT), hepatitis B virus DNA (HBV-DNA), alpha-fetoprotein (AFP), and liver imaging; at least annually during the 2-year follow-up period. The qualitative component involved semi-structured interviews with thematic and content analysis.

Results: Among the 402 eligible CHB outpatients, only 103 (25.6%) patients presented good adherence to GBM. Specifically, 171 (42.5%) patients were monitored at least annually for ALT and HBV-DNA, while 107 (26.6%) were monitored for AFP and liver imaging. The factors associated with adherence to GBM included receiving antiviral treatment (OR = 3.54 (1.59–7.86)) and completing initial liver imaging (OR = 4.78 (2.04–9.83)). The reasons for non-adherence included inadequate monitoring tests and health education by healthcare providers, patients' perception of not needing frequent monitoring, forgetfulness, cost concerns, and complex hospital visit procedures.

Conclusions: Adherence to GBM among CHB patients was suboptimal despite guideline recommendations. Enhanced efforts and interventions, such as combining technology-driven tools, targeted education for providers and patients, and primary care integration are essential.

Key words: adherence; chronic hepatitis B; monitoring; quantitative; qualitative.

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Introduction

According to the World Health Organization (WHO), approximately 254 million people were living with chronic hepatitis B (CHB) in 2022, with 1.2 million new hepatitis B virus (HBV) infections and 1.1 million deaths annually, primarily due to cirrhosis and hepatocellular carcinoma (HCC) [1,2]. CHB is a complex disease that often presents with few or no symptoms in the early stage, leading to underdiagnosis. Once patients experience clinical discomfort, the disease has usually progressed to an advanced stage, including decompensated cirrhosis and HCC, which limits treatment options. Therefore, long-term systematic monitoring of HBV-infected patients is essential and unanimously recommended. The WHO 2024 guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection; the American Association for the Study of Liver Diseases (AASLD) 2018 hepatitis B guidance; and the Chinese guidelines for the prevention and treatment of chronic hepatitis B (version 2022) recommend that laboratory tests and liver imaging should be used for monitoring disease progression and HCC surveillance [1,3–6].

Regular monitoring is helpful for assessing the progression of liver disease, resulting in early diagnosis of the occurrence of HCC and determining the appropriate time for initiating treatment; which was ultimately cost-effective in the long-term [7,8]. Early diagnosis and access to first-line curative treatments, such as antiviral therapy, liver resection and local ablation, and liver transplantation can improve the survival rate [9]. Implementing HCC surveillance every 6 months has been shown to decrease HCC-related deaths by 37% [10]. A study by Li *et al.* reported that surveillance was associated with a 55% decrease in the overall survival risk in CHB patients [11]. CHB guidelines recommend that all CHB patients need to monitor alanine aminotransferase (ALT) and hepatitis

B virus DNA (HBV-DNA) [1,3–6]. Consistently high levels of ALT and HBV-DNA have emerged as crucial predictors of future complications in CHB patients [12]. The decision to initiate antiviral treatment for CHB is primarily guided by the outcomes of these two key laboratory tests. Studies indicate that early antiviral treatment for CHB patients is recommended as it reduces the risk of disease progression, HCC, and mortality [13]. It is worth noting that HCC can develop without cirrhosis or liver enzyme abnormalities. The guidelines emphasize the importance of HCC screening for CHB patients, and recommend abdominal ultrasound and alpha-fetoprotein (AFP) tests for monitoring. Furthermore, early diagnosis combined with liver resection, local ablation, or transplantation increase the 5-year survival rate for HCC patients from 40% to 70% [11].

There are several studies on the management and monitoring of hepatitis B, including the actual adherence and analysis of influencing factors. Most of these studies focus on HCC surveillance mainly by liver imaging [14,15], while there are relatively fewer studies on ALT and HBV-DNA monitoring. Most study populations included patients who were not receiving antiviral treatment or patients with liver cirrhosis [12,16,17]. Other studies have focused on adherence of patient follow-up rather than monitoring examinations [18,19]. However, there are even fewer studies on the adherence to guideline-based monitoring (GBM) of CHB patients in China. We conducted a quantitative study to explore the extent of adherence to GBM among CHB patients and associated factors; as well as a qualitative study to further investigate the reasons for non-adherence from patient perspective.

Methodology

Study design and population

A mixed quantitative and qualitative study was conducted in Zhongshan Hospital (Xiamen), Fudan University, China. CHB patients who visited the outpatient department between January 2018 and December 2018 were included for the quantitative component. The sample was selected using the International Classification of Diseases, Tenth Revision (ICD-10) via the electronic medical record database. The inclusion criteria were patients with CHB-related diseases, including CHB (B18.107), HBsAg carriers (Z22.502), hepatitis B e antigen (HBeAg)-negative hepatitis B (Z22.503), HBeAg-positive hepatitis B (Z22.504), and hepatitis B compensatory cirrhosis (K74.600X003). The exclusion criteria were: 1) patients with any cancer or malignancy (C00-C97), 2) patients with decompensated cirrhosis (K74.602-607), 3) patients having liver transplantation (Z94.400) or resection (Z98.800x115), 4) cases where death occurred within 2 years of follow-up, and 5) patients refusing to participate in this study. Purposive sampling was used for the qualitative component by selecting patients with chronic HBV infection who were not in adherence to GBM and visited the outpatient department from May to July 2021 regarding different CHB-related diseases. The final sample size was determined based on the level of information saturation. The research object was selected while analyzing the interview data. Sampling was discontinued when the researcher could not gain more information from the next interviewee.

