Review Article

Health-Related Quality of Life in Patients with Chronic Hepatitis B: A Meta-Analysis of Observational Studies

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Abstract

Background: Chronic hepatitis B virus (CHB) infection is one of the most common liver infections worldwide. Approximately 240 million patients are diagnosed with CHB. The objective of this meta-analysis was to identify the effect of CHB on the affected patients' health-related quality of life and compare with the control group.

Methods: A comprehensive search was conducted through PubMed, Medline, ProQuest, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and Web of Science databases up to Jul 2022.

Results: Five primary observational studies using SF-36 and WHOQOL surveys with 1135 participants (646 with CHB and 489 healthy individuals) included in the meta-analysis. We evaluated the scores of physical and mental component summaries. HRQoL was comparable in both groups. The disease's impact appears to slightly affect the mental component summary than the physical component summary.

Conclusion: The HRQoL in CHB patients is mainly reflected in the impairment of the mental aspect. It is vital to focus on optimally managing care, family and social support, stress management.

Keywords: Quality of life; Health-related quality of life; Chronic hepatitis B patients; Meta-analysis

Introduction

Chronic hepatitis B virus (CHB) infection has become a significant public health concern worldwide (1-3). This infection has been the object of many types of researches since the XX century. Approximately 240 million patients have CHB with a varying HBsAg prevalence geo- graphically from high (>8%), intermediate (2-7%) to low (<2%) level (1, 4-6).

The Global Health Sector Strategy of World Health Assembly calls for eliminating CHB as a public health threat by 2030, including reducing new infections by 90% and deaths by 65% (7).

CHB is unlikely to be cured, and patients have to live with the disease for long time (8). CHB is related to an increased risk of progressive liver damage and the occurrence of potentially fatal complications such as liver fibrosis, cirrhosis, hepatocellular carcinoma (9, 10). They may lead to severe incidence and high mortality rates of patients. Moreover, CHB complications may be characterized clinically by ascites, jaundice, pain in the abdomen, nausea, esophageal and gastric variceal bleeding, vomiting, fever, diarrhea, and appetite loss, weakness, tiredness, joint pain, work loss, etc. (11).

After diagnosis, patients with CHB should be informed about antiviral therapy, further lifestyle changes, prevention of transmission, and the importance of quality of life (QOL) monitoring by physicians (12).

During the past decades, researchers have shown an increased interest in studying patients' QOL. It has been established as a major concept of a person's general well-being status and an overall critical measure (13-16).

Moreover, in recent years, several studies have investigated the detailed impact of CHB on the QoL or HRQoL (11, 17-25). CHB has a direct correlation with QoL, and the patients with more chronicity of disease have more deranged QoL (11) due to the influence of systemic characteristics such as exhaustion, non-encephalopathic cognitive dysfunction, and sleep disturbance (26,27). Besides, several studies have investigated the impact of psychological intervention and self-management on HRQOL in chronic liver patients (17, 28).

To determine the effect of CHB on QoL and HRQoL, various generic and disease-specific instruments are used. They include the Short Form 36 Health Survey (SF-36), the European Quality of Life-5 Dimensions (EQ5D), the World Health Organization Quality-of-Life Scale (WHOQOL), the Chronic Liver Disease Questionnaire (CLDQ), the Liver Disease Quality of Life Instrument (LDQOL), the Hepatitis B Quality of Life (HBQOL).

Therefore, in this study, we tried to conduct a meta-analysis of published observational studies on the effect of CHB on patients' HRQoL using SF-36 and WHOQOL survey, and compare with the control group.

Methods

Data sources and search strategy

A comprehensive literature search was performed through PubMed, Medline, ProQuest, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and Web of Science databases from inception until Jul 2022. Search strings contained MESH terms and key words such as "Quality of Life", "Health-related Quality of Life", "Hepatitis B, Chronic", and "Patient Reported Outcome". Additional articles were not identified by manually searching the references of retrieved eligible articles. No restrictions of language, date or geographical location were placed. This meta-analysis was reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (29).

