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Original Research Article.

Assessment of Alanine Aminotransferase (ALT) Level as a Risk Factor Among Chronic Hepatitis B Infection Patients: A Retrospective Analysis Over a Period of 20 Years

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ABSTRACT

Introduction: Liver conditions such as liver cirrhosis and HCC are caused by CHB progression. ALT; is a marker of hepatocyte inflammation. Repeated periodic testing is recommended for liver evaluation. High results of ALT suggest a significant hepatic inflammation, and several studies show that it could increase the risk of disease progression. In this study, we want to find out if the time period of different stages of CHB infection progression is affected by the level of ALT, by tracing the patients' medical and treatment history for the past 20 years in one of the tertiary governmental hospital in KSA.

Materials and Methods: The present retrospective cohort study consisted analysis of 384 cases of patients who were diagnosed and treated for CHB infection at King Fahad General Hospital (600 bed capacity), Jeddah City. The data was extracted from the medical records dated January1996 to December 2016. Data was evaluated using the Kaplan–Meier method and the log-rank test. The univariate and multivariate Cox regression model were applied to identify independent predictors of failure with the likelihood ratio test as the measure of significance.. P values less than 0.05 were considered as statically significant.

Results: The mean change from enrollment of ALT is (-41.57) with a SD of (131.08) and a median of (-15.1). The P value based on Wilcoxson Signed Rank Test is <0.0001, which means the ALT reduction from enrollment is statistically significant. High ALT level were not significantly prompting the development of the Compensated Cirrhosis (CC) and decompensated cirrhosis (DC).

Conclusion: In contrast to many studies in the literature, high levels of ALT did not correlate to the long-term outcome of HBV infection in this research. Different population characteristics might be the major reason behind those differences in results.

Keywords: Alanine Aminotransferase (ALT); Cirrhosis; Hepatitis; Viral Diseases.

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INTRODUCTION

According to the World Health Organization (WHO) statistics, an estimated 220 million people are living with the hepatitis B virus (HBV) infection. Globally, the prevalence of HBV is high in the Western pacific region where the prevalence rate is 6.2% and the African region (6.1%) of the adult population.

Comparatively, the Eastern Mediterranean region, the approximated prevalence rate of 3.3% while the South-East Asia region and the European region based on the WHO statistics, had a prevalence rate of 2% and 1.6% respectively. In United State of America (USA), the prevalence rate of HBV is at 0.7% of the general population.[1]

Chronic HBV is a high prevalent disease and was considered as the second most common viral disease in KSA. It causes significant morbidity and mortality, and makes a great burden on the economy of health care system. The impact of the resource expenditure on the HBV cases is not yet known because the progression of the disease is not measured. Therefore, studying the outcome of CHB infection will help in developing better management guidelines to be applied in hospitals.[2]

Currently within Kingdom of Saudi Arabia (KSA), the available literature on prevalence of HBV is quite scanty.[2] However, many studies have relied on medical reports to approximate the epidemiology of the virus in KSA.

Before 1990, KSA was considered as one of the most hyperendemic regions in terms of the HBV infections.[3] A survey undertaken in the 1980s indicated that incidence of HBV was 8%.[2] After introducing the national HBV vaccination program for infants on 1999, the incidence of the disease has dropped to 3.3%.[3]