The study protocol was approved by the Ethics Committee of Zhongshan Hospital (Xiamen), Fudan University(B2020-009) and conducted in accordance with the Declaration of Helsinki. The confidentiality and privacy of the study participants were strictly maintained. During the quantitative study, the only contact between the subjects and the clinical research was the archived informed consent document. When patients were unwilling to come to the hospital for signing the consent form, verbal consent was initially obtained over the phone, and supported by an audio recording as evidence. The paper informed consent forms were obtained from participants later on when they visited the hospital for medical reasons. There was no identifiable information present in the quantitative analysis. Qualitative participants gave informed consent for the study and were interviewed voluntarily after signing the informed consent form and provided consent to publish. Only the age and gender of the patients were included in the qualitative analysis, ensuring that patients could not be identified based on the given information.

Definition and guideline recommendations

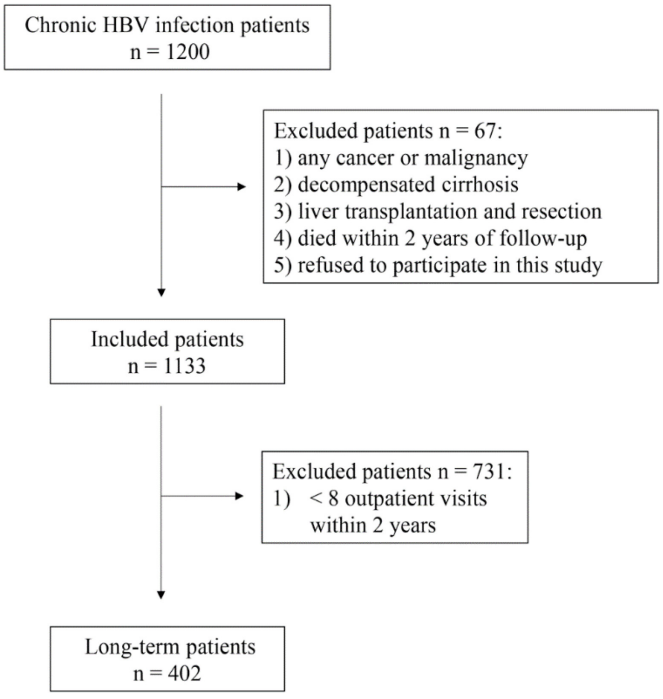
The 2-year follow-up period was defined as starting with the first outpatient visit during January 2018 to December 2018, and continuing for the next 2 years. Long-term outpatients were defined as individuals who had ≥ 8 outpatient visits during the 2-year follow-up period. Adherence to GBM was defined as regular monitoring of ALT, HBV-DNA, AFP, and liver imaging at least annually during the 2-year follow-up period. ALT and HBV-DNA serve as markers to monitor viral breakthroughs, and disease progression. It is recommended that they should be monitored at least annually [1,3–6]. There is no consensus on the best strategy or frequency of HCC surveillance in CHB patients. However, most studies and guidelines

suggested that CHB patients should be screened for HCC by liver imaging and AFP at least annually [1,3–6]. The initial examination—including ALT, HBV-DNA, AFP, and liver imaging—was defined as the examination completed during the first outpatient visit from January 2018 to December 2018. ALT was measured by Roche cobas c702 (Roche Diagnostics, Basel, Switzerland), with a value ≤ 40 U/L considered normal. HBV-DNA was screened by Roche cobas e801 (Roche Diagnostics, Basel, Switzerland), with a result below the detection limit defined as negative. AFP was assessed by Roche cobas z480 (Roche Diagnostics, Basel, Switzerland), with a concentration of < 20 ng/mL considered normal.

Quantitative component: data collection

The participants were selected based on the inclusion and exclusion criteria, as well as following the definition of long-term outpatients. Information on all analyzed cases included demographics, disease-related information, HBV infection-related laboratory tests, and imaging data. The demographics included age, gender, healthcare insurance, and the number of outpatient visits to the hospital. The disease-related information referred to the use of antiviral drugs. HBV infection-related laboratory tests included detected times of visit and initial level of ALT, HBV-DNA, and AFP in the outpatient department. Liver imaging included ultrasound or computed tomography or magnetic resonance imaging. Each patient's data was recorded by two independent reviewers to ensure accuracy.

Figure 1. Flowchart of study population.



HBV: hepatitis B virus.

Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0 (SPSS Inc., IL, USA). Descriptive statistics were reported as proportions (%) for categorical variables, and mean ± standard deviation or median and percentile for continuous variables. The association between categorical variables were analyzed using the Chi-square test and continuous variables were analyzed by the t-test. Subsequently, the associated factors were assessed by binary logistic regression analysis. $p < 0.05$ was considered statistically significant.

Qualitative component

A one-on-one face-to-face semi-structured interview approach was employed for the qualitative component. The interview outline was developed by referring to relevant literatures. It centered on chronic HBV infection, monitoring status, and reasons for non-adherence to GBM. Prior to the interview, the study's

Table 1. Demographic and clinical characteristics of the study population.

Variables	Analyzed patients (n = 402)
Age (years)	41.6 ± 11.7
Gender, n (%)	
Male	242 (60.2)
Female	160 (39.8)
Healthcare insurance, n (%)	
Yes	367 (91.3)
No	35 (8.7)
Outpatient visit times	13 (10, 20)
Receiving antiviral treatment, n (%)	
Yes	225 (56.0)
No	177 (44.0)
Initial ALT, n (%)	
Completed	181 (45.0)
Uncompleted	221 (55.0)
Initial ALT level	
Normal	125 (69.1)
Elevated	56 (30.9)
Initial AFP, n (%)	
Completed	128 (31.8)
Uncompleted	274 (68.2)
Initial HBV-DNA, n (%)	
Completed	185 (46.0)
Uncompleted	217 (54.0)
Initial HBV-DNA level (lg copies/mL)	
Lower detection limit	35 (18.9)
1–3	34 (18.4)
4–6	83 (44.9)
≥ 7	33 (17.8)
Initial liver imaging, n (%)	
Completed	113 (28.1)
Uncompleted	289 (71.9)

ALT: alanine aminotransferase; AFP: alpha-fetoprotein: HBV: hepatitis B virus.

purpose and significance were clarified to the participants, and the interview process was recorded with their consent. The interviews were conducted in outpatient clinics; each lasting approximately 10 minutes and facilitated by a single researcher. The recordings were made using a voice recorder recording app developed by Shanghai Xiaoling Technology Company. During the interviews, the interviewer refrained from guiding or judging the interviewees' opinions. Post-interview, the data were promptly organized within 24 hours, and the recorded content was transcribed. Subsequently, two researchers reviewed all interview data, analyzed key and frequently mentioned statements based on the interview outline, and then summarized and categorized the findings using thematic and content analysis methods.

Results

Quantitative component

A total of 1200 CHB outpatients were retrieved based on the inclusion criteria from January 2018 to December 2018. Then, 67 outpatients were excluded based on the exclusion criteria, and 731 outpatients were excluded because they had less than 8 follow-up visits in 2 years. Finally, 402 outpatients were analyzed. The schematic process of sample selection is illustrated in Figure 1. The demographic and clinical characteristics of the outpatients are presented in Table 1. The overall mean age at baseline was 41.6 ± 11.7 years and comprised 242 (60.2%) males. Moreover, 367 (91.3%) had healthcare insurance, and 225 (56.0%) had received antiviral treatment. The median outpatient visit was 13 times in 2 years. Among the participants, initial ALT levels were completed in 181 (45.0%) outpatients, of which 125 (69.1%) were found to be within the normal range. In addition, 128 (31.8%), 185 (46.0%) and 113 (28.1%) outpatients completed initial AFP, HBV-DNA and liver imaging, respectively.

Only 103 (25.6%) outpatients presented good adherence to GBM. Specifically, outpatients monitored at least annually within the following 2 years were as follows: 197 (49.0%) for ALT, 151 (37.6%) for HBV-DNA, 186 (46.3%) for AFP, 127 (31.6%) for liver imaging, 171 (42.5%) for ALT and HBV-DNA, and 107 (26.6%) for AFP and liver imaging (Table 2). The results of univariate and multivariate analyses are shown in Tables 2 and 3, respectively. Adherence to GBM was associated with receiving antiviral treatment

Table 2. Univariable analysis of GBM, ALT and HBV-DNA, AFP, and liver imaging in chronic hepatitis B outpatients.