Quality of life instruments

We applied the following measures to all studies:
The Short Form 36 Health Survey (SF-36): SF-36 questionnaire consists of 36 items measuring the following 8 domains: physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role functioning (RE), and mental health (MH). These domains are grouped into two summary measures: physical component summary (PCS) and mental component summary (MCS) (30). The physical component summary included the PF, RP, BP, and GH scales, and the mental component summary included the VT, SF, RE, and MH scales. For each question, the raw score was transformed into a scale from 0 (means worst possible health state) to 100 (means best possible health state) (31).

The World Health Organization Quality-of-Life Scale (The WHOQOL-BREF) is a 26-item patient-reported outcome measure that produces four domain scores (Physical Health, Psychological Health, Social Relationships, Environment).

The score was transformed into a scale from 0 (means worst possible health state) to 100 (means best possible health state) (32).

Study selection
Following the PICOS (participants, intervention, controls, outcomes, study design) criteria, we included studies assessing:
P: People with CHB
I: None
C: People without CHB
O: Quality of life
S: Observational (case–control, cross-sectional, cohort studies)

Inclusion criteria
Peer-reviewed journal articles that reported an impact of CHB on patients' QoL/HRQoL using SF-36 and WHOQOL-BREF compared to control group (healthy and normal individuals) were included in this meta-analysis.

Exclusion criteria
Case reports, letters, commentaries, editorials, expert opinions, article reviews, and conference abstracts were excluded. Studies that used other instruments for measuring the QoL/HRQoL were excluded as well.

Screening
Studies identified through database searching were screened for eligibility. First, duplicates were removed. Following this, the authors independently screened the titles and, if necessary, abstracts and full texts based on specified inclusion and exclusion criteria and removed the ineligible ones.

Methodological quality assessment
All studies meeting the selection criteria were assessed for their methodological quality using the STROBE checklist (33). This checklist includes questions related to different aspects of a study, including the study design, type of study, sample size, objectives, study population, inclusion and exclusion criteria, samples matching method, analyzing method, and appropriate reporting of re-sults based on the objectives in which for each question a score has been considered and any study that obtains at least eight scores is selected for including in meta-analysis.

Data Extraction
Studies that met the inclusion criteria and passed the methodological quality assessment were examined comprehensively, and needed data was extracted in an Excel data spreadsheet recording: authors, publication year, country of study, study type, sample size, a quality-of-life instrument used, and quality-of-life scores reported (mean and standard deviation), the proportion of males and females, mean age. These data were extracted, if possible, for those with CHB and for controls, respectively.

Outcomes
The primary outcomes were considered the mean values and the correspondent standard deviations (SDs) of the validated tools of QoL, comparing the values of participants with CHB and the controls. If the data were reported in other ways, e.g., median and interquartile ranges, they were transformed into means and SD.

Risk of bias in individual studies
We assessed risk of bias at the study level using the modified Newcastle–Ottawa Scale (34). Studies were assessed on the domains of selection, comparability, exposure (i.e. frailty) and outcome (i.e. QOL). Outcome assessment scored one star for self-report because of the appropriateness of this for QOL measurement. As per the NOS grading in past reviews, we graded studies as having a high (< 5 stars), moderate (5–7 stars) or low risk of bias (≥ 8 stars) (35). Thus, scores of five stars or more were considered moderate to good quality, although studies were incorporated in the synthesis regardless of rating.

Data synthesis and statistical analysis
All analyses were performed using the STATA 16-64 (Texas) software. All analyses, a *P* value

less than 0.05 was considered statistically significant.

The primary analysis compared the values of QoL tests between participants with CHB vs. healthy controls, according to the test used for assessing the QoL. We calculated the difference between the means of the CHB and control groups through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model (36). We then applied the indications for interpreting the magnitude of the SMD in the sciences, as suggested by Cohen (37), i.e., small, SMD=0.2–0.5; medium, SMD=0.5–0.8; and large, SMD > 0.8. The data were also reported as forest plots, in a graphical way.

