ORIGINAL PAPER

Progression of liver fibrosis and associated factors among chronic hepatitis B patients at a general hospital in Northern Vietnam

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ABSTRACT

Evaluation of liver fibrosis is necessary to make the therapeutic decision and assess the prognosis of CHB patients. The current study aimed to describe the progression and identify some influencing factors in patients with chronic hepatitis B at a General Hospital in Northern Vietnam. The longitudinal study included 55 eligible subjects diagnosed Hepatitis-B-virus. Dependent variable was the aspartate aminotransferase/platelet ratio index and we collected some demographic variables and disease related and behaviour variables. Bayesian Model Averaging was used to select variables into model. Mixed-effect linear models were used to evaluate the change of the aspartate aminotransferase/platelet ratio index over time and identify related factors. the aspartate aminotransferase/platelet ratio index differences between examinations, age of participants, working status were statistically significant. This pattern indicated that the average the aspartate aminotransferase/platelet ratio index of the population decreased by 0.005 (95% CI=-0.009; –0.001) after each patient's visit, and increased by 0.013 if the patient's age increased by 1 year (95% CI=0.005; 0.0219). For non-working patients, the aspartate aminotransferase/platelet ratio index was lower, coefficient was –0.054 (95% CI=-0.108; 0.001). Other variables such as gender, education level, time for disease detection, drinking tea, alcohol consumption, forgetting to take medicine and the aspartate aminotransferase/platelet ratio index were not significantly different. The study showed that the majority of study subjects had average the aspartate aminotransferase/platelet ratio index, and were relatively well controlled and treated during the study. Age and working status are factors that influence the the aspartate

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aminotransferase/platelet ratio index.

Keywords: liver fibrosis, associated factors, APRI index, mixed-effect model, hepatitis B virus infection

Abbreviations:
APRI: aspartate aminotransferase/platelet ratio index
HBV: hepatitis B virus

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the leading causes of chronic liver diseases, such as hepatocellular carcinoma and cirrhosis. The number of people being infected with HBV over the world is estimated to be more than 400 million, and infection-related complications have become a serious global health issue.[1] Evaluation of liver fibrosis is critical for therapeutic decision-making and prognostic assessment of CHB patients.[2]

Although a variety of noninvasive diagnostic methods, namely aspartate transaminase and platelet ratio index (APRI), Fibrosis-4, Hepascore, Fibroscan, Fibrotouch, Fibroindex and Forn's index, are available,[3] data on the performance of non-invasive tests for liver fibrosis in patients with hepatitis B are limited. Of the common non-invasive methods, the APRI has been recognized as an inexpensive and accurate method with easy performance routinely in patients. There are evidences demonstrating the clinical value of the APRI in staging liver fibrosis and inflammation with various etiologies. The detection of this index has been recommended by World Health Organization (WHO) for evaluation and monitoring of the liver disease status in treatment and prevention of HBV.[4]

Vietnam is one of the countries with a relatively high prevalence of people infected with HBV. Recent studies have found that prevalence of HBV infection (HBsAg+) in the general population ranges from 10% to 20%.[5-7] In order to provide HBV patients with effective treatment, monitoring and following up the patients as well as identifying the factors related to liver fibrosis are of great importance. Nevertheless, research on this issue in Vietnam remains scarce. Phu Tho General Hospital is a large general hospital in the North of Vietnam, in which the management and monitoring system for hepatitis B patients has been well-recognized for its quality. Therefore, we conducted a longitudinal study entitled "Progression of liver fibrosis and associated factors among chronic hepatitis B patients at a General Hospital in Northern Vietnam: Mixed-effect Model" to describe the progression, identify some factors associated with the disease situation in patients with chronic hepatitis B, and thus, assess the effectiveness of HBV treatment.

MATERIALS AND METHODS

Research design and location

A longitudinal study was performed to describe the changes in APRI and identify some related factors among patients diagnosed Hepatitis-B-virus. The majority of data were retrospectively collected from medical records, except some variables obtained by contacting study subjects via telephone.

Sample size and participants

A total of 66 participants were included in this study. They were Hepatitis B patients over

16 years of age who were treated in Phu Tho General Hospital and revisited the hospital on a monthly basis, from January 2017 to August 2018. Patients were treated by NA (Tenofovir 300mg/day) as long as they met the following criteria: 1) experiencing HBeAg-positive chronic hepatitis B with HbsAg-positive more than 6 months and DNA-HBV more than 105 copies/ml, ALT over 2 times higher compared with normal value; or 2) being HBeAg-negative chronic hepatitis B with HbsAg-positive more than 6 months and DNA-HBV more than 104 copies/ml, ALT over 2 times higher compared with normal value. Patients were excluded from this study if they declined to participate, had decompensated cirrhosis with complications of portal hypertension such as ascites, esophageal varices, hepatic encephalopathy, hepatic-renal syndrome; had liver tumors and had BMI ≥ 25 or was pregnant. In addition, the research team ruled out 7 patients who did not complete 20 examinations and 4 patients who did not cooperate during the interview process. Finally, we had 55 patient medical records that met the requirement for data analysis.