Prevalence of HBV differ among the different regions of KSA, the highest prevalence was found in both Eastern and South-Western regions, 6.7% and 5.4% respectively, and the lowest prevalence of 1.5% was found in the Center of KSA.[3] A recent research study has shown that even the prevalence rate in KSA has been declined, the morbidity and mortality rate of the virus is still considerably high in the country.[3] Whenever a patient progress in HBV disease to decompensated cirrhosis (DC) or HCC, there will be a need to intensive care and costly interventions and treatments, which exaggerate the burden on KSA healthcare system.[2] Liver conditions such as liver cirrhosis and HCC are caused by CHB progression.[4] Conventionally; CHB infection has been noted to progress from chronic stage through the compensated cirrhosis (CC) and eventually to the DC stage and even death.[5] ALT; is a marker of hepatocyte inflammation. Repeated periodic testing is recommended for liver evaluation. High results of ALT suggest a significant hepatic inflammation, and several studies show that it could increase the risk of disease progression.[5] The identification of the progression period of different stages in treated CHB infection patients and evaluation the risk factors and the effects of these factors on the progression of the disease could help in determining treatment guidelines, and forecasting the outcome of long-term prognosis, which has not been studied before in KSA to the limit of our knowledge.[6]

In this research, we want to find out if the time period of different stages of CHB infection progression is affected by the level of ALT, by tracing the patients' medical and treatment history for the past 20 years in one of the tertiary governmental hospital in KSA.

MATERIALS AND METHODS

The present retrospective cohort study consisted analysis of 384 cases of patients who were diagnosed and treated for CHB infection at King Fahad General Hospital (600 bed capacity) which is a tertiary care governmental hospital in Jeddah City. The data was extracted from the medical records dated January 1996 to December 2016. Approval for the research and data collection was obtained from health authority and ethical committee in Jeddah. All data has been kept confidential and it has not been disclosed except for the study purpose. Patient name was concealed. The sample size was determined using sample size calculator for two group-survival analyses, which is developed by a team of University of California- San Francisco (UCSF) medical center researchers[7] and the estimated sample size was 384. We employed a systematic random sample technique. We started the sampling procedure by extracting all chronic HBV labeled medical records files who diagnosed during the last 20 years from the computerized archives system. We had a total of 782 HBV cases in the hospital. We divided the total number of HBV cases by our sample size to get our sample interval (782/384= 2.03). So, 2 was our sample interval. The first case was selected randomly. Then we selected every 2nd case and were listed according to the date of diagnosis (from old to new cases).

The inclusion criteria was labeled patients' medical records according to ICD10 with CHB infections, age of >18 years, Saudi and non-Saudi patients of the previous 20 years were included in the study in Jeddah City. The exclusion criteria was patients who had cirrhosis or HCC at the time of HBV diagnosis or during the first 6 months after HBV has been diagnosed was excluded (because the outcome is already occurred and it is considered as late stage and the treatment will not be effective as if we treat the patient before development of disease complications.[8,9] Patients with low immunity caused by HIV (AIDS), any type of cancers or on chemotherapy, patients with end stage renal disease using immunosuppressive medication were also excluded.

A self-constructed questionnaire validated by 3 different consultants (Gastroenterologist, Epidemiologist, and Clinical Statistician) was used to analyse results. The questionnaire contains the date of diagnosis of chronic HBV, fibrosis, CC, DC, HCC, death) and different factors the affect the progression of the disease. Alanine aminotransferase (ALT) levels were measured twice, at the time of enrollment and at the endpoint. In the present study, it was considered that a subject entered into the risk of failure after his/her birth and he/she entered into study at the time when diagnosed CHB. The person exits from the study either at the event time or censored due to study ends or loss of follow-up. The data is left truncated and right censored. We used STATA software version 13 for data entry, which was entered by the researcher, data management and analysis and we used. SPSS software for descriptive statistics. Variables were entered, coded and a codebook was saved. As survival time data contained censorings, this compares the survival times of the two groups. It was evaluated using the Kaplan–Meier method and the log-rank test. The univariate and multivariate Cox regression model were applied to identify independent predictors of failure with the likelihood ratio test as the measure of significance. The Cox proportional hazards regression analysis was adjusted for possible confounding among several different covariates. P values less than 0.05 were considered as statically significant.

Table 1: Alanine aminotransferase (ALT) level among Chronic Hepatitis B infection

	At Enrolment		At Endpoint		Difference		
Test	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**P value***
ALT	76.8 ± 130.31	45.0	35.2 ± 36.13	25.3	-41.6 ± 131.08	-15.1	**< .0001**

* P value is from Wilcoxson Signed Rank test.