Heterogeneity across studies was proceeded using Cochrane Q-statistic (whereby $P \leq 0.05$ was set as statistically significant), and homogenicity of studies was rejected. The I2-statistic was also followed to show the percentage of total heterogenicity across studies (38, 39). The following suggested cut-off points were used: I2=0%-25%, no heterogeneity; I2=25%-50%, moderate heterogeneity; I2=50%-75%, large heterogeneity; I2=75%-100%, extreme heterogeneity. The *P*-value for Q was >0.05 but a fixed-effect model was not used as I2 was >50%.

As the homogeneity hypothesis rejected we use a random-effect model. The significance of the pooled risk ratio was evaluated with the Z test and its two-tailed *P*-value. Forest plots with risk ratios and their 95% CI were used to visualize all results. Unfortunately, the small amount of combinative data published to date did not allow any analysis of publication bias or validation, but the reported values in the present work can be considered consistent.

Results

Search result
Our research identified a total number of 121 studies from which 5 studies met the eligibility and inclusion criteria to be included in the meta-analysis (17, 24, 40-42). Figure 1 shows a review and selection process of these studies (29).

Qualitative synthesis
Included studies were cross-sectional and cohort. The period of publishing was 2008-2021. Sample sizes depended on observation period and varied from 30 to 268 in study group. Geographically, studies covered China, Turkey, and Singapore (Table 1).

Meta-analyses
To evaluate the scores of physical and mental component summaries we performed two meta-analyses. Figures 2 and 3 present these summaries in the primary studies. We calculated odds ratios and transformed these to Hedges's d following the recommendations (43).

A random-effects meta-analysis of the physical component between treated and healthy control groups summary revealed an overall effect size of d =-1.31, 95% CI (-2.46, -0.17). This effect size differs statistically from zero, P=0.02. A random-effects meta-analysis of the mental component summary between treated and healthy control groups revealed an overall effect size of d = -1.91, 95% CI (−3.83, 0.01). This effect size differs statistically, P=0.05. These analyses showed that impairment in the mental component summary of CHB patients expressed more than the physical component.