Variables	GBM (n = 103)	NGBM (n = 299)	*p* value	ALT and HBV-DNA			AFP and liver imaging		
				Monitored (n = 171)	Unmonitored (n = 231)	*p* value	Monitored (n = 107)	Unmonitored (n = 295)	*p* value
Age (years)	38.4 ± 10.1	42.7±12.0	0.001	38.6 ± 10.2	43.8 ± 12.2	< 0.001	38.6±10.0	42.7±12.0	0.001
Gender, n (%)			0.039			0.003			0.030
Male	70 (68.0)	172 (57.5)		117 (68.4)	125 (54.1)		73 (68.2)	169 (57.3)	
Female	33 (32.0)	127 (42.5)		54 (31.6)	106 (45.9)		34 (31.8)	126 (42.7)	
Healthcare insurance, n (%)			0.075			0.312			
Yes	98 (95.1)	269 (90.0)		158 (92.4)	209 (90.5)		102 (95.3)	265 (89.8)	0.058
No	5 (4.9)	30 (10.0)		13 (7.6)	22 (9.5)		5 (4.7)	30 (10.2)	
Outpatient visit times	18 (11, 31)	14 (10, 26)	0.488	18 (11, 31)	13 (10, 24)	0.017	14 (10, 26)	18 (11, 31)	0.443
Receiving antiviral treatment, n (%)			0.018			< 0.001			0.028
Yes	55 (53.4)	122 (40.8)		92 (53.8)	85 (36.8)		56 (52.3)	121 (41.0)	
No	48 (46.6)	177 (59.2)		79 (46.2)	146 (63.2)		51 (47.7)	174 (59.0)	
Initial ALT, n (%)			< 0.001			0.001			< 0.001
Completed	73 (70.9)	108 (36.1)		108 (63.2)	73 (31.6)		74 (69.2)	107 (36.3)	
Uncompleted	30 (29.1)	191 (63.9)		63 (36.8)	158 (68.4)		33 (30.8)	188 (63.7)	
Initial ALT Level(U/L)			0.005			0.001			0.007
Normal	42 (57.5)	83 (76.9)		65 (60.2)	60 (82.2)		43 (58.1)	82 (76.6)	
Elevated	31 (42.5)	25 (23.1)		43 (39.8)	13 (17.8)		31 (41.9)	25 (23.4)	
Initial AFP, n (%)			< 0.001			< 0.001			< 0.001
Completed	57 (55.3)	71 (23.7)		76 (44.4)	52 (22.5)		60 (56.1)	68 (23.1)	
Uncompleted	46 (44.7)	228 (76.3)		95 (55.6)	179 (77.5)		47 (43.9)	227 (76.9)	
Initial HBV-DNA, n (%)			< 0.001			< 0.001			< 0.001
Completed	70 (68.0)	115 (38.5)		109 (63.7)	76 (32.9)		71 (66.4)	114 (38.6)	
Uncompleted	33 (32.0)	184 (61.5)		62 (36.3)	155 (67.1)		36 (33.6)	181 (61.4)	
Initial HBV-DNA level (lg copies/mL)			0.420			0.026			0.392
Lower detection limit	13 (18.6)	22 (19.1)		23 (21.1)	12 (15.8)		13 (18.3)	22 (19.3)	
1–3	9 (12.9)	25 (21.7)		13 (11.9)	21 (27.6)		9 (12.7)	25 (21.9)	
4–6	33 (47.1)	50 (43.5)		49 (45.0)	34 (44.7)		34 (47.9)	49 (43.0)	
≥ 7	15 (21.4)	18 (15.7)		24 (22.0)	9 (11.8)		15 (21.1)	18 (15.8)	
Initial liver imaging, n (%)			< 0.001			< 0.001			< 0.001
Completed	52 (50.5)	61 (20.4)		64 (37.4)	49 (21.2)		54 (50.5)	59 (20.0)	
Uncompleted	51 (49.5)	239 (79.6)		107 (62.6)	182 (78.8)		53 (49.5)	236 (80.0)	

Data is expressed as either proportion or mean ± SD or median and range (25^{th} and 75^{th} percentiles). GBM: guideline-based monitoring; N-GBM: non-guideline-based monitoring; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; HBV: hepatitis B virus.

Table 3. Multivariable logistic regression analysis of GBM, ALT and HBV-DNA, AFP and liver imaging in chronic hepatitis B outpatients.

	OR	95% CI	*p* value
GBM			
Receiving antiviral treatment	3.54	1.59–7.86	0.002
Completed initial liver imaging	4.78	2.04–9.83	< 0.001
ALT and HBV-DNA			
Age (years)	0.95	0.91–0.99	0.018
Gender (female)	0.33	0.14–0.77	0.010
Outpatient visit times	1.08	1.01–1.15	0.036
Receiving antiviral treatment	3.51	1.04–11.90	0.044
AFP and liver imaging			
Receiving antiviral treatment	3.30	1.50–7.25	0.003
Completed initial liver imaging	4.00	1.83–8.50	< 0.001

GBM: guideline-based monitoring; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; HBV: hepatitis B virus.

(odds ratio (OR) = 3.54 (1.59–7.86), p = 0.002) and completed initial liver imaging (OR = 4.78 (2.04–9.83), $p < 0.001$). Adherence to monitoring of ALT and HBV-DNA was associated with age (OR = 0.95 (0.91–0.99), p = 0.018), gender (OR = 0.33 (0.14–0.77), p = 0.010), outpatient visit times (OR = 1.08 (1.01–1.15), p = 0.036), and receiving antiviral treatment (OR = 3.51 (1.04–11.90), p = 0.044). Adherence to monitoring of AFP and liver imaging for HCC surveillance was associated with receiving antiviral treatment (OR = 3.30 (1.50–7.25), p = 0.003) and completed initial liver imaging (OR = 4.00 (1.83–8.5), $p < 0.001$).

