Research Article

Journal of Infectious Diseases (ISSN 2831-8064)

Longitudinal analysis of quality of life in primary lung adenocarcinoma patients with chronic Hepatitis B infection: a time-to-deterioration model.

Lingling Zheng[1#], Maolin Liu[2#], Zishan Chen[3#], Jianfeng Xie[4], Jinman Zhuang[2], Xi Chen[2], Mingqiang Kang[5]*, Fei He[2,6,7]*

1. Department of Public Health, Fujian Medical University Union Hospital, Fuzhou, China.
2. Department of Epidemiology and Health Statistics, School of Public Health, Fujian Medical University, Fuzhou, China.
3. Department of Healthcare, Maternal and Child Health Care Hospital of Fuzhou Second General Hospital, Fuzhou, China.
4. AIDS/STD Prevention and Treatment Institute, Fujian Provincial Center for Disease Control and Prevention, Fuzhou, China.
5. Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China.
6. Fujian Provincial Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, China.
7. Fujian Digital Tumor Data Research Center, Fuzhou, China.

# Contributed equally

***Corresponding author**

Fei He ,
Department of Epidemiology and Health Statistics, School of Public Health, Fujian Medical University, Fuzhou, China..
Email: i.fei.he@fjmu.edu.cn

Mingqiang Kang,
Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China.
Email: kangmingqiang0799@163.com

Received Date : November 05, 2024
Accepted Date : November 06, 2024
Published Date : December 06, 2024

ABSTRACT

Background: Lung cancer is a malignant tumor that poses a serious threat to human health. The health-related quality of life (HRQoL) of patients should be a focus of attention. This study aims to investigate the impact of Hepatitis B virus (HBV) infection on the quality of life of patients with lung adenocarcinoma (LUAD).
Methods: This hospital-based prospective study collected general patient information and HBV infection status through questionnaires and medical record systems. The EORTC QLQ-C30 and QLQ-LC13 questionnaires were used to assess the quality of life at baseline and during follow-up. HRQoL scores were calculated, and deterioration events were identified. Cox regression analysis was employed to evaluate the impact of different HBV infection statuses on HRQoL.
Results: During the follow-up period, the physical functioning deterioration event was the most common on the EORTC QLQ-C30 functional scale, while dyspnea was the most common on the symptom scale. Preoperative HBV infection was associated with a shorter time to deterioration in role functioning (HR=1.910, 95% CI: 1.043-3.498, P=0.036). In the EORTC QLQ-LC13, dyspnea had the highest incidence of deterioration events, followed by coughing. Preoperative HBV infection was associated with a shorter time to deterioration in pain in arm or should (HR=3.427, 95% CI: 1.054-11.141, P=0.041).
Conclusion: HBV infection can adversely affect the quality of life and prognosis of LUAD patients. We hypothesize that HBV infection may influence the occurrence of multiple HRQoL deterioration events in lung adenocarcinoma patients, exacerbating declines in role functioning and pain in arm or should.

Keywords: Hepatitis B virus, Health-related quality of life, lung adenocarcinoma, Time to deterioration.

INTRODUCTION

Lung cancer is one of the leading causes of cancer-related mortality worldwide and has the highest incidence, accounting for 12.4% of all cancer cases. It is currently the leading cause of cancer death, with a mortality rate of 18.7%.[1] Most patients are diagnosed at an advanced stage, missing the optimal window for surgery, resulting in a very low five-year

Journal of Infectious Diseases (ISSN 2831-8064)

survival rate. In China, the overall five-year survival rate for lung cancer patients diagnosed between 2012 and 2015 was only 19.7%.[2] With the continuous improvement in living standards and the increase in screening methods, especially the use of low-dose computed tomography (LDCT) for high-risk populations, many early-stage lung cancer patients can be effectively treated, reducing lung cancer mortality by 20%. [3] The expected ten-year survival rate for patients with stage I lung cancer detected through screening can significantly increase to 88%.[4]

As survival time increases, the health of many cancer survivors is compromised. Recently, researchers have shifted their focus from merely improving cure rates and extending survival time to also enhancing patients' health-related quality of life (HRQoL). HRQoL reflects the positive and negative aspects of a patient's life under the influence of disease or disability, encompassing social, physical, and emotional functions. [5] It is more dynamic and sensitive, making it easier to reflect the effects of disease, treatment methods, and other healthcare measures. HRQoL is a valuable indicator of cancer survival outcomes. Research on the quality of life of lung cancer patients helps provide an overall assessment of the health status of tumor patients and aids in the selection of treatment plans and evaluation of drug efficacy.

