European Review for Medical and Pharmacological Sciences 2014; 18: 2332-2336

Serum alanine aminotransferase has limited predictive value for liver disease in chronic hepatitis C

S.A. ARAIN[1], S. YAEESH[2], S.A. MEO[3], Q. JAMAL[4]

[1,4]Department of Pathology, Ziauddin University, Karachi, Pakistan
[1,2]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[3]Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Abstract. – OBJECTIVES: Serum alanine aminotransferase (ALT) levels are sometimes used to identify patients with progressive liver disease in chronic hepatitis C. We assessed the predictive value of serum ALT at various cut-off levels, for the identification of liver disease severity.

PATIENTS AND METHODS: This cross sectional study was carried out at Ziauddin University and Pakistan Medical Research Council, Karachi. Liver biopsy specimens were staged and graded according to METAVIR scoring system. Identification of overall significant liver disease (F2 or A2 and above) was the primary outcome variable. Diagnostic value of ALT was assessed through receiver operating characteristic (ROC) curve analysis.

RESULTS: Out of 98 patients, 42 (43%) had significant fibrosis and 26 (27%) had significant inflammatory activity. Overall significant liver disease was present in 46 (47%) patients of which 13 had widespread fibrosis. Area under the ROC curve for overall significant disease was 0.727 (95% CI 0.627-0.826). A clinically acceptable cut off level to rule out presence of clinically significant disease was found to be ≤ 20 U/L. This low level of ALT was present in 13 (13%) patients. At this cut off, sensitivity was 96%, specificity was 19%, positive predictive value was 49% and negative predictive value was found to be 85%.

CONCLUSIONS: Serum ALT level of ≤ 20 U/L can reliably exclude significant liver disease. Values of ALT above 20U/L do not reliably differentiate between minimal and significant disease.

Key Words:
Chronic hepatitis C, Liver disease, METAVIR grading and staging, Predictive value, Alanine aminotransferase.

Introduction

Around 130-150 million people have hepatitis C viral (HCV) infection globally. It is one of the major health problems all over the world in the form of chronic hepatitis and its complications; end-stage liver disease and hepatocellular carcinoma[1]. Chronic infection with HCV induces injury and inflammation of the liver, which appears to be responsible for the associated increase in serum ALT levels and fibrosis progression[2].

Rate of fibrosis progression varies markedly from person to person. The risk of developing cirrhosis varies from 10% to 20% over a period of 20 years[3]. Therefore, the future course of disease is difficult to predict in an individual. Of the several prognostic variables, inflammatory grade and fibrosis stage appear to be most reliable. Treatment is recommended for the patients with bridging fibrosis and compensated cirrhosis, if liver histology is known[4]. However, liver biopsy, the current gold standard for the estimation of liver histology, is not possible in many cases because of various reasons[5].

Treatment of chronic hepatitis C (CHC) is complex, costly and associated with side effects that are difficult to accept especially in a predominantly asymptomatic population. Furthermore, about half of the patients with genotype 1 and slightly lesser than that in other genotypes, fail to respond to anti-viral therapy[6,7]. The situation warrants a strong need to rationalize the need for therapy.

Many patients (25-30%) with chronic viremia have persistently normal serum ALT values[8]. In addition to that 40% have values below twice the upper limit of normal (ULN)[9]. Furthermore, serum ALT levels have repeatedly been shown to correlate with the degree of fibrosis and rate of its progression[10]. Treatment is sometimes recommended for patients having serum ALT levels above 1.5 to 2 times ULN for six month or more[11].

The purpose of this study is to evaluate the predictive value of serum ALT, at different cut off levels, for the severity of liver disease.

Corresponding Author: Sultan Ayoub Meo, Ph.D; e-mail: sultanmeo@hotmail.com/smeo@ksu.edu.sa

Patients and Methods

It was a cross sectional study conducted at Ziauddin University and Pakistan Medical Research Council, Karachi. PCR proven chronic hepatitis C patients were included in the study. Blood was collected at the time of liver biopsy for the estimation of serum ALT. Patients with HBV co-infection, history of alcohol intake and blood disorders requiring frequent blood transfusions were excluded. A written informed consent was taken. This study was approved by the Ethics Review Committee of Ziauddin University.

A percutaneous liver biopsy was performed with 16-18 gauge modified Menghini aspiration needle (Surecut® TSK, Japan). Biopsy specimens were processed for light microscopic examination. Liver biopsy specimens of only more than 10mm length having at least five portal tracts were included in the study[12].