Risk of bias within studies
The risk of bias, evaluated through the NOS, was fully reported in Table 1 (as total score). The median score of the modified Newcastle–Ottawa Scale was 6 (range 4 to 7). Two study suffered on low quality (high risk of bias) as indicated by a NOS ≤ 5/8. Most studies recruited broad, representative samples, but few provided sample size calculations or described comparability with non-respondents.
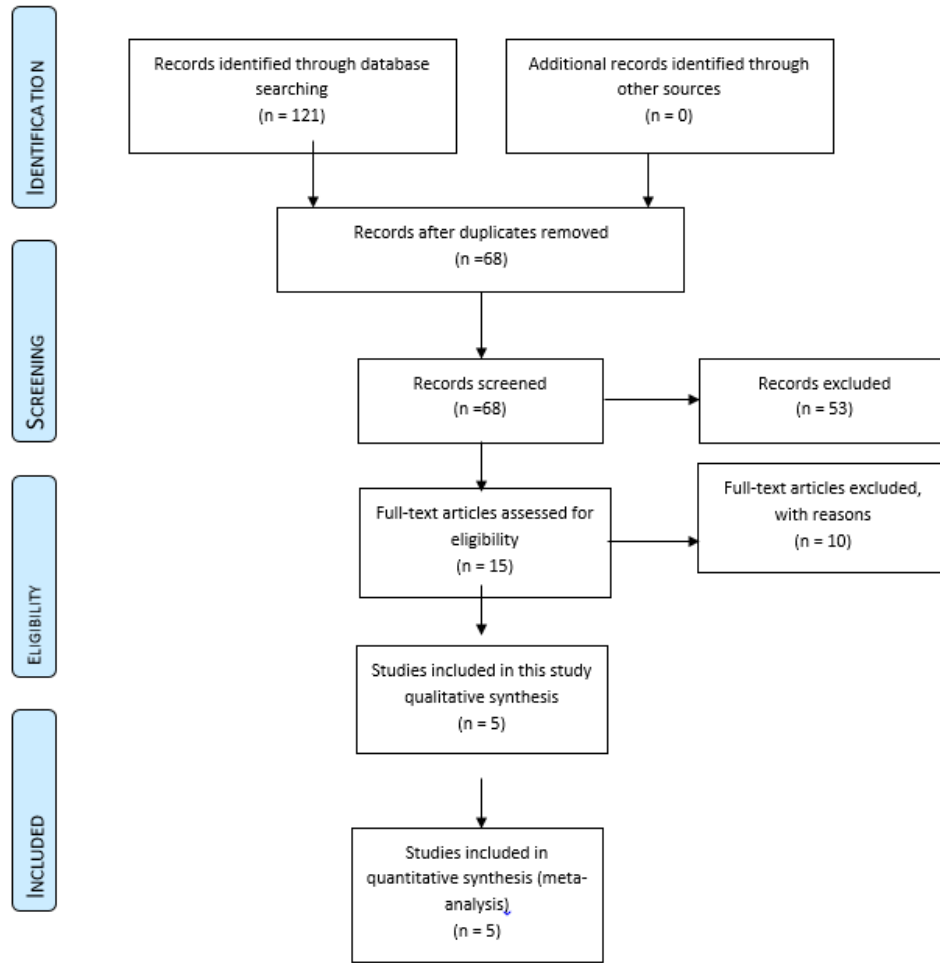
Fig. 1: Flow diagram showing a review and selection process of the studies included in the meta-analysis
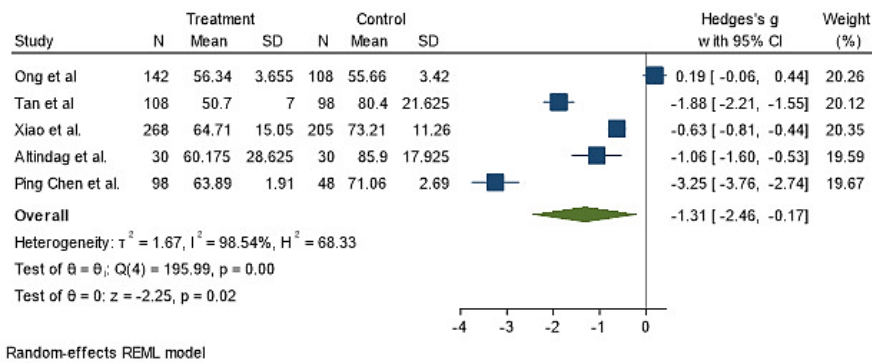

Fig. 2: Forest plot of the overall estimation of the physical component summary

Table 1: Main methodological characteristics of included studies in the quantitative analysis (meta-analysis)