HBV infection is a global public health issue. According to the World Health Organization, in 2022, there were 1.2 million new HBV infections worldwide, with 254 million people suffering from chronic hepatitis B (CHB). [6] After HBV infection, the body generates a sustained immune response, often leading to CHB, which can progress to cirrhosis or even liver cancer, severely threatening patients' health. HBV infection can affect lung cancer patients in multiple ways, including further imbalance of T lymphocyte subsets and reduced immune function, accelerating disease progression and shortening survival time. Treatments such as chemotherapy, radiotherapy, targeted drugs, and HBV reactivation can cause liver function damage.[7] Studies have also shown that HBV infection is a risk factor for the prognosis of lung cancer patients.[8]

The time-to-degeneration (TTD) model is a longitudinal time-event analysis method used to evaluate changes in HRQoL over time in cancer patients after treatment. [9] Currently, there are no studies on the relationship between HBV infection and HRQoL in lung cancer patients. In this study, we arm to analyze the relationship between HBV infection status and HRQoL TTD in lung adenocarcinoma (LUAD) patients, providing relevant evidence for the treatment plans of lung cancer patients with HBV infection.

METHODS

Sample Selection

This study selected patients diagnosed with lung adenocarcinoma through fiberoptic bronchoscopy or histological examination, who were hospitalized in the Thoracic Surgery Department of Fujian Medical University Union Hospital, from March 2019 to March 2022. Inclusion criteria: (a) Diagnosed with non-small cell lung cancer with confirmed pathological results. (b) Underwent surgical treatment. (c) Has clear test results for hepatitis B infection. (d) Capable of comprehending and completing the questionnaire, and able to independently sign the informed consent form. Exclusion criteria: (a) Diagnosed with secondary or metastatic lung cancer. (b) History of any other type of cancer. (c) Incapable of clearly understanding or answering the questionnaire. The study protocol was approved by the Ethics Committee of Fujian Medical University, and written informed consent was obtained from all patients before enrollment.

Information collection

A structured questionnaire was designed for this study, and data were collected face-to-face by professionally trained investigators. The questionnaire collected general patient information (age, gender, education level, height, weight), smoking history, and alcohol consumption history. Additionally, quantitative detection data of HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb were collected. Based on the test results, patients were divided into the HBV-positive group with chronic hepatitis B infection and the HBV-negative group without hepatitis B infection. All data collection was completed at the time of patient admission.

Quality of Life Assessment

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30) and the EORTC Lung Cancer Quality of Life Questionnaire (EORTC QLQ-LC13) were utilized to evaluate the quality of life at baseline and during follow-up.

The EORTC QLQ-C30 is a comprehensive questionnaire consisting of 30 items, divided into 5 functional scales, 9 symptom scales, and 1 global health scale.[10] Each item is rated from 1 to 4. The average score for each dimension, referred to as the raw score (RS), is converted to a standardized score (SS) using a linear transformation method, which scales it to a percentage. For functional dimensions and overall quality of life, higher SS values indicate better functioning. For symptom dimensions, higher SS values indicate more severe symptoms and a lower quality of life. The EORTC QLQ-LC13 module includes 13 questions that assess symptoms related to lung cancer, side effects from treatment, and pain medication usage.[11] Higher scores in the QLQ-LC13 indicate a higher level of symptoms.

Journal of Infectious Diseases (ISSN 2831-8064)

Follow-Up

The survival time of patients was defined as the time from pathological diagnosis to the last follow-up date. Patients were followed up every 3-6 months during the first year and annually thereafter. There were three follow-up statuses: (1) patients who died during follow-up, with survival time defined as the time from pathological diagnosis to the date of death; (2) patients lost to follow-up, considered censored data, with survival time defined as the time from pathological diagnosis to the last follow-up date; (3) patients still alive at the end of follow-up, with survival time defined as the time from pathological diagnosis to the end of follow-up.

Time to Deterioration Model

Time to deterioration (TTD) refers to the time from study inclusion to the first clinically significant deterioration in HRQoL. The minimal clinically important difference is the smallest difference in HRQoL scores considered clinically significant, serving as an important indicator of clinical relevance. In this study, TTD refers to the time when a significant deterioration greater than 5 points was first observed, and subsequently, the score did not decrease by less than 5 points compared to the baseline score.

Statistical Analysis

R language was used to calculate HRQoL scores and to count all TTD events in the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. Median and interquartile ranges were used to describe HRQoL scores and TTD. The chi-square test was used to assess differences in sociodemographic and clinical characteristics, and TTD event incidence between patients with different HBV infection statuses. The Kruskal-Wallis test was used to compare baseline HRQoL scores between the two HBV infection statuses. After controlling for confounding factors, univariate and multivariate Cox regression analyses were performed for survival analysis, with results presented as hazard ratios (HR) with 95% confidence intervals (CI). All statistical analyses were conducted using R 3.5.2 and SPSS 20.0.