Histological features of the liver biopsy specimens were analyzed according to METAVIR group scoring system[13,14], by one pathologist (QJ) who was unaware of serum ALT levels. Every specimen was staged for fibrosis on a five-point scale, F0, no fibrosis, F1, portal fibrosis without septa, F2, portal fibrosis with rare septa, F3, numerous septa without cirrhosis and F4, cirrhosis. F0 or F1 were classified as minimal fibrosis and F2 to F4 as significant fibrosis. Furthermore, a fibrosis stage of F3 and above was classified as wide-spread fibrosis. Necroinflammatory activity was graded on a four-point scale, A0, no histological activity, A1, mild activity, A2, moderate activity and A3, severe activity. A0 or A1 were classified as minimal activity and A2 or A3 as significant activity. Necroinflammatory lesions were graded through an algorithm, based on focal lobular inflammation/necrosis and piecemeal necrosis. Portal inflammation was not included in the grading algorithm, but was recorded as prerequisite for the diagnosis of chronic hepatitis. Histological lesions were divided in two overall severity groups, minimal disease ($F < 2$ and $A < 2$) and significant disease ($F \geq 2$ and/or $A \geq 2$). Furthermore, F3 and F4 were analyzed separately as widespread fibrosis[15].

ALT was performed by IFCC standardized UV enzymatic method.[16] Reagents from Roche diagnostics (Cat. No. 10851132) were used according to manufacturer's instructions. An ALT level of ≤ 40 U/L was considered normal.

Statistical analysis was performed using IBM SPSS version 21.0. Results are expressed as mean ± standard deviation (SD) for quantitative variables and frequency and percentages for qualitative variables. Identification of overall significant disease was the primary outcome variable. Receiver operating characteristics curve (ROC) analysis was carried out to evaluate the diagnostic value of ALT for different histological categories. Sensitivity, specificity, positive predictive value and negative predictive value were calculated at different serum levels of ALT.

Results

Initially, 103 patients were included in the study. Five patients were excluded; biopsy of four patients had less than five portal tracts and one biopsy showed granuloma. Table I summarizes baseline demographic and histological features of the 98 patients included in the study. Mean age of the patients was 36.0 ± 10.5, with a range of 20 to 60 year. Fifty two (53%) were male. Mean serum ALT level was 42.2 ± 30.9 U/L. Twenty one patients had no fibrosis (F0), 35 had fibrosis limited to portal tracts (F1), 29 had rare fibrous septa (F2), 10 had numerous septa (F3) and three patients had cirrhosis (F4) on liver biopsy. Necroinflammatory activity was graded as absent (A0) in 32 patients, mild (A1) in 40, moderate (A2) in 20 and severe (A3) in six patients. When classified in different histological categories, 56 had minimal and 42 patients had significant fibrosis. Minimal activity was found in 72 while significant activity was present in 26 patients. Forty six patients were classified as having clinically significant overall disease out of which 13 had widespread fibrosis.

ROC curve analysis for diagnostic value of ALT level, for different histological categories, is shown in Table II. Best diagnostic value of ALT was obtained for significant activity (AUROC; 0.774, 95% CI; 0.672-0.877) and was lowest for significant fibrosis (AUROC; 0.673, 95% CI; 0.567-0.780), with widespread fibrosis being midway (AUROC; 0.731, 95% CI; 0.600-0.863). Area under the curve for overall disease was found to be 0.727 (95% CI; 0.627-0.826, $p = < 0.001$) and is shown in Figure 1.

Diagnostic performance was analyzed further for overall disease category. Specificity, sensitivity, PPV and NPV at different cut-off levels is shown in Table III. Different cut-off levels were chosen to identify the best possible highest ALT

Table I. Baseline features of all patients (n = 98).

Characteristic	Value [Mean ± SD or n (%)]
Age in years	36.0±10.55
Male	52 (53)
ALT (U/L)	42.2±30.9
Fibrosis/Staging	
F0, No fibrosis	21 (21)
F1, Portal fibrosis without septa	35 (36)
F2, Portal fibrosis with rare septa	29 (30)
F3, Numerous septa without cirrhosis	10 (10)
F4, Cirrhosis	03 (03)
Necroinflammation/Grading	
A0, Absent	32 (33)
A1, Mild	40 (41)
A2, Moderate	20 (20)
A3, Severe	06 (06)
Fibrosis (stage)	
Minimal (<F2)	56 (57)
Significant (F2 and above)	42 (43)
Necroinflammation (grade)	
Minimal (<A2)	72 (73)
Significant (A2 and above)	26 (27)
Overall liver disease	
Minimal (<A2F2)	52 (53)
Significant (≥A2 or F2)	46 (47)
Widespread fibrosis	
Absent (<F3)	85 (87)
Present (F3 and F4)	13 (13)

level with clinically acceptable negative predictive value (probability to exclude the presence of significant disease). With an ALT level of ≤ 20 U/L as cut off, a NPV of 85% was obtained that dropped to 65% with a cut off level of ≤ 40 U/L. Overall only 13 out of 98 patients had ALT level of ≤ 20 U/L.