Qualitative component

A total of 7 male and 8 female outpatients participated in the qualitative part of this study, and the mean age was 43.2 ± 12.3 years. The characteristics of the interviewees are presented in Table 4. Based on the qualitative interviews with patients, the reasons for non-adherence to GBM were as follows:

Healthcare providers provide inadequate monitoring tests and health education

P1: "Currently, I monitor liver function and HBV-DNA tests regularly, but I do not undergo liver cancer screening. Because the doctor only told me to regularly monitor liver function and HBV-DNA, but not liver cancer screening".

P6: "I monitor liver function and HBV-DNA annually, liver ultrasound semiannually. I do not know whether AFP is monitored or not, and I do not know about this test".

P14: "Doctors have given me health education on monitoring test, but it was not particularly detailed. They advised me to monitor every year. I have never heard of monitored HBV-DNA, but I know liver function, liver ultrasound, and AFP. I regularly monitored these items in the annual physical examination organized by the company".

Patients think they don't need frequent monitoring

P2: "I do not have regular monitoring at present, because I think I feel fine and am in good health".

P5: "I did regular monitoring at beginning and there was no change in each test, so I think don't need frequent tests".

P7: "I monitor liver function and HBV-DNA every year, and the result was normal. Therefore, I consider it is unnecessary to monitor more frequently".

P15: "Sometimes when I went to the hospital, the doctor suggested me to do the tests and I did it. I don't monitor regularly, because I think I have a good lifestyle and a positive attitude. It is good to my disease".

P8: "I haven't regularly monitored before. Last year, my relatives died of liver cancer, and I started monitoring regularly every six months".

P10："I only monitor liver function and ultrasound semi-annually, and sometimes HBV-DNA, but I think it is useless".

Patients forget to monitor

P9: "I monitor sometimes half a year, sometimes once a year, not very regular, mainly because of forgetting the monitoring time".

P13: "Three years ago, I went to the hospital due to poor sleep, and found abnormal liver function, HBeAg-

Table 4. Characteristics of the interviewees.

Patient	Age (years)	Gender
P1	27	Male
P2	63	Female
P3	33	Female
P4	56	Male
P5	40	Male
P6	35	Female
P7	53	Female
P8	36	Male
P9	34	Male
P10	32	Male
P11	64	Male
P12	56	Female
P13	39	Female
P14	48	Female
P15	32	Female

positive hepatitis B, and high HBV-DNA. Then, I did regular 6-month monitoring examinations on liver function and HBV-DNA, but liver cancer screening was missed from the beginning".

Concerns about cost

P5: "I monitor liver function and liver cancer screening annually, but less HBV-DNA, the results of which had no change each time and the cost is a little expensive, and I feel it is unnecessary".

Complicated visit procedures at hospital

P12: "I do not regularly monitor, the reason is afraid of trouble, the hospital procedures are complicated, ultrasound is not easy to book and I am busy recently".

Discussion

There is limited mixed study from China on the adherence to GBM, which includes monitoring of ALT, HBV-DNA, AFP, and liver imaging; and further exploration of the reasons for non-adherence from patient perspective. The quantitative study revealed that only approximately one quarter of CHB outpatients adhered to GBM. Specifically, less than half of the outpatients monitored ALT and HBV-DNA at least annually, while approximately one quarter of the outpatients monitored AFP and liver imaging for HCC surveillance at least annually. The qualitative study showed that the reasons for non-adherence to GBM were as follows: healthcare providers provide inadequate monitoring tests and health education, patients think they don't need frequent monitoring and forget to monitor, cost concerns, and complicated visit procedures at hospital.

The quantitative results from this study suggest that many CHB outpatients did not undergo all the examinations recommended by the guidelines at each follow-up visit. ALT assessment was carried out most frequently, followed by AFP, HBV-DNA, and liver imaging. A study by Juday *et al.* reported that the HBV-DNA monitoring rates were lower than the rates of ALT monitoring [12]. This may be explained by the results of the qualitative interviews where some patients had never heard of monitoring parameters such as HBV-DNA or AFP, and some patients complained that ultrasound was not easy to book. In this study, less than half of outpatients monitored ALT and HBV-DNA at least annually. A study by Wu *et al.* reported that 29% of inactive HBV carriers did not undergo timely ALT/HBV-DNA assessment, at least every 12 months [16]. In another study, Juday *et al*. reported that among the CHB patients who were not receiving antiviral treatment, 53.3% monitored ALT and 39.0% monitored HBV-DNA, at least every 12 months, and 35.1% monitored both [12]. Additionally, Spradling *et al.* reported that among CHB patients, 78% had at least one annual ALT level assessment, while 37% had at least one annual HBV-DNA level assessment [14]. The result from these studies differed due to the different populations included in the analyses. Overall, they indicate suboptimal monitoring of ALT and HBV-DNA in CHB patients; and this was also observed in the present study. HCC surveillance is crucial for improving prognosis and facilitating access to curative treatments by enabling early detection. This study revealed that only 26.6% of CHB patients undergo AFP and liver imaging for HCC surveillance at least annually. Several studies have explored the adherence rate of HCC surveillance and associated factors, particularly in high-risk patients, consistently indicating suboptimal implementation. A meta-analysis which included 4 studies and 3272 CHB patients presented a higher adherence of 32% because it included patients who underwent liver imaging with or without AFP [20]. However, guidelines and related studies have demonstrated that AFP is recommended in conjunction with liver imaging to improve HCC screening accuracy [21].