RESULTS

Baseline Characteristics

A total of 392 participants completed the baseline questionnaire, all pathologically diagnosed with primary LUAD. Among the 392 LUAD patients, 353 completed the first follow-up with the EORTC QLQ-C30 and QLQ-LC13 questionnaires, 9 completed the second follow-up, and 1 completed the third follow-up. All patients included in our analysis (n=353) completed the baseline questionnaire and at least one follow-up with the EORTC QLQ-C30 and QLQ-LC13 questionnaires. No patients died during the follow-up period, with a median follow-up time of 6.7 months. Thirty-nine patients were lost to follow-up (loss to follow-up rate: 9.9%). The sociodemographic and clinical characteristics of LUAD patients in different HBV groups are shown in Table 1. There were no significant differences between the two groups in terms of age, gender, body mass index (BMI), TNM stage, alcohol consumption, and smoking. Baseline HRQoL scores of patients are presented as medians and interquartile ranges in Table 2. There were no significant differences between the two groups in the EORTC QLQ-C30 and QLQ-LC13 scales.

Table 1: Characteristics of study patients in demographics and clinical message at baseline.

Characteristic	n (%)	Groups of HBV (n=353)		χ^2	P
		Negative N=304 n (%)	Positive N=49 n (%)		
Gender				1.362	0.243
Male	146 (41.4)	122 (40.1)	24 (49.0)		
Female	207 (58.6)	182 (59.9)	25 (51.0)		
Age				0.092	0.761
≤60	180 (51.0)	156 (51.3)	24 (49.0)		
>60	173 (49.0)	148 (48.7)	25 (51.0)		
BMI				0.015	0.993
<18.5	8 (2.3)	7 (2.3)	1 (2.0)		
[18.5, 24)	200 (56.8)	172 (56.8)	28 (57.1)		
≥24	144 (40.9)	124 (40.9)	20 (49.8)		
Smoker				0.011	0.918
No	279 (79.0)	240 (78.9)	39 (79.6)		
Yes	74 (21.0)	64 (21.1)	10 (20.4)		
Drinker				<0.001	1.000a
No	343 (97.2)	295 (97.0)	48 (98.0)		

Journal of Infectious Diseases (ISSN 2831-8064)

Yes	10 (2.8)	9 (3.0)	1 (2.0)		
TNM stage				0.010	0.920a
I	336 (95.2)	290 (95.4)	46 (93.9)		
II and above	17 (4.8)	14 (4.6)	3 (6.1)		