| Author/s. Year (Ref.no.)	Location Country	Objective	Study design	Trial time period	Participants	Sample size	Tool for quality of life	Newcastle–Ottawa Scale
Ong et al., 2008 (17)	Singapore	to determine the relationship between HRQoL and stages of chronic hepatitis B infection compared with normal and with a disease control.	Cohort study	2003-2006	Adults, patients having hepatitis B surface antigen positive for more than 6 months	142/108	SF-36 MCS + PCS	6
Tan et al., 2008 (24)	Singapore	To determine the quality of life of patients with chronic HBV infection (HBV carriers) on conservative management.	Cross-sectional survey	No data	Adults patients, aged ≥ 12 years, and with two consecutive positive HBV surface antigen tests	108/98	SF-36 MCS + PCS	5
Xiao et al., 2012 (40)	China	To survey patients with chronic hepatitis B (CHB) to determine their perceptions of CHB-related quality of life (QOF) and to determine the factors influencing this measure.	Cross-sectional survey	No data	Adults patients	268/205	WHOQOL-BREF	6
Altindag et al., 2009 (41)	Turkey	To measure HRQOL and level of depression among patients with non-cirrhotic chronic hepatitis B patients and HBsAg carriers	Cohort study	2005	Adults patients diagnosed with chronic hepatitis B	30/30	SF-36 MCS + PCS	7
Chen P et al., 2021 (42)	China	to analyze HRQoL in patients diagnosed with HB	Cross-sectional study	2013	Adults patients diagnosed with chronic hepatitis B	98/48	SF-36 MCS + PCS	7
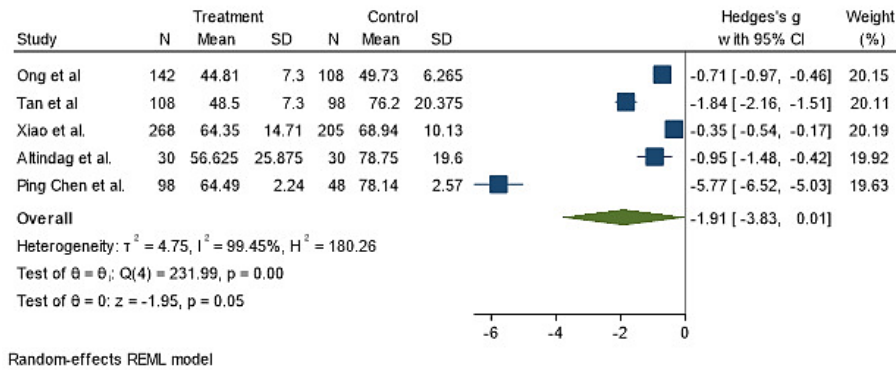
Fig. 3: Forest plot of the overall estimation of the mental component summary

Discussion

WHO records that 240 million people are chronically infected with hepatitis B, and more than 780,000 people die every year due to CHB complications (44). In the last few decades, an increase in the evaluation of HRQOL among patients with chronic liver disease has been observed in parallel with the recognized significance of patient QoL (22). Characterizing the HRQoL of CHB patients also has consequences for patient expectations of the need for antiviral treament, compliance toward follow-up, (17), also improvement of care and treatment services, that fit with the global hepatitis elimination targets set by the WHO (7, 45).

One study (46) investigated HRQoL impairment in black African patients with CHB patients expressed an impaired HRQoL more deteriorated in those with HBeAg negative CHB, low viral load or HBs antigenemia. Meanwhile, physical or mental distress did not depend on the educational level.

Evaluation of HRQoL of patients was examined with CHB reported life quality scores were found to be significantly lower in women, the elderly, in those who did not work, who had an additional disease and who did not perform regular physical activity (47).

In our study, HRQoL was comparable in study and control groups. The presence of CHB was significantly associated with poor QoL. These results, even if characterized by a high heterogeneity and a potential high risk of bias, are of importance, since they add new insight regarding this vital topic.

Overall, our results demonstrated that patients with CHB exhibited similar impairment of physical and mental HRQoL as reported in the United States (48).

Our finding about CHB association with poor mental and physical health is consistent with other findings in the literature (49, 50). Stressful life events and unemployment were important factors related to both their mental and physical health status. CHB patients who have social support have better mental health.

Antiviral treatment can improve interrelated deranged physical and mental health associated with CHB (11). Our results indicate that the CHB disease's impact appears to affect the mental component summary than the physical component summary. It is clear from these results that patients can have a frequent positive affect, absence of psychological distress, and limitations in usual social and role activities due to emotional problems.

Our results are consistent with a multicenter study (51) reported that physical HRQoL was not impaired in the CHB stage, while mental HRQoL was significantly impaired. The PCS scores of patients with CHB were found to be similar to those of the general population, while the MCS scores were lower than those of the general population (*P*<0.05).