The present study also revealed that CHB patients who had not received antiviral treatment and had not completed initial liver imaging exhibited poor adherence to GBM and HCC surveillance. CHB patients who were older, female, had less outpatient-visit times, and were not receiving antiviral treatment exhibited poor adherence to monitoring ALT and HBV-DNA. Studies exploring the associated factors have yielded different results. Spradling *et al*. concluded that patients aged < 60 years, females, and those who had not received antiviral treatment were more likely to exhibit poor adherence to monitoring ALT and HBV-DNA [14]. Meanwhile, Juday *et al.* identified female gender as a predictor for poor adherence to monitoring HBV-DNA [12]. Additionally, Kushner *et al*. reported that CHB patients with fewer visits were positively associated with poor adherence to monitoring ALT [22].

Most patients who did not receive antiviral therapy had such a short, mild, and asymptomatic course of disease that it was easy to underestimate the importance of monitoring. Patients who had not completed the initial liver imaging exhibited poor adherence, underscoring the critical role of disease education at the early stage in fostering subsequent monitoring adherence. Therefore, it is crucial to educate patients

about the importance of disease monitoring, particularly at the time of initial diagnosis, to ensure adherence with recommendation.

The adherence rates to GBM in CHB patients were found to be suboptimal. Based on qualitative interviews, factors related to healthcare providers, hospitals, and the patient themselves contributed to the non-adherence to GBM. A review from the United States identified key barriers to monitoring, including patients' lack of disease knowledge (often resulting from physicians' insufficient awareness), financial constraints, and inadequate patient education [23]. Nguyen *et al.* reported that patients cite cost as a barrier to HCC surveillance [24]. Another study revealed that primary care providers have significant misconceptions about HCC surveillance, with over a quarter mistakenly believing that liver enzymes are useful for detecting HCC, and encouraged provider education [25]. The patients exhibited inadequate practice in the long-term monitoring of disease progression and HCC surveillance, indicating a pressing need for improvement in this area. Interventional studies have implemented programs, such as mailed outreach, clinical reminder, and education to improve adherence to disease monitoring [26–28].

The department of infectious disease at the Third affiliated hospital, SUN Yat-sen University from Guangzhou of China has set up a special follow-up clinic for CHB and adopted various methods (including short message, WeChat, website, and phone calls to book a return visit in advance) to remind and urge patients to regular monitoring [29]. Beste *et al.* implemented a clinical reminder program to increase the HCC surveillance rate from 18.2% to 51% [30]. Additionally, many patients might underestimate the severity of the disease and the importance of disease monitoring. CHB takes a long time to develop into severe liver disease, and patients' awareness of the seriousness of HBV infection decreases over time. Therefore, frequent educational efforts focused on disease monitoring are needed. A study by Ma *et al.* reported that HBV-related knowledge was significantly associated with performing CHB-monitoring behaviors [18]. In recent years, clinical management of hepatitis B advocates transition from specialist to primary care. The Third National Hepatitis B Strategy 2018–2022 identifies general practice as a 'priority setting' for delivering education, prevention, treatment, and care services. Managing CHB patients in primary care provide long-term continuous service, reduces waiting times at specialist clinics, and improves patient adherence [31].

The suboptimal adherence to GBM in CHB patients necessitates multifaceted interventions addressing systemic-, provider-, and patient-level barriers. Three pillars of action are proposed to overcome these challenges:

1. Technology-drive: In the present internet age, medical institutions can develop clinical tools, such as electronic medical reminders and progress note templates to improve patient adherence.
2. Education reinforcement: Healthcare provider education must prioritize correcting misconceptions, while patient education should emphasize HBV progression risks and monitoring benefits, as the knowledge gaps directly correlate with poor adherence.
3. Structural integration: Decentralizing CHB management to primary care ensures continuity, reduces specialist burdens, and enhances accessibility.

While these strategies demonstrate promise in bridging adherence gaps, further research is imperative to evaluate their long-term efficacy, cost-effectiveness, and adaptability across diverse healthcare settings.

This study not only used quantitative methods to identify the low GBM adherence rates among CHB patients, but also supplemented with qualitative interviews to further identify the reasons for non-adherence from the patient perspective. Nevertheless, the present study has several limitations. Only one hospital was included in the quantitative study and HBV-related examination conducted at other medical institutions might have been missed. In order to counteract these disadvantages, long-term and consecutive outpatient population were used as participants. A prospective study with a larger sample size and scope is required.