a Pearson's Chi-squared test with Yates' continuity correction

Table 2: Baseline of patients QoL scores

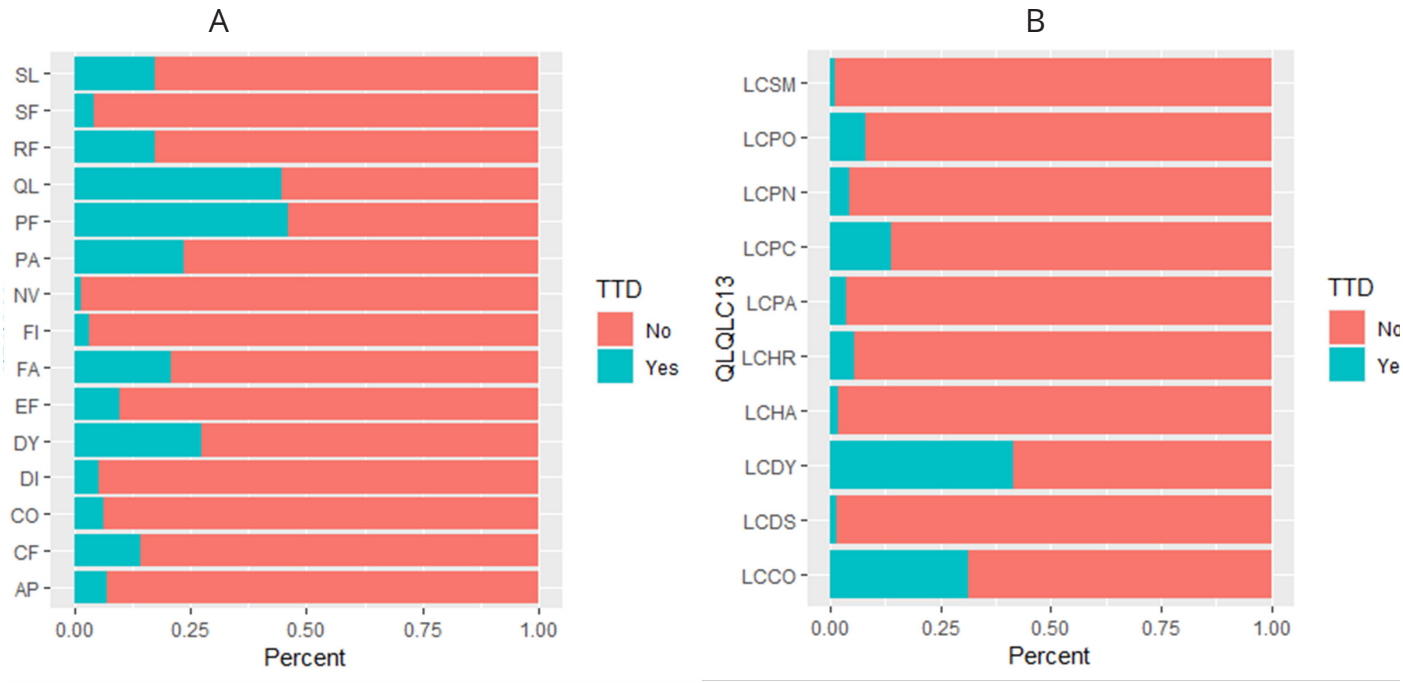
	Groups of HBV (n=353)		W	P
	Negative (M(P25,P75))	Positive (M(P25,P75))		
QLQ-C30				
Global health status (QL)	83.33 (83.33, 100.00)	83.33 (83.33, 100.00)	7416.5	0.960
Functional scales				
Physical functioning (PF)	100.00 (100.00, 100.00)	100.00 (100.00, 100.00)	7596.5	0.748
Role functioning (RF)	100.00 (100.00, 100.00)	100.00 (100.00, 100.00)	7413.0	0.921
Emotional functioning (EF)	100.00 (66.67, 100.00)	100.00 (66.67, 100.00)	7277.0	0.769
Cognitive functioning (CF)	100.00 (100.00, 100.00)	100.00 (100.00, 100.00)	7377.5	0.776
Social functioning (SF)	100.00 (100.00, 100.00)	100.00 (100.00, 100.00)	7420.0	0.923
Symptom scales/items				
Fatigue (FA)	0.00 (0.00, 0.00)	0.00 (0.00, 11.11)	6566.5	0.094
Nausea and vomiting (NV)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7644.0	0.253
Pain (PA)	0.00 (0.00, 16.67)	0.00 (0.00, 16.67)	7333.5	0.827
Dyspnoea (DY)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7101.5	0.433
Insomnia (SL)	0.00 (0.00, 33.33)	0.00 (0.00, 33.33)	7575.5	0.812
Appetite loss (AP)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7234.0	0.421
Constipation (CO)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7569.5	0.641
Diarrhoea (DI)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7239.5	0.336
Financial difficulties (FI)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7186.0	0.301
QLQ-LC13				
Dyspnoea (LC-DY)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7225.5	0.639
Coughing (LC-CO)	0.00 (0.00, 33.33)	0.00 (0.00, 33.33)	7620.5	0.743
Haemoptysis (LC-HA)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7497.0	0.574
Sore mouth (LC-SM)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7497.0	0.574
Dysphagia (LC-DS)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7448.0	1.000
Peripheral neuropathy (LC-PN)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7121.5	0.397
Alopecia (LC-HR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7394.5	0.696
Pain in chest (LC-PC)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7662.0	0.600
Pain in arm or should (LC-PA)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7344.5	0.773
Pain in other parts (LC-PO)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	7810.0	0.346

Time to Deterioration and HRQoL Events

In the functional scales of the EORTC QLQ-C30, physical functioning (PF) deterioration events were the most common during the follow-up period in our cohort, while dyspnoea (DY) was the most common in the QLQ-C30 symptom scales (Figure 1a). In the EORTC QLQ-LC13, dyspnoea (LC-DY) had the highest incidence of TTD events, followed by coughing (LC-CO) (Figure 1b). TTD was calculated using the Kaplan-Meier method, showing a decline in HRQoL over time. The TTD for all scales of the EORTC QLQ-C30 and LC13 are displayed in Supplementary Figures 1 and 2 in the supplementary materials.