Measures

Dependent variable was the aspartate aminotransferase (AST)/platelet ratio index (APRI). The formula for calculation of APRI is

$$APRI = \frac{AST\ level\ (/ULN)}{Platelet\ count\ (10^9/L)} \times 100$$

APRI = {(AST/ULN)/Platelet count} × 100 (ULN = upper limit of normal; 34 U/L for females, 36 U/L for males).

Independent variables

We collected demographic variables including age, gender (male and female), education attainment (primary, secondary, high, college, and university), occupation (worker, farmer, office, business, and others), marital status (single, married, divorce);

Disease related and behaviour variables consist of average working time (per hour), time from Hepatitis B detection (years), alcohol consumption (According to Alcohol Use Disorders Identification Test: score 0–7: low risk, 8–15: risky, 16–19: harmful, 20 or more: high-risk), green tea consumption (every day, a few days per week, a few days per month, not drink tea), treatment adherence (continuous use, do not forget any doses during research period) and treatment time.

Data analysis

Data collection was performed by medical staff at Phu Tho General Hospital.

Patients' information and test results were collected and recorded in medical records when they revisited the Hospital for a health check following an appointment with a physician during 20 months, from Jan 2017 to August 2018. After this period, the medical staff at Phu Tho General Hospital collected related information from the medical records. Besides, the staff also interviewed the patients via telephone to collect some additional information.

Data were entered into the computer using EPI DATA 3.1, and transferred to Stata 14 and R software 3.5.3 for further analysis. Descriptive statistics (number, proportion, mean, standard deviation) were used to describe characteristic of participants and the variation of APRI index.

As this study obtained multiple measurements over time of APRI index per participant (repeated measurement), mixed model analysis was applied to investigate sources of random variability in APRI index. The data of APRI was not normally distributed and tended to reach a gamma distribution, hence we used gamma mixed-effect models to evaluate the difference of

APRI among patients, examinations and identify factors that influenced the APRI index. Bayesian Model Averaging was used to select variables into model.

Research ethics

This study was scientifically and ethically reviewed and approved by the Scientific Panel of the Phu Tho General Hospital at Decision Number 2019/QĐ-BV on December 11, 2018.

RESULTS

Characteristics of the participants

Table 1 General characteristics of the study group

Characteristics	n	%
Age (median, iqr)	50 (23)	
Gender		
Male	40	72.7
Female	15	27.3
Education		
Secondary school	8	14.6
High school	17	30.9
University/College	29	52.7
Postgraduate	1	1.8
Job		
Working	27	49.1
Retired/Non-Working	28	50.9
APRI (median, iqr)	0.42 (0.23)	
Hepatitis B detection years (median, iqr)	7 (4)	
Using tea		
No	26	47.3
Yes	29	52.7
Alcohol consumption (AUDIT) (median, iqr)	12 (4)	
Forget taking medicine during treatment period		
No	43	78.2
Yes	12	21.8
Number of time forgetting taking medicine		
0 time	43	78.2
1 time	5	9.1
2 times	4	7.3
3 times	2	3.6
>3 times	1	1.8