In China, depression, anxiety of CHB patients were associated with low HRQoL in all domains of the WHOQOL-BREF including psychological domain. Permanent counseling for people with CHB can help them improve their HRQoL, cope with stress, and boost their self-esteem (52).

Vu et al (53) investigated socioeconomic vulnerability to depressive symptoms found lower HRQoL was related to a higher risk of depression.

The mental HRQoL impairment suggested that physiological support therapy should be strengthened, rather than just focusing on the normality of clinical indicators.

Moreover, our findings are contrast with one study (54) investigated North American patients and one Canadian study (55) which found no differences in HRQoL between CHB patients and population norms.

The findings of our study should be interpreted within its limitations. First, cohort and cross-sectional studies were included, and these studies have inherent limitations, potentially introducing a reverse bias (i.e., people with poor QoL for other reasons may experience CHB). Second, the results were highly heterogeneous and thus it is not possible to explain this issue through a meta-regression, since the data reported for the moderators and planned in our protocol are too inconclusive. Finally, several studies are at high risk of bias. Of importance, no study preformed matching between participants with CHB and controls, potentially introducing a bias.

Conclusion

The HRQoL status in CHB is contrast to that of normal individuals by impact of mental component summary. This work, mainly based on cross-sectional and cohort studies at high risk of bias, highlights the necessity of future longitudinal studies for better understanding the importance of CHB in determining QoL. We believe that an assessment of the QoL can be taken as an important indicator in the treatment of CHB. Therefore, it is necessary to focus on optimally managing care, family and social support, stress management, further develop measures and explore new solutions for improving the HRQoL of patients with CHB. Future studies focusing on the comparative analysis taking into account medico-social characteristics of CHB patients, stage of the disease, and the factors relating to and affecting the HRQoL are required to further investigate detailed CHB's impact.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1. Sarin SK, Kumar M, Lau GK et al (2016). Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int,* 10:1–98.
2. Lu JB, Cai SH, Pan YH et al (2018). Altered epidermal fatty acid-binding protein expression in hepatocellular carcinoma predicts unfavorable outcomes. *Cancer Manag Res*, 10:6275–6284.
3. Xiao YB, Cai SH, Liu LL et al (2018). Decreased expression of peroxisome proliferator-activated receptor alpha indicates unfavorable outcomes in hepatocellular carcinoma. *Cancer Manag Res,* 10:1781–1789.
4. Lok AS, McMahon BJ (2009). Chronic hepatitis B: update 2009. *Hepatology*, 50:661–662.
5. Cai S, Cao J, Yu T et al (2017). Effectiveness of entecavir or telbivudine therapy in patients with chronic hepatitis B virus infection pretreated with interferon compared with de no-

vo therapy with entecavir and telbivudine. *Medicine (Baltimore),* 96:e7021.

6. Ott JJ, Stevens GA, Groeger J et al (2012). Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*, 30:2212-2219.

7. World Health Organization (2016). Global health sector strategy on viral hepatitis 2016-2021. *Global Hepatitis Programme Department of HIV/AIDS*, 56.

8. Wang T (2009). Model of life expectancy of chronic hepatitis b carriers in an endemic region. *J. Epidemiol*, 19,311–318.

9. Dakhil N, Junaidi O, Befeler AS (2009). Chronic viral hepatitis. *Mo Med*, 06(5):361-5.

10. Ryder SD, Beckingham IJ (2001). ABC of diseases of liver, pancreas, and biliary system: Acute hepatitis. *BMJ*, 322(7279):151-3.

11. Ansari S, Siddiqui M, Malhotra S et al (2019). Unani Formulation Improved Quality of Life in Indian Patients of Chronic Hepatitis B. *Journal of Young Pharmacists*,11(4):353-360.