Journal of Infectious Diseases (ISSN 2831-8064)

Figure 1: The occurrence of TTD events in EORTC QLQ-C30 (a) and EORTC QLQ-LC13 (b)



Association Between HBV and TTD

As shown in Table 3, the proportion of patients with deterioration in role functioning (RF) in the EORTC QLQ-C30 was significantly higher in the HBV+ group compared to the HBV- group (P=0.0299). The deterioration in pain in arm or should (LC-PA) was also higher in the HBV+ group (P=0.028). HBV infection was used as a categorical variable to explore the relationship between HBV and HRQoL in LUAD patients. In univariate Cox regression analysis, HBV+ was associated with a decrease in HRQoL for role functioning (HR=1.656, 95% CI: 0.912-3.009, P=0.098) and pain in arm or should (HR=3.063, 95% CI: 0.996-9.424, P=0.051). To minimize the impact of potential confounding factors, we adjusted for all baseline variables (including age, gender, BMI, TNM stage, smoking, and alcohol consumption) in multivariate Cox regression analysis. The results were similar to those of the univariate analysis. HBV was associated with shorter time to deterioration in role functioning (HR=1.910, 95% CI: 1.043-3.498, P=0.036) and pain in arm or should (HR=3.427, 95% CI: 1.054-11.141, P=0.041) (Table 4).

Table 3: Comparison of time to deterioration event in different HBV group and univariate cox regression analysis of HBV and time to deterioration.

	Time todeterioration event n(%)		χ^2	P	Time to deterioration M (P25, P75)		HR (95% CI)	P
	Negative	Positive			Negative	Positive		
QLQ-C30								
Global health status (QL)	132 (43.3)	26 (53.1)	1.586	0.208	6.60 (5.77,7.40)	6.64 (5.95,7.49)	1.076 (0.706-1.642)	0.732
Functional scales								
Physical functioning (PF)	138 (45.4)	25 (51.0)	0.537	0.464	6.64 (5.78,7.59)	6.60 (5.72,7.26)	1.045 (0.682-1.602)	0.840
Role functioning (RF)	48 (15.8)	14 (28.6)	4.762	0.029	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.656 (0.912-3.009)	0.098
Emotional functioning (EF)	31 (10.2)	4 (8.2)	0.034	0.854[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.703 (0.248-1.995)	0.508
Cognitive functioning (CF)	42 (13.8)	8 (16.3)	0.219	0.640	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.057 (0.495-2.253)	0.887
Social functioning (SF)	12 (3.9)	3 (6.1)	0.102	0.750[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.214 (0.337-4.368)	0.767
Symptom scales/items								
Fatigue (FA)	64 (21.1)	10 (20.4)	0.011	0.918	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.878 (0.450-1.714)	0.703

Journal of Infectious Diseases (ISSN 2831-8064)

Nausea and vomiting (NV)	6 (2.0)	0 (0.0)		1.000[b]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.038 (0.000-634.138)	0.511
Pain (PA)	69 (22.7)	15 (30.6)	1.458	0.227	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.194 (0.680-2.097)	0.537
Dyspnoea (DY)	81 (26.6)	16 (32.7)	0.764	0.382	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.072 (0.626-1.835)	0.801
Insomnia (SL)	51 (16.8)	11 (22.4)	0.938	0.333	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.145 (0.595-2.205)	0.685
Appetite loss (AP)	22 (7.2)	3 (6.1)	<0.001	1.000[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.672 (0.199-2.266)	0.521
Constipation (CO)	21 (6.9)	1 (2.0)	0.979	0.322[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.251 (0.034-1.867)	0.177
Diarrhoea (DI)	16 (5.3)	3 (6.1)	<0.001	1.000[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.959 (0.278-3.304)	0.947
Financial difficulties (FI)	10 (3.3)	1 (2.0)	<0.001	0.981[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.434 (0.055-3.456)	0.431
QLQ-LC13								
Dyspnoea (LC-DY)	123 (40.5)	23 (46.9)	0.730	0.393	6.64 (5.78,7.54)	6.64 (5.95,7.49)	1.002 (0.641-1.567)	0.994
Coughing (LC-CO)	94 (30.9)	16 (32.7)	0.059	0.808	6.64 (5.78,7.54)	6.64 (5.95,7.49)	0.940 (0.551-1.602)	0.819
Haemoptysis (LC-HA)	5 (1.6)	2 (4.1)		0.252[b]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.642 (0.314-8.582)	0.557
Sore mouth (LC-SM)	2 (0.7)	2 (4.1)		0.094[b]	6.62 (5.78,7.59)	6.64 (5.95,7.49)	4.459 (0.613-32.420)	0.140
Dysphagia (LC-DS)	5 (1.6)	0 (0.0)		1.000[b]	6.62 (5.78,7.59)	6.64 (5.95,7.49)	0.035 (0.000-551.664)	0.497
Peripheral neuropathy (LC-PN)	14 (4.6)	1 (2.0)	0.197	0.657[a]	6.62 (5.78,7.59)	6.64 (5.95,7.49)	0.409 (0.054-3.113)	0.388
Alopecia (LC-HR)	15 (4.9)	5 (10.2)	1.318	0.251[a]	6.64 (5.77,7.59)	6.64 (5.95,7.49)	1.671 (0.590-4.730)	0.334
Pain in chest (LC-PC)	42 (13.8)	7 (14.3)	0.008	0.930	6.64 (5.78,7.59)	6.64 (5.95,7.49)	0.897 (0.402-2.001)	0.790
Pain in arm or should (LC-PA)	8 (2.6)	5 (10.2)	4.854	0.028[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	3.063 (0.996-9.424)	0.051
Pain in other parts (LC-PO)	23 (7.6)	5 (10.2)	0.122	0.727[a]	6.64 (5.78,7.59)	6.64 (5.95,7.49)	1.086 (0.406-2.903)	0.870