Table II. Diagnostic value of serum ALT for different histopathological categories.

Category	AUROC (95% CI)
Overall liver disease	0.727 (0.627-0.826)
Fibrosis	0.673 (0.567-0.780)
Activity	0.774 (0.672-0.877)
Wide spread fibrosis	0.731 (0.600-0.863)

Abbreviations: AUROC, area under ROC curve, CI, confidence interval.

Discussion

Chronic hepatitis C is one of leading health problems all over the world. Disease burden and mortality are expected to increase with progression of disease in infected population[17]. It seems unlikely that treatment can be offered to every patient. Thus, there is a need to identify patient categories to which antiviral therapy should be offered.

Predictive value of ALT in chronic hepatitis C has been the subject of many studies and is sometimes used to make treatment decisions[11].

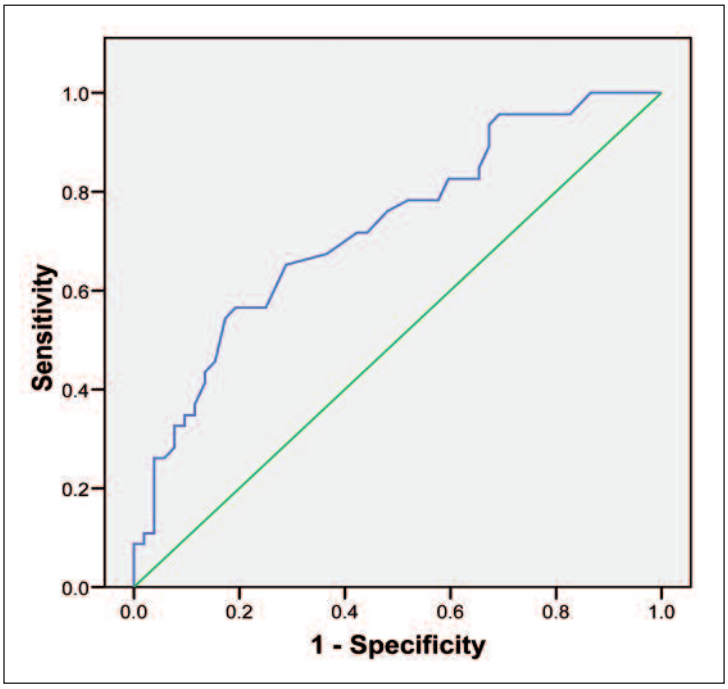

Figure 1. Receiver operating characteristics curve showing the sensitivity and specificity of ALT for the prediction of clinically significant liver disease on biopsy.

Table III. Diagnostic value of ALT at different cut-off levels for overall liver disease

	Cutoff	Sensitivity	Specificity	*PPV	NPV
1/2N	(≤ 20 U/L)	96	19	49	85
N	(≤ 40 U/L)	57	77	67	68
1.5N	(≤ 60 U/L)	26	94	79	61
2N	(≤8 0 U/L)	13	96	74	57

Abbreviations: PPV, positive predictive value, NPV, negative predictive value, N, normal, *PPV and NPV were calculated for a prevalence of 45%. All the values are expressed in percent.

We assessed its value in overall disease category which includes both fibrosis stage and activity grade. This histopathological category is clinically more relevant because necroinflammatory activity grade is equally important in making treatment decisions as is fibrosis stage[18].

PPV and NPV were calculated for a significant disease prevalence of 45%. Prevalence is highly variable; in hospital based studies the prevalence of significant fibrosis remained around 45% and has been used for the evaluation of other noninvasive markers[15,19].

ROC curve analysis showed that area under the curve for the diagnosis of significant overall disease was 0.727. Like ours, in most of the previous studies, although, ALT was found to be associated with degree of fibrosis, its predictive value remained modest with AUROC remaining 0.75 or less with a sensitivity ranging from 61% to 71% and specificity ranging from 66% to 94% at different cutoffs[20,21]. We evaluated the diagnostic performance of ALT at different cut-off levels to identify the maximum ALT level with clinically acceptable negative predictive value, the current clinical use of ALT levels.

In our study, an acceptable negative predictive value of 85% was observed at a level of ≤ 20 U/L. This low ALT level was present in 13 out of 98 of our patients. Two cases of significant disease were wrongly diagnosed (false negative) at this cut off; both had F2 fibrosis without any significant necroinflammation. In our study, ALT predicts absence of clinically significant disease only in 13% of the chronic hepatitis C patients.