Table 2: Survival Analysis of Time from HBV Diagnosis to Stage of Fibrosis

				Survival Probability			
Strata	**Strata Level**	**Median Survival Time**	**95% Confidence Interval**	**5 Years**	**10 Years**	**15 Years**	**Log-Rank P Value**
Overall *(n=331)*		**6.44**	**5.77 - 8.63**	**0.5952**	**0.3831**	**0.3059**	
High Level ALT: >2*Upper	No	6.24	5.39 - 8.16	0.5851	0.3684	0.3297	0.2094
normal Limit *(n=331)*	Yes	9.82	6.11 - 16.91	0.6650	0.4763	0.2381	

*Not Estimatable

Table 3: COX Regression of ALT level at enrollment to generate hazard ratio.

Risk Factor	Hazard Ratio	Hazard Ratio (95% CI)	P Value
High Level ALT: >2×Upper Normal Range (Yes vs. No)	0.677	0.384 - 1.192	0.1764

NE: Not Estimatable. A P value of <0.05 indicates that the effect is statistically significant; CI: Confidence Interval

Table 4: Survival Analysis of Time from CHB Diagnosis to CC (Kaplan–Meier log-rank test)

		Survival Probability			
Strata	**Strata Level**	**5 Years**	**10 Years**	**15 Years**	**Log-Rank P Value**
Overall (n=349)		***0.9581***	***0.8055***	***0.6929***	
High Level ALT: >2*Upper Normal	**No**	0.9553	0.7942	0.6594	0.3533
Limit (n=349)	**Yes**	0.9762	0.8679	0.8011	

Table 5: Cox Regression of Time from HBV Diagnosis to Compensated Cirrhosis.

Risk Factor	Hazard Ratio	Hazard Ratio (95% CI)	P Value
High Level ALT: >2×Upper Normal Range (Yes vs. No)	0.632	0.207 - 1.933	0.4214

NE: Not Estimatable. A P value of <0.05 indicates that the effect is statistically significant.

Table 6: Impact of high ALT on survival curve from HBV infection to decompensated cirrhosis (Kaplan–Meier Log-rank Test)

		Survival Probability			
Strata	**Strata Level**	**5 Years**	**10 Years**	**15 Years**	**Log-Rank P Value**
High Level ALT: >2*ULN	No	0.9602	0.8552	0.8315	0.3777
(n=333)	Yes	0.9744	0.9338	0.8559	

Table 7: COX regression of risk factors and survival probability from HBV to stage of decompensated cirrhosis

Risk Factor	Hazard Ratio	Hazard Ratio (95% CI)	P Value
High Level ALT: >2×Upper Normal Range (Yes vs. No)	0.370	0.081 - 1.692	0.1997

NE: Not Estimatable. A P value of >0.05 indicates that the effect is statistically insignificant.

RESULTS

In total, 384 subjects with CHB infections, age of >18 years, were enrolled into the study, the mean age at the enrolment is 46.92 years old with a standard deviation (SD) of 13.61 and a median of 47.18. Majority of the CHB patients selected for the study were Saudi (93.8%, n=360). The non-Saudis were represented by (6.3%, n=24) of the respondents. From the study of the 384 patients, it was established that the mean of ALT was (76.8) at the enrolment of the patient. The SD and the median of ALT values were (130.3) and (45.0) respectively. At the endpoint of the patient, ALT mean was (35.2) with a SD of (36.13) and a median of (25.3). The mean change from enrollment of ALT is (-41.57) with a SD of (131.08) and a median of (-15.1). The P value based on Wilcoxson Signed Rank Test is <0.0001, which means the ALT reduction from enrollment is statistically significant (table 1).

To further quantify the extent of the impact of high ALT levels on the development of stage of fibrosis, Cox regression was utilized to generating the hazard ratio. The model was built with the time from diagnosis of CHB to fibrosis as the dependent variables and with high ALT level as the independent variables.

To determine the impact of the high ALT on the development of CC, the survival probability distribution of participants was determined using Kaplan–Meier log-rank test. Table 4 shows that high ALT levels were not significantly prompting the development of the Compensated Cirrhosis (CC).

To further quantify the extent of the impact of a risk factor while adjusting the impact of high ALT on the development of CC, Cox regression was utilized to generating the hazard ratio. The model was built with time from diagnosis of CHB to CC as the dependent variables and high ALT level as the independent variables.

The overall survival probability (probability of not developing decompensated cirrhosis) at 5 years, 10 years, 15 years after diagnosis of CHB is 0.9621, 0.8682, and 0.8281 respectively. As more than 80% participants survived from DC in the end of the study, the median survival time cannot be estimated. High ALT level was not significantly prompting the development of the DC (table 6).

To further quantify the extent of the impact of high ALT on the development of DC, Cox regression was utilized to generating the hazard ratio. The model was built with the time from diagnosis of CHB to DC as the dependent variables and high ALT level as the independent variables. The results from the COX regression are shown in table 7 shows the hazard ratio for the risk factor of high ALT was 0.370 with a 95% confidence internal of 0.081 - 1.692, which means the hazard rate of participants who have high ALT was 0.370 times than the hazard rate of the participants who do not have high ALT, and the P value was 0.1997, >0.05, which mean the difference of the hazard rate is statistically insignificant (table 7).

DISCUSSION

Despite the continuous efforts of the health sectors in KSA, the prevalence rate, as well as the complications rate, of HBV infection remains high. In an attempt to understand thoroughly the nature and the progress of the disease, this research was conducted. Alanine aminotransferase (ALT) activity is an important screening, diagnostic, and monitoring test for liver disease.[10] In the present study, Kaplan-Meier Log-rank test was utilized to explore the impact of ALT levels on CHB progression to more advanced staged. Additionally, Cox regression was used to quantify the extent of impact of high ALT level by calculating the hazards ratio (HR) while eliminating the confounding effect of other possible risk factors. With respect to HBV infection, ALT elevation is often observed in the process of the cytolytic immune response (acute phase) and the following ineffective HBV clearance (chronic phase). ALT activity is a crucial reference indicator in treatment selection and the evaluation of prognosis in patients infected with HBV.[11]

Conry-Cantilena C et al[12] reported that approximately 68% of patients with positive HCV-RNA levels have ALT elevations in asymptomatic blood donors who tested positive for antibodies to the HCV (anti-HCV). Ruhl CE et al[10] examined cut-offs for ALT for their ability to discriminate between persons with positive hepatitis C virus (HCV) RNA and those at low risk for liver injury in the U.S. population and study revealed that Alanine aminotransferase (ALT) is an important test for liver disease, ALT discriminates persons infected with HCV from those at low risk of liver disease, but would be considered elevated in a large proportion of the U.S. population. Liaw et al[13] have described a fluctuation in ALT activity during the process of HBV infection. However, in contrast to Liaw et al, present study did not seem to affect the disease progression in the studied sample. Moreover, the p value based on Wilcoxson Signed Rank Test was <0.0001, which means the ALT reduction from enrollment was statistically significant. Lai et al[14] reported significant fibrosis and inflammation in 37% of patients infected with HBV and persistently normal ALT levels.

Medical files of hepatic patients are often large, commonly divided into a couple of volumes, and full of clinical, laboratory, imaging, and progress, which distributed between the paper and electronic file for the same patient. This made data compiling time-consuming. For instance, the average time spent to gather data for a patient in this research was about 30 minutes.

CONCLUSION

In contrast to many studies in the literature, high levels of ALT did not correlate to the long-term outcome of HBV infection in this research. Different population characteristics might be the major reason behind those differences in results.

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