a Pearson's Chi-squared test with Yates' continuity correction

b Fisher's exact test

Table 4: Multivariate Cox analysis for time to deterioration event ≥ 5 points.

Items	**HR (95%CI)**	**P**
QLQ-C30		
Role functioning (RF)	1.910 (1.043-3.498)	0.036
QLQ-LC13		
Pain in arm or should (LC-PA)	3.427 (1.054-11.141)	0.041

Adjusted for all baseline variables (including age, gender, BMI, TNM stage, smoking and drinking), boldface means P<0.05

DISCUSSION

This study aimed to investigate the impact of HBV infection on HRQoL in LUAD patients and the association between HBV infection and time to deterioration (TTD) of HRQoL. We found that LUAD patients in the HBV+ group had significantly lower HRQoL in role functioning (RF) and pain in arm or should (LC-PA) compared to the HBV- group. Moreover, HBV infection was an independent risk factor for shorter TTD in RF and LC-PA. These results suggest that HBV infection may adversely affect the quality of life and prognosis of LUAD patients.

HBV infection has a well-established causal relationship with liver cancer. [12] In recent years, its impact on other malignancies has also gained attention. Epidemiological studies have found that HBV infection adversely affects the prognosis and treatment outcomes of lung cancer. [8, 13] The relationship between HBV infection and the occurrence and development of LUAD is complex. On one hand, HBV infection can induce the occurrence of liver cancer and other tumors through mechanisms such as chronic inflammation, oxidative stress, immune suppression, and genetic mutations. [14, 15] On the other hand, HBV infection can also affect tumor treatment response and prognosis by influencing the tumor microenvironment, immune evasion, and drug metabolism. [7]

HRQoL is an important indicator for evaluating the quality of life of cancer patients. It reflects not only the physical, psychological,

and social functions of patients but is also closely related to their prognosis. The EORTC QLQ-C30 and QLQ-LC13 are HRQoL assessment tools specifically designed for lung cancer patients and have been widely used in clinical and research settings. [16] This study utilized these two scales and defined deterioration events and TTD based on changes in patients' HRQoL. TTD is an objective and sensitive indicator that can reflect the dynamic changes in HRQoL and prognosis risk in LUAD patients. [17, 18] Currently, there are few studies on the impact of HBV infection on HRQoL in LUAD patients, and there is a lack of follow-up data and TTD analysis. This study is the first to use the TTD method to evaluate the impact of HBV infection on HRQoL in LUAD patients, finding that TTD in RF and LC-PA was significantly shorter in the HBV+ group, indicating faster deterioration in these aspects of HRQoL.

HBV infection may affect the role functioning of LUAD patients, which refers to the ability and satisfaction of patients in performing different roles in daily life (such as work, family, and social roles). It is an important dimension of HRQoL and an indicator of patients' quality of life and satisfaction. The decline in role functioning due to HBV infection may involve multiple factors, including immune, symptomatic, socioeconomic, and psychological aspects.

Firstly, compared to non-HBV-infected individuals, lung cancer patients with HBV infection may have immune response functions suppressed by various HBV infection-related pathways, leading to T cell exhaustion, B cell dysfunction, and an increase in regulatory cells. [19-21] These immune deficiencies not only allow HBV to persist but may also exacerbate liver damage, increase the risk of liver cancer, reduce treatment efficacy, and increase drug resistance. [22] Additionally, the decline in immune function may increase patients' susceptibility to other pathogens, causing various infectious complications. These complications can increase the physical burden on patients, affecting their work and daily living abilities, thereby reducing their role functioning. Secondly, HBV infection can cause chronic inflammatory responses in the liver, leading to pathological changes such as hepatocyte necrosis, fibrosis, cirrhosis, and liver cancer. [23] These liver damages can result in decreased liver function, affecting the metabolism and excretion of drugs, toxins, and endogenous substances, causing systemic metabolic disorders and endotoxemia. Clinical manifestations such as fatigue, loss of appetite, nausea, vomiting, jaundice, ascites, and encephalopathy may occur, [24] increasing the disease burden and treatment costs for patients, severely impacting their daily activities and social interactions, and leading to a decline in role functioning. In terms of socioeconomic and psychological aspects, HBV infection is a chronic disease that is difficult to cure, bringing symptoms and economic pressure, as well as significant psychological stress and emotional distress to patients. Patients may develop negative psychological states due to their physical condition and economic pressure, [25] and may experience anxiety, depression, and fear due to concerns about their health and future prognosis. Additionally, patients may feel guilt, self-blame, and isolation due to concerns about transmitting the infection to family or friends. [26, 27] These negative emotions can affect patients' self-worth and confidence, causing them to lose motivation and initiative in work or family roles, thereby reducing their role functioning. Therefore, HBV infection may reduce the role functioning of LUAD patients through multiple pathways, causing difficulties and challenges in work, family, and social aspects, and affecting their quality of life and prognosis.

