The Correlation of Serum Transaminase Values with Fibrosis Staging and Necroinflammatory Activity Scores in Chronic Hepatitis

Kronik Hepatitte Serum Transaminaz Değerleri ile Fibrozis Evrelemesi ve Nekroinflamatuar Aktivite Skorlarının İlişkisi

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ABSTRACT Objective: The aim of this study is to compare the necroinflammatory activity score / histological activity index (HAI) and fibrosis score detected in liver biopsies with serum transaminase levels of chronic hepatitis B, C and steatohepatitis. **Material and Methods:** This retrospective study included total of 398 cases whose liver biopsies were performed because increased liver enzyme levels and had the diagnoses of chronic hepatitis B, hepatitis C or steatohepatitis ofter liver biopsy between 2003-2007. The HAI and fibrosis scores of all cases were evaluated according to ISHAK classification criteria and then the results were compared with the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at the time of biopsy. **Results:** When all cases were considered, serum AST values emerged as the most statistically significant variable for hepatic fibrosis (r:0.311; p<0.01). Additionally, there was a correlation between AST values and HAI (r:0.295; p<0.01). On the other hand, serum ALT values did not correlate with (r:0.094; p>0.05) the extent of hepatic fibrosis but correlated weakly with HAI (r:0.242; p<0.01). **Conclusion:** Serum AST level is found to be a significant indicator of histological activity index and fibrosis as well as hepatic damage. These findings suggested that, among other factors, serum AST values should be considered in decisions regarding the need for liver biopsy and treatment in patients with chronic hepatitis.

Key Words: Aspartate aminotransferases; hepatitis, chronic; fibrosis

ÖZET Amaç: Bu çalışmanın amacı kronik hepatit B, hepatit C ve steatohepatitteki serum transaminaz düzeyleri ile karaciğer biyopsisinde tespit edilen nekroinflamatuvar aktivite derecesi / histolojik aktivite indeksi (HAİ) ve fibrozis skorunu karşılaştırmaktır. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya 2003-2007 yılları arasında kronik hepatit B, hepatit C veya yüksek karaciğer enzim seviyeleri nedeniyle karaciğer biyopsisi yapılıp steatohepatit tanısı alan toplam 398 olgu dahil edildi. Tüm olguların HAİ ve fibrozis skorları ISHAK sınıflama kriterlerine göre değerlendirildi ve ardından sonuçlar biyopsi anındaki serum alanin aminotransferaz (ALT) ve aspartat aminotransferaz (AST) düzeyleri ile karşılaştırıldı. **Bulgular:** Tüm olgular göz önüne alındığında, serum AST değerleri hepatik fibrozis için en anlamlı değişken olarak ortaya çıktı (r: 0.311; p <0.01). Ayrıca, AST değerleri ve HAI arasında da bir ilişki vardı (r: 0.295; p <0.01). Diğer taraftan, serum ALT değerleri ile hepatik fibrozisin derecesi arasında korelasyon olmamakla birlikte (r: 0.094; p> 0.05) HAI ile zayıf korelasyon saptandı (r: 0.242; p <0.01). **Sonuç:** Serum AST düzeyinin histolojik aktivite indeksi, fibrozis ve aynı zamanda karaciğer hasarının önemli bir göstergesi olduğu saptamıştır. Bu bulgular diğer faktörlerle birlikte değerlendirildiğinde, serum AST değerlerinin karaciğer biyopsisine karar verme ve kronik hepatitli hastalarda tedavi ihtiyacı konusunda yönlendirici olabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Aspartat aminotransferazlar; hepatit, kronik; fibrozis

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Natural history studies indicate that advanced fibrosis and cirrhosis develop in about 20-40% of patients with chronic hepatitis B or C, and in similar proportion of those with alcoholic or non-alcoholic steatohepatitis (NASH).[1,2] Previous studies demonstrated that mild inflammatory activity and increased fibrosis were associated with increased and decreased response rates to interferon therapy, respectively.[3] Liver biopsy is the gold standard for assessment of hepatic fibrosis. However, it is invasive with possible complications, costly and prone to sampling errors.[1,2,4] The aim of this study was to assess the predictive values of age, gender and serum aminotransferase values on the histological findings in patients with chronic hepatitis.