12. Lok AS, McMahon BJ (2007). Chronic hepatitis B. *Hepatology*, 45(2):507-39.

13. Fayers P, Machin D (2013). *Quality of Life: the assessment, analysis and interpretation of patient-reported outcomes*. 2nd ed. John Wiley & Sons. Chichester.

14. Staquet M, Berzon R, Osoba D et al (1996). Guidelines for reporting results of quality of life assessments in clinical trials. *Qual Life Res*, 5(5):496–502.

15. World Health Organization (2015). World report on ageing and health. *Health Services for the Aged,* 260.

16. Schipper H, Clinch JJ, Olweny CL (1996). *Quality of life studies: Definitions and conceptual issues*. 2nd ed. Lippincott-Raven. New York.

17. Ong SC, Mak B, Myat OA et al (2008). Health-related quality of life in chronic hepatitis B patients. *Hepatology,* 47: 1108–1117.

18. Ha Y, Hwang S, Chon Y et al (2019). Validation of the Liver Disease Quality of Life Instrument 1.0 in Patients with Chronic Hepatitis B: A Prospective Study. *J Clin Med*, 8(5):656.

19. Lam ET, Lam CL, Lai CL et al (2009). Health-related quality of life of Southern Chinese with chronic hepatitis B infection. *Health Qual Life Outcomes*, 7:52.

20. Chao J, Song L, Zhang H et al (2013). Effects of comprehensive intervention on health-related quality of life in patients with chronic hepatitis B in China. *BMC Health Serv Res*, 13:386.

21. Chen MC, Hung HC, Chang HJ et al (2017). Assessment of Educational Needs and Quality of Life of Chronic Hepatitis Patients. *BMC Health Serv Res*,17(1):148.

22. Karacaer Z, Cakir B, Erdem H et al (2016). Quality of life and related factors among chronic hepatitis B-infected patients: a multicenter study, Turkey. *Health Qual Life Outcomes*, 14(1): 153.

23. Lam ET, Lam CL, Lai CL et al (2009). Psychometrics of the chronic liver disease questionnaire for Southern Chinese patients with chronic hepatitis B virus infection. *World J Gastroenterol*, 15(26): 3288–3297.

24. Tan NC, Cheah SL, Teo EK et al (2008). Patients with chronic hepatitis B infection: What is their quality of life? *Singapore Med J*, 49(9): 682–687.

25. Zhou K, Zhang M, Wu Q et al (2013). Reliability, validity and sensitivity of the Chinese (simple) short form 36 health survey version 2 (SF-36v2) in patients with chronic hepatitis B. *J Viral Hepat*, 20(4): e47-55.

26. Patanwala N, Elliot C, Frith J et al (2010). Functional capacity is significantly impaired in primary biliary cirrhosis and related to orthostatic symptoms. *Gut,* 59:A19–20.

27. Newton JL, Pairman J, Sutcliffe K et al (2008). A predictive model for fatigue and its aetiological associations in primary biliary cirrhosis. *Clin Gastroenterol Hepatol*, 6:228–3.

28. Sharif F, Mohebbi S, Tabatabaee HR et al (2005). Effects of psycho-educational intervention on health-related quality of life (QOL) of patients with chronic liver disease referring to Shiraz University of Medical Sciences. *Health Qual Life Outcomes*, 3: 81-86.

29. Moher D, Liberati A, Tetzlaff J et al (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*, 6:e1000097.

30. RAND Corporation (2019). 36-Item Short Form Survey (SF-36). www.rand.org.

31. Ware JE, Snow KK, Kosinski M et al (1993). *SF-36 Health Survey Manual and Interpretation Guide*. New England Medical Center. Boston.

Available at: http://ijph.tums.ac.ir

32. The WHOQOL Group Development of the World Health Organization WHOQOL-BREF quality of life assessment (1998). *Psychol Med,* 28(3):551–558.

33. Von Elm E, Altman DG, Egger M et al (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med,* 85(11): 867–872.

34. Wells GA, Tugwell P, O'Connell D et al (2015). The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *Clin Epidemil,* 2:4-10.