Conclusions

Despite guideline recommendations, adherence to GBM among CHB patients was found to be suboptimal, especially among those who did not receive antiviral treatment and those who did not complete initial liver imaging examination. Various factors from the patient, healthcare provider, and hospital contribute to patients' non-adherence to GBM. Combining technology-driven tools, targeted education for providers, and patients and primary care integration is essential to improve CHB monitoring adherence. Future studies should focus on cost-effectiveness and scalability of these strategies to guide global implementation.

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Authors' contributions

C-LH, concept or design, data acquisition, data interpretation, manuscript draft; HY, concept or design, critical revision for important intellectual content; JG, concept or design, data interpretation, critical revision for important intellectual content; YY, concept or design; C-DL, data acquisition, data interpretation. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Conflict of interest

No conflict of interest is declared.

References

1. You H, Wang F, Li T, Xu X, Sun Y, Nan Y, Wang G, Hou J, Duan Z, Wei L, Jia J, Zhuang H (2023) Guidelines for the prevention and treatment of chronic hepatitis B (version 2022). J Clin Transl Hepatol 11: 1425–1442. doi: 10.14218/JCTH.2023.00320.
2. WHO (2023) Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030. Available: https://www.who.int/publications/i/item/9789240053779. Accessed: 24 September 2024.
3. Terrault NA, Lok A, Mcmahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RJ, Bzowej NH, Wong JB (2018) Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67: 1560–1599. doi: 10.1002/hep.29800.
4. WHO (2024) Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Available: https://www.who.int/publications/i/item/9789240090903. Accessed: 24 September, 2024.
5. WHO (2015) Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization. Available: https://www.who.int/publications/i/item/9789241549059. Accessed: 24 September, 2024.
6. Chinese Society of Hepatology, Chinese Society of Infectious Diseases, Chinese Medical Association (2019) Guidelines for the prevention and treatment of chronic hepatitis B (2019 version) Chinese Journal of Hepatology 27: 962–979. doi: 10.3760/cma.j.issn.1007-3418.2019.12.007.
7. Post SE, Sodhi NK, Peng CH, Wan K, Pollack HJ (2011) A simulation shows that early treatment of chronic hepatitis B infection can cut deaths and be cost-effective. Health Aff (Millwood) 30: 340–348. doi: 10.1377/hlthaff.2008.0905.
8. Cadier B, Bulsei J, Nahon P, Seror O, Laurent A, Rosa I, Layese R, Costentin C, Cagnot C, Durand-Zaleski I, Chevreul K (2017) Early detection and curative treatment of hepatocellular carcinoma: a cost-effectiveness analysis in France and in the United States. Hepatology 65: 1237–1248. doi: 10.1002/hep.28961.
9. Singal AG, Mittal S, Yerokun OA, Ahn C, Marrero JA, Yopp AC, Parikh ND, Scaglione SJ (2017) Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. Am J Med 130: 1099–1106. doi: 10.1016/j.amjmed.2017.01.021.
10. Zhang BH, Yang BH, Tang ZY (2004) Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 130: 417–422. doi: 10.1007/s00432-004-0552-0.
11. Li ZL, Wu H, Wei YP, Zhong Q, Song JC, Yu JJ, Li C, Wang MD, Xu XF, Li JD, Han J, Xing H, Lau WY, Wu MC, Shen F, Yang T (2020) Impact of surveillance in chronic hepatitis B patients on long-term outcomes after curative liver resection for hepatocellular carcinoma. J Gastrointest Surg 24: 1987–1995. doi: 10.1007/s11605-019-04295-w.
12. Juday T, Tang H, Harris M, Powers AZ, Kim E, Hanna GJ (2011) Adherence to chronic hepatitis B treatment guideline recommendations for laboratory monitoring of patients who are not receiving antiviral treatment. J Gen Intern Med 26: 239–244. doi: 10.1007/s11606-010-1549-9.
13. Lim YS, Kim WR, Dieterich D, Kao JH, Flaherty JF, Yee LJ, Roberts LR, Razavi H, Kennedy P (2023) Evidence for benefits of early treatment initiation for chronic hepatitis B. Viruses 15: 997. doi: 10.3390/v15040997.
14. Spradling PR, Xing J, Rupp LB, Moorman AC, Gordon SC, Teshale ET, Lu M, Boscarino JA, Trinacty CM, Schmidt MA, Holmberg SD (2016) Infrequent clinical assessment of chronic hepatitis B patients in United States general healthcare settings. Clin Infect Dis 63: 1205–1208. doi: 10.1093/cid/ciw516.
15. Pham T, Toy M, Hutton D, Thompson W, Conners EE, Nelson NP, Salomon JA, So S (2023) Gaps and disparities in chronic hepatitis B monitoring and treatment in the United States, 2016–2019. Med Care 61: 247–253. doi: 10.1097/MLR.0000000000001825.
16. Wu Y, Johnson KB, Roccaro G, Lopez J, Zheng H, Muiru A, Ufere N, Rajbhandari R, Kattan O, Chung RT (2014) Poor adherence to AASLD guidelines for chronic hepatitis B management and treatment in a large academic medical center. Am J Gastroenterol 109: 867–875. doi: 10.1038/ajg.2014.72.
17. Nguyen VH, Le AK, Trinh HN, Chung M, Johnson T, Wong C, Wong C, Zhang J, Li J, Levitt BS, Nguyen HA, Nguyen KK, Henry L, Cheung R, Nguyen MH (2019) Poor adherence to