MATERIAL AND METHODS

This retrospective study was based on data related to patients with hepatitis B, hepatitis C and steatohepatitis who were evaluated in our pathology department between 2003 and 2007. Three hundred and ninety-eight consecutive patients, including 87 cirrhotics, with chronic hepatitis B and C, and NASH were studied. Serum ALT and AST levels and histogical activity index (HAI) were assessed in all liver biopsies. It was verified that none of the cases had other problems which might cause high ALT and AST levels or steatosis in liver (i.e. hereditary metabolical diseases, infectious causes and chronic kidney failure). Liver biopsies were graded for the degree of fibrosis and histological activity

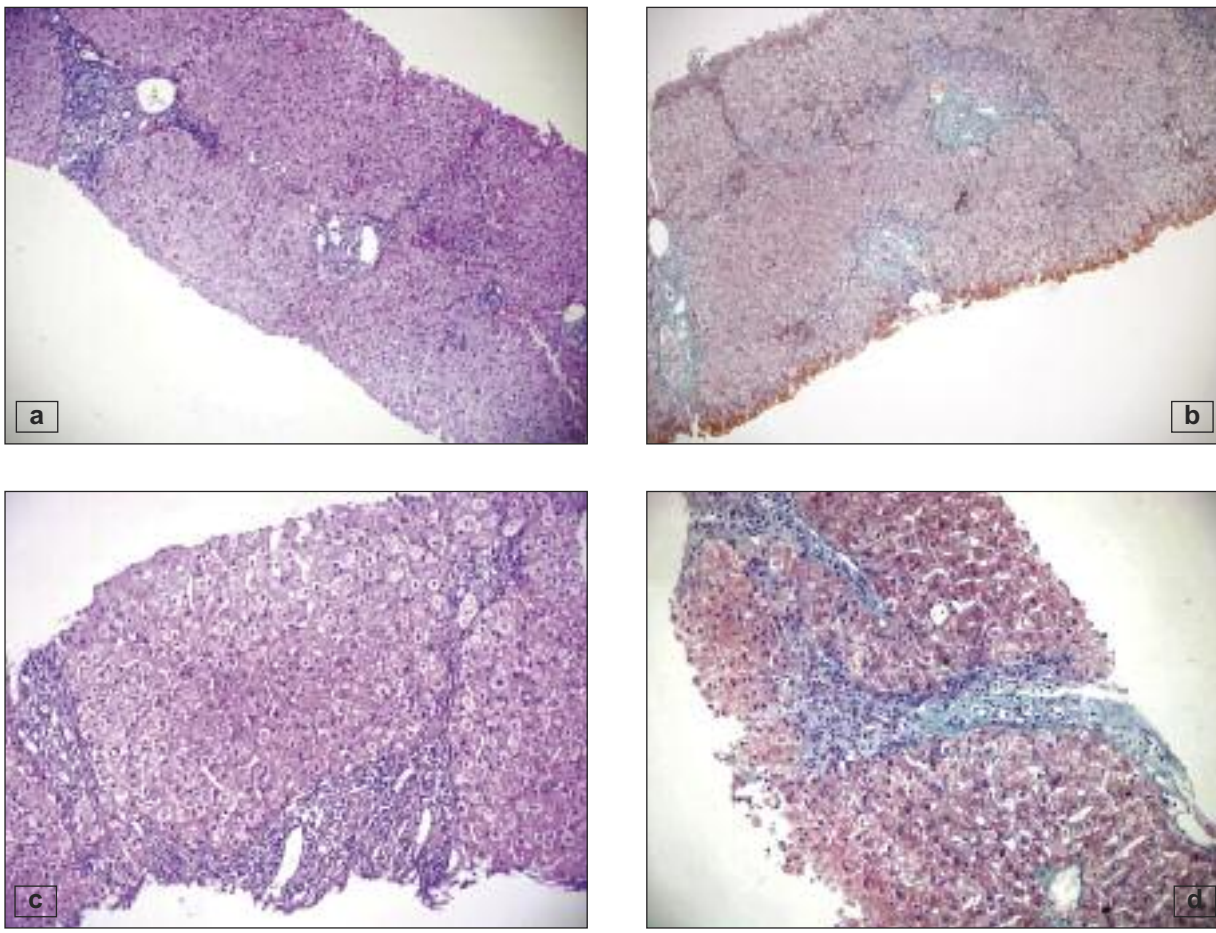


FIGURE 1: a) Chronic hepatitis C with midly inflamed portal tracts as well as one showing lymphocytes aggregate (H&E x100). **b)** The same case with fibrosis score 1 (masson's trichrome stain x100). **c)** Portal inflammation, mild periportal interface hepatitis and ground glass hepatocytes in chronic hepatitis B (H&ex200). **d)** The same case with fibrosis score 3 (masson's trichrome stain x200).

using "modified HAI" of Ishak et al (Figure 1).[5] Steatohepatitis and cirrhosis were also recorded (Figure 2). Cirrhosis was defined by a fibrosis score 5-6 in "modified HAI" classification.

For the statistical evaluation of data, SPSS for Windows 10.0 was used. In statistical analysis, descriptive statistical methods (mean, standard deviation, median, 26-75%) were used. In the comparison of parameters between the groups that did not show normal distribution, Mann Whitney U test was used, and for the evaluation of inter-parameter relationships, Spearsman's correlation analysis was