35. Luchini C, Stubbs B, Solmi M et al (2017). Assessing the quality of studies in meta-analysis: advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal,* 5:1–48.

36. Higgins JPT, Green S (2008). *Cochrane handbook for systematic reviews.* Hoboken. Chichester.

37. Cohen J (1992). Statistical power analysis. *Curr Dir Psychol Sci,* 1:98–101.

38. Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med,* 21:1539–1558.

39. Higgins JPT, Thompson SG, Deeks JJ et al (2003). Measuring inconsistency in meta-analyses. *BMJ,* 327:557–560.

40. Xiao J, Chen P, Li XB et al (2012). Survey of patients with chronic hepatitis B to identify factors that influence quality of life. *Zhonghua Gan Zang Bing Za Zhi,* 20(9):649-53.

41. Altindag A, Cadirci D, Sirmatel F (2009). Depression and health related quality of life in non-cirrhotic chronic hepatitis B patients and hepatitis B carriers. *Neurosciences,* 14(1):56-9.

42. Chen P, Zhang F, Shen Y et al (2021). Health-Related Quality of Life and Its Influencing Factors in Patients with Hepatitis B: A Cross-Sectional Assessment in Southeastern China. *Can J Gastroenterol Hepatol,* 7:9937591.

43. Borenstein M, Hedges LV, Higgins JPT et al (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods, 1*(2):97–111.

44. World Health Organization (2015). Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. *World Health Organization,* 1-166.

45. World Health Organization (2016). Combating hepatitis B and C to reach elimination by 2030. *World Health Organization,* 1–16.

46. Mahassadi AK, Team Machekam O, Attia AK (2020). The Impact of Virologic Parameters and Liver Fibrosis on Health-Related Quality of Life in Black African Patients with Chronic Hepatitis B: Results from a High Endemic Area. *Clin Exp Gastroentero,* 13:407-418.

47. Oral B, Gun E, Cetinkaya F (2020). Evaluation of Health-Related Life Quality of Patients with Chronic Hepatitis Admitted to a Medical Faculty Hospital. *Viral Hepatitis Journal,* 26(3):151-157.

48. Bondini S, Kallman J, Dan A et al (2007). Health-related quality of life in patients with chronic hepatitis B. *Liver Int,* 27(8):1119–1125.

49. Daida YG, Boscarino JA, Moorman AC et al (2020). Mental and physical health status among chronic hepatitis B patients. *Qual Life Res,* 29(6):1567-1577.

50. Kim SJ, Han KT, Lee SY et al (2015). Quality of life correlation with socioeconomic status in Korean hepatitis-B patients: a cross sectional study. *Health Qual Life Outcomes,* 13:55.

51. Zhang M, Li Y, Fan Z et al (2021). Assessing health-related quality of life and health utilities in patients with chronic hepatitis B-related diseases in China: a cross-sectional study. *BMJ Open,* 11(9):e047475.

52. Li G, Wang G, Hsu FC et al (2020). Effects of Depression, Anxiety, Stigma, and Disclosure on Health-Related Quality of Life among Chronic Hepatitis B Patients in Dalian, China. *Am J Trop Med Hyg,* 102(5):988-994.

53. Vu TTM, Le TV, Dang AK et al (2019). Socioeconomic Vulnerability to Depressive Symptoms in Patients with Chronic Hepatitis B. *Int J Environ Res Public Health,* 16(2):255.

54. Evon DM, Lin HS, Khalili M et al (2020). Patient-reported outcomes in a large North American cohort living with chronic hepatitis B virus: a cross-sectional analysis. *Aliment Pharmacol Ther,* 51(4):457-468.

55. Woo G, Tomlinson G, Yim C et al (2012). Health state utilities and quality of life in patients with hepatitis B. *Can J Gastroenterol,* 26(7):445–451.