guidelines for treatment of chronic hepatitis B virus infection at primary care and referral practices. Clin Gastroenterol Hepatol 17: 957–967. doi: 10.1016/j.cgh.2018.10.012.
18. Ma GX, Zhu L, Lu W, Tan Y, Truehart J, Johnson C, Handorf E, Nguyen MT, Yeh MC, Wang MQ (2022) Examining the influencing factors of chronic hepatitis B monitoring behaviors among Asian Americans: application of the information-motivation-behavioral model. Int J Environ Res Public Health 19: 4642. doi: 10.3390/ijerph19084642.
19. Chi H, Japhary A, de Man RA, de Knegt RJ, Janssen H, Hansen BE (2018) Younger age and language barriers are associated with nonadherence to clinical follow-up in hepatitis B treatment. J Viral Hepat 25: 1216–1219. doi: 10.1111/jvh.12920.
20. Zhao C, Jin M, Le RH, Le MH, Chen VL, Jin M, Wong GL, Wong VW, Lim YS, Chuang WL, Yu ML, Nguyen MH (2018) Poor adherence to hepatocellular carcinoma surveillance: a systematic review and meta-analysis of a complex issue. Liver Int 38: 503–514. doi: 10.1111/liv.13555.
21. Harris PS, Hansen RM, Gray ME, Massoud OI, Mcguire BM, Shoreibah MG (2019) Hepatocellular carcinoma surveillance: an evidence-based approach. World J Gastroenterol 25: 1550–1559. doi: 10.3748/wjg.v25.i13.1550.
22. Kushner T, Lam R, Gray DL, Kaplan DE, Serper M (2017) Identifying patient and provider-specific gaps in care among patients with hepatitis B. J Clin Gastroenterol 51: 900–906. doi: 10.1097/MCG.0000000000000806.
23. Ispas S, So S, Toy M (2019) Barriers to disease monitoring and liver cancer surveillance among patients with chronic hepatitis B in the United States. J Community Health 44: 610–625. doi: 10.1007/s10900-018-00604-7.
24. Nguyen MH, Roberts LR, Engel-Nitz NM, Bancroft T, Ozbay AB, Singal AG (2022) Gaps in hepatocellular carcinoma surveillance among insured patients with hepatitis B infection without cirrhosis in the United States. Hepatol Commun 6: 3443–3456. doi: 10.1002/hep4.2087.
25. Simmons OL, Feng Y, Parikh ND, Singal AG (2019) Primary care provider practice patterns and barriers to hepatocellular carcinoma surveillance. Clin Gastroenterol Hepatol 17: 766–773. doi: 10.1016/j.cgh.2018.07.029.
26. Singal AG, Tiro JA, Marrero JA, Mccallister K, Mejias C, Adamson B, Bishop WP, Santini NO, Halm EA (2017) Mailed outreach program increases ultrasound screening of patients with cirrhosis for hepatocellular carcinoma. Gastroenterology 152: 608–615. doi: 10.1053/j.gastro.2016.10.042.
27. Ma GX, Zhu L, Lu W, Handorf E, Tan Y, Yeh MC, Johnson C, Guerrier G, Nguyen MT (2022) Improving long-term adherence to monitoring/treatment in underserved Asian Americans with chronic hepatitis B (CHB) through a multicomponent culturally tailored intervention: a randomized controlled trial. Healthcare (Basel) 10: 1944. doi: 10.3390/healthcare10101944.
28. Ma GX, Zhu L, Tan Y, Zhai S, Ma X, Ogunwobi OO, Yang WJ, Ting T, Kim S, Wang MQ (2023) A comparative trial of improving care for underserved Asian Americans infected with hepatitis B virus. Dig Dis Sci 68: 2333–2343. doi: 10.1007/s10620-023-07840-5.
29. Zhu CH, Wu YK, Li XY, Lin GL, Jie YS, Yang FJ, Chong YT (2016) Patient compliance and its influencing factors in a long-term follow-up cohort of chronic HBV infection. Guangdong Med 37: 3578–3582. doi: 10.13820/j.cnki.gdyx.20161227.011.
30. Beste LA, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA (2015) Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. Clin Gastroenterol Hepatol 13: 172–179. doi: 10.1016/j.cgh.2014.04.033.
31. Wallace J, Richmond J, Allard N, Howell J, Adamson E, Xiao Y, O'Reilly C, Hellard M (2020) Facilitating hepatitis B clinical management in general practice: a qualitative investigation. Aust J Gen Pract 49: 599–604. doi: 10.31128/AJGP-02-20-5225.