HBV infection affects pain in arm or should in postoperative LUAD patients, which refers to any type or degree of pain or discomfort felt in the chest or back. Pain in arm or should is a common tumor-related pain, mainly caused by tumor invasion of surrounding nerves, blood vessels, bones, and other structures. It can affect patients' daily activities, sleep quality, and emotional state, thereby reducing HRQoL. HBV infection may exacerbate pain in arm or should through the following pathways: First, HBV infection can cause liver damage, leading to complications such as portal hypertension and ascites, [28, 29] increasing upper abdominal pressure, compressing or stretching the brachial plexus, and causing pain in arm or should. Second, HBV infection can induce systemic inflammatory responses, releasing various pro-inflammatory factors such as TNF-α, IL-1β, IL-6, and IFN-γ, [30] stimulating or sensitizing the peripheral and central nervous systems, enhancing the transmission and perception of pain in arm or should. Additionally, due to common immune disorders in HBV infection, [31] patients are more prone to autoimmune arthritis, rheumatoid arthritis, and other joint diseases, [32] leading to joint redness, swelling, stiffness, limited mobility, and severe pain. Pain in arm or should not only affects the HRQoL of lung adenocarcinoma patients but also impacts their treatment compliance and tolerance, thereby affecting their survival time. Treating HBV infection in lung adenocarcinoma patients may help reduce postoperative pain in arm or should, improve their quality of life, and extend their survival time.

This study has the following strengths: (1) It used professional HRQoL assessment tools, ensuring the reliability and validity of the results; (2) It employed the TTD method, which can reflect the dynamic changes in HRQoL, avoiding the limitations of single measurements; (3) It adjusted for multiple potential confounding factors, enhancing the robustness of the results. However, this study also has some limitations: (1) As a single-center study, the sample size was relatively small, which may affect the representativeness and generalizability of the results; (2) The study did not evaluate HBV viral load, genotype, or antiviral treatment, which may affect the accuracy and detail of the results. Future studies

need to conduct larger-scale, longer-term, and more detailed multicenter prospective cohort studies to further verify the impact of HBV infection on HRQoL in LUAD patients and explore its potential mechanisms and clinical significance.

CONCLUSION

This study investigated the impact of HBV infection on HRQoL in LUAD patients and the association between HBV infection and HRQoL deterioration time. We found that LUAD patients in the HBV+ group had significantly lower HRQoL in role functioning and pain in arm or should compared to the HBV- group. Moreover, HBV infection was an independent risk factor for shorter deterioration time in role functioning and pain in arm or should. These results suggest that HBV infection may adversely affect the quality of life and prognosis of LUAD patients. We hypothesize that HBV infection may shorten HRQoL deterioration time by influencing the occurrence and development of lung adenocarcinoma, exacerbating declines in role functioning and pain in arm or should, and reducing treatment efficacy and survival time. Effective antiviral treatment for HBV+ LUAD patients may help improve their HRQoL and prognosis.

Data Availability Statement

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent but are available upon reasonable request from the corresponding author.

Ethics declarations

The study was approved by the Institutional Review Board of Fujian Medical University (Fuzhou, China). All participants signed informed consent forms.

Funding

This work were supported by The Major Health Research Project of Fujian Province (No. 2021ZD01001). We would like to thank Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare.