One of the limitations in our study might be the selection bias. Most of the patients (91 out of 98) subjected to biopsy were having serum ALT ≤ 80 U/L. Furthermore, majority of the patients with minimal disease had F1 fibrosis and those with significant disease had F2 fibrosis. Fewer patients were classified in extreme stages (F0, F3 or F4). This might have affected the discriminative value of ALT.

Conclusions

Serum ALT levels have a limited clinical application. Use of liver biopsy for the assessment of liver histology is not always possible because of its drawbacks and poor patient compliance. Risk of a significant liver disease, on the other hand, makes treatment decisions difficult in an individual patient. Non-invasive indexes consisting of multiple biomarkers for the prediction of liver disease have been developed and some of them are already in clinical use [22,23]. There is a need for the evaluation of similar non-invasive indexes in this population. An algorithm based on the combined use of demographic characteristics of the patients, serum ALT levels, other non-invasive markers and liver biopsy may help identifying different clinically significant patient categories.

Acknowledgements

The authors are thankful to the Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia for supporting the work through research group project (RGP-VPP 181). We also extend our thanks to Ziauddin University, Karachi and Pakistan Medical and Research Council (PMRC) Islamabad, Pakistan.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Hepatitis C. World Health Organization (WHO). April 2014. Retrieved 2014-05-26.
2) Irshad M, Mankotia DS, Irshad K. An insight into the diagnosis and pathogenesis of hepatitis C virus infection. World J Gastroenterol 2013; 19: 7896-909.
3) Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006; 3: 47-52.
4) Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374.
5) Poynard T, Ratziu V, Bedossa P. Appropriateness of liver biopsy. Can J Gastroenterol 2000; 14: 543-548.

6) Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.

7) Idrees M, Riazuddin S. A study of best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in naive chronic hepatitis C patients. BMC Gastroenterol 2009; 9: 5.

8) Puoti C, Castellacci R, Montagnese F, Zaltron S, Stornaiuolo G, Bergami N, Bellis L, Precone DF, Corvisieri P, Puoti M, Minola E, Gaeta GB. Histological and virological features and follow-up of hepatitis C virus carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). J Hepatol 2002; 37: 117-123.

9) Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, Rodríguez-Torres M, Lardelli P, Blotner S, Zeuzem S. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. Clin Gastroenterol Hepatol 2006; 4: 645-652.

10) Boccato S, Pistis R, Noventa F, Guido M, Benvegnù L, Alberti A. Fibrosis progression in initially mild chronic hepatitis C. J Viral Hepat 2006; 13: 297-302.

11) Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J; Pakistan Society of Gastroenterology. PSG Consensus Statement on management of Hepatitis C Virus Infection--2003. J Pak Med Assoc 2004; 54: 146-150.

12) Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol 2004; 99: 1160-1174.

13) [No authors listed]. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994; 20: 15-20.

14) Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996; 24: 289-293.

15) Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T; MULTIVIRC Group. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001; 357: 1069-1075.

16) Bergmeyer HU, Hørder M, Rej R. International Federation of Clinical Chemistry (IFCC) Scientific Committee, Analytical Section: approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 3. IFCC method for alanine aminotransferase (L-alanine: 2-oxoglutarate aminotransferase, EC 2.6.1.2). J Clin Chem Biochem 1986: 24: 481-489.

17) Deuffic S, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. Hepatology 1999; 29: 1596-1601.

18) Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, Ghanem KG, El-Kamary SS, Sulkowski M, Bass EB. Role of liver biopsy in management of chronic hepatitis C: a systematic review. Hepatology 2002; 36(5 Suppl 1): S161-172.

19) Bhatty SA, Shaikh NA, Akhter SS. Liver histology in hepatitis C virus positive patients with normal and elevated alanine amino transferase levels. J Pak Med Assoc 2009; 59: 832-834.

20) Sanai FM, Benmousa A, Al-Hussaini H, Ashraf S, Alhafi O, Abdo AA, Alameri HF, Akbar HO, Bzeizi KI. Is serum alanine transaminase level a reliable marker of histological disease in chronic hepatitis C infection? Liver Int 2008; 28: 1011-1018.

21) Mirza S, Siddiqui AR, Hamid S, Umar M, Bashir S. Extent of liver inflammation in predicting response to interferon & Ribavirin in chronic hepatitis C patients: a cohort study. BMC Gastroenterol 2012; 12: 71.

22) Arain SA, Jamal Q, Omair A. "Liverscore" is predictive of both liver fibrosis and activity in chronic hepatitis C. World J Gastroenterol 2011; 17: 4607-4613.

23) Shaheen AA, Wan AF, Myers RP. Fibro Test and Fibro Scan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol 2007; 102: 2589-2600.