AUDIT: Alcohol Use Disorders Identification Test
IQR: interquartile range

Median age of patients was 50 ± 23 years. Male participants accounted for 73%, while the figure for female was 27%. The percentages of participants having finished high school and university/college were 30.9% and 52.7%, respectively. Patients who were still at work made up 49.1%. More than half of the patients (52.7%) were tea consumers. The number of patients having forgotten to take medicine while receiving treatment occupied 21.8% of. For Alcohol consumption, the median AUDIT Score was 12, and IQR=4.
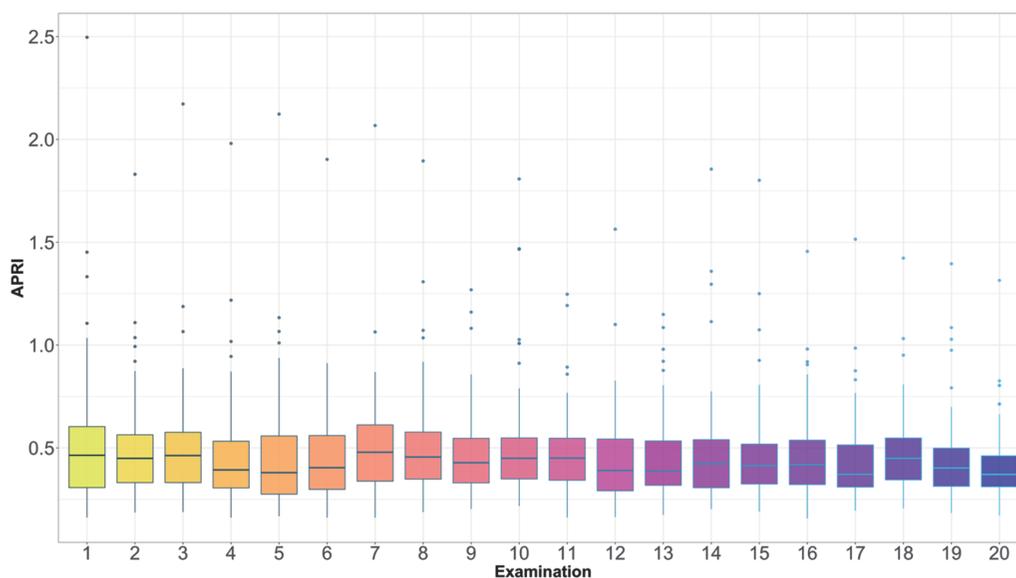
Fig. 1   The variation of average APRI Index of 55 patients over 20 times of examination

The box plot in Figure 1 shows that the APRI of the study subjects fluctuated over the 20 times of examination.
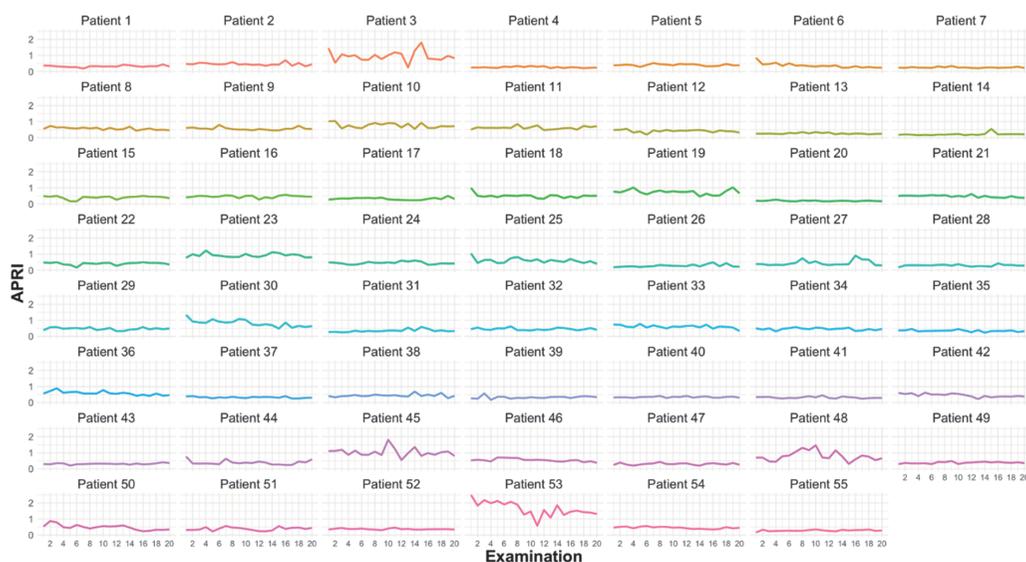
Fig. 2 The variation of APRI Index by 55 par

This Figure 2 illustrates the changing of APRI Index by each participant over 20 times of examination.

Table 2 Factors associated with fibrosis over time, as measured by the APRI score (Mixed-effect model)

Regression coefficients	Coefficient	95% CI	p-value
Fixed effect			
Examination	–0.005	–0.009, –0.001	<0.001
Age	0.013	0.005, 0.0219	<0.001
Gender			
Female	ref	ref	ref
Male	0.011	–0.148, 0.364	0.408
Education level			
Secondary school	ref	ref	ref
High school	–0.180	–0.509, 0.148	0.281
University/College	0.066	–0.206, 0.338	0.635
Postgraduate	–0.201	–0.982, 0.581	0.615
Job			
Working	ref	ref	ref
Non-working	–0.054	–0.108, 0.001	0.05
Time for disease detection (years)	–0.012	–0.030, 0.007	0.218
Drinking tea			
No	ref	ref	ref
Yes	–0.085	–0.350, 0.181	0.533
Forget to take medicine			

No	ref	ref	ref
Yes	–0.002	–0.246, 0.242	0.988
Audit score	0.011	–0.032, 0.054	0.614
Random effect	**Variance**	**95% CI**	
APRI patients variance	0.0001	0.000, 0.002	
Baseline APRI of patients variance	0.1965	0.130, 0.297	

APRI: aspartate aminotransferase (AST)/platelet ratio index
ref: reference group
CI: confidence interval

In the fixed-impact estimation, APRI differences between examinations, age of participants and working status were statistically significant. The average APRI of the population decreased by –0.005 (95% CI=–0.009; –0.001) after each patient's visit, and increased by 0.013 if the patient's age increased by 1 year (95% CI=0.005; 0.0219). For non-working patients, the APRI score was lower, with the coefficient of –0.054 (95% CI=–0.108; 0.001).

DISCUSSION

Liver fibrosis progression

We longitudinally assessed changes in APRI score of 55 HBC patients for 20 months. These patients were relatively old with median (IQR) of 50 (23), and the majority of participants were male. More than half of the subjects graduated from university or obtained higher degrees and were employed. It is notable that approximately 90% of participants had AUDIT score from 10 to 16, which indicates that the subjects had only moderate risk of harm. The percentage of people who were not in compliance with the treatment, i.e. forgeting to tkae drugs at least once during the treatment process, was only 20%, and about 5% of which reported that they forgot taking the medicine 3 times or more.

Each subject was re-examined once a month, which helped to see the changes in the indicators for determining fibrosis. The change of these indicators in the study subjects showed a downward trend over time. In our study, the median APRI index measured by patients was 0.42, IQR=0.23, which is similar to the previous study.[8,9]

Our results showed a statistically significant difference in APRI scores between visits, and the median of APRI decreased slightly after each visit. This suggests that treatment, follow-up, and patient re-examination can be effective in treatment. This might be attributable to the fact that Phu Tho General Hospital is one of the leading medical facilities in Vietnam, and thus, patients are provided with adequate treatment conditions to achieve the high treatment quality. In addition, the study subjects' disease progression was monitored monthly during 20 months, along with close monitoring and consultation from doctors. These efforts can result in participants' good health behaviors, such as following healthy diet, limiting alcohol consumption, giving up smoking, and strictly adhering to the treatment. These factors have also been shown to have influence on the treatment outcome of liver fibrosis in several studies.[10-13]

Factors associated with liver fibrosis progression

In our mixed-effect model, we identified two independent variables associated with the APRI index, which are age and working status. Firstly, the APRI was higher along with the increase

in participants' age. Age is a significant factor that affects the histological activity and stage of liver disease. This finding was consitent with studies in China, Iran and the USA.[14-16] Aging has been demonstrated to increase vulnerability to acute liver injury and susceptibility to the fibrotic response.[14]

In terms of working status, those who retired or were not working had lower APRI scores. This result might be derived from the pressure at work. A study revealed that stress played an important role in the progression and outcome of some serious liver diseases. Psychosocial stress has complicated associations with inflammation and the progression of liver fibrosis during the course of hepatitis,[17] for instance, exaggerate inflammatory and fibrosing change in the cirrhotic liver.[18,19]

Notwithstanding the evidences that confirm the key role of adherence in the effectiveness of CHB treatment,[12,20,21] in our study, forgetting taking medicine did not show an association with the APRI index. This can be explained by the relatively low proportion of people forgetting taking medicine, at 20%, and there were only a few times the patients forgetting taking medicine during treatment. This suggested that health workers in the study location might have done a good job in controlling medication non-adherence.

Highly educated subjects generally had a lower APRI, however, the difference is not statistically significant in our study.

Some studies suggest that alcohol consumption is a risk factor that may accelerate the course of liver fibrosis progression.[13] In this study, we also conducted a survey of AUDIT index to assess the level of alcohol abuse by study subjects. However, there was no difference between AUDIT scores and APRI indicators. This finding is attributable to the fact that all participants had a history of drinking alcohol, and the AUDIT score in our study ranged from 10 to 21. It can thus be concluded that alcohol consumption and a possible moderate alcohol use disorder increased the risk of health problems among participants.

A study from China showed that Green tea intake may reduce the risk of liver disease[22]; however, in our study, no significant difference of APRI between people drinking tea and those did not was found.

Limitations of the study

Our research has some limitations to be acknowledged. Firstly, the number of patients who visited the hospital and had at least 20 follow-up visits during the study period was modest, therefore it may not be representative. Moreover, since the information collected via telephone was self-reported and subjective, recalling errors might occur.

CONCLUSIONS

The majority of participants in this study had average APRI, and their disease situation were relatively well controlled during the study. Age and working status are factors associated with the APRI index.

AUTHOR CONTRIBUTIONS

Luu Ngoc Minh and Nguyen Thi Kim Thuy equally contributed to this work.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

FUNDING STATEMENT

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