REFERENCES

1. Bray, F., et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2024. 74(3): p. 229-263.
2. Li, C., et al., Global burden and trends of lung cancer incidence and mortality. Chin Med J (Engl), 2023. 136(13): p. 1583-1590.
3. National Lung Screening Trial Research, T., et al., Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med, 2011. 365(5): p. 395-409.
4. International Early Lung Cancer Action Program, I., et al., Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med, 2006. 355(17): p. 1763-71.
5. Haraldstad, K., et al., A systematic review of quality of life research in medicine and health sciences. Qual Life Res, 2019. 28(10): p. 2641-2650.
6. Organization, W.H. Hepatitis B. 2023 [cited 2023 10.28]; Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
7. Wu, Y.T., et al., Hepatitis B virus reactivation and antiviral prophylaxis during lung cancer chemotherapy: A systematic review and meta-analysis. PLoS One, 2017. 12(6): p. e0179680.
8. Peng, J.W., et al., Hepatitis B Virus Infection Is Associated with Poor Prognosis in Patients with Advanced Non Small Cell Lung Cancer. Asian Pac J Cancer Prev, 2015. 16(13): p. 5285-8.
9. Hamidou, Z., et al., Time to deterioration in quality of life score as a modality of longitudinal analysis in patients with breast cancer. Oncologist, 2011. 16(10): p. 1458-68.
10. Nolte, S., et al., General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer, 2019. 107: p. 153-163.
11. Koller, M., et al., An international study to revise the EORTC questionnaire for assessing quality of life in lung cancer patients. Ann Oncol, 2017. 28(11): p. 2874-2881.
12. El-Serag, H.B., Hepatocellular carcinoma. N Engl J Med, 2011. 365(12): p. 1118-27.
13. Zhang, X., et al., Association of hepatitis B virus infection status with outcomes of non-small cell lung cancer patients undergoing anti-PD-1/PD-L1 therapy. Transl Lung Cancer Res, 2021. 10(7): p. 3191-3202.
14. Zhang, X., H. Zhang, and L. Ye, Effects of hepatitis B virus X protein on the development of liver cancer. J Lab Clin Med, 2006. 147(2): p. 58-66.
15. Schinzari, V., V. Barnaba, and S. Piconese, Chronic

hepatitis B virus and hepatitis C virus infections and cancer: synergy between viral and host factors. Clin Microbiol Infect, 2015. 21(11): p. 969-74.

16. Claassens, L., et al., Health-related quality of life in non-small-cell lung cancer: an update of a systematic review on methodologic issues in randomized controlled trials. J Clin Oncol, 2011. 29(15): p. 2104-20.

17. Zhuang, J., et al., Association between physical activity and health-related quality of life: time to deterioration model analysis in lung adenocarcinoma. J Cancer Surviv, 2023. 17(6): p. 1769-1779.

18. Fiteni, F., et al., Health-related quality of life as an endpoint in oncology phase I trials: a systematic review. BMC Cancer, 2019. 19(1): p. 361.

19. Chen, Y. and Z. Tian, HBV-Induced Immune Imbalance in the Development of HCC. Front Immunol, 2019. 10: p. 2048.

20. Zheng, J.R., Z.L. Wang, and B. Feng, Hepatitis B functional cure and immune response. Front Immunol, 2022. 13: p. 1075916.

21. Nevola, R., et al., HBV Infection and Host Interactions: The Role in Viral Persistence and Oncogenesis. Int J Mol Sci, 2023. 24(8).

22. Liu, Y., S. Maya, and A. Ploss, Animal Models of Hepatitis B Virus Infection-Success, Challenges, and Future Directions. Viruses, 2021. 13(5).

23. Suhail, M., et al., Potential mechanisms of hepatitis B virus induced liver injury. World J Gastroenterol, 2014. 20(35): p. 12462-72.

24. Dong, V., R. Nanchal, and C.J. Karvellas, Pathophysiology of Acute Liver Failure. Nutr Clin Pract, 2020. 35(1): p. 24-29.

25. Daida, Y.G., et al., Mental and physical health status among chronic hepatitis B patients. Qual Life Res, 2020. 29(6): p. 1567-1577.

26. Gupta, R., et al., Psychiatric Morbidity, Fatigue, Stigma and Quality of Life of Patients With Hepatitis B Infection. J Clin Exp Hepatol, 2020. 10(5): p. 429-441.

27. Li, G., et al., 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, 2020. 102(5): p. 988-994.

28. Premkumar, M. and A.C. Anand, Overview of Complications in Cirrhosis. J Clin Exp Hepatol, 2022. 12(4): p. 1150-1174.

29. Iwakiri, Y., Pathophysiology of portal hypertension. Clin Liver Dis, 2014. 18(2): p. 281-91.

30. Vinhaes, C.L., et al., Chronic Hepatitis B Infection Is Associated with Increased Molecular Degree of Inflammatory Perturbation in Peripheral Blood. Viruses, 2020. 12(8).

31. Maya, R., M.E. Gershwin, and Y. Shoenfeld, Hepatitis B virus (HBV) and autoimmune disease. Clin Rev Allergy Immunol, 2008. 34(1): p. 85-102.

32. Canzoni, M., et al., Prevalence of Hepatitis B Virus Markers in Patients with Autoimmune Inflammatory Rheumatic Diseases in Italy. Microorganisms, 2020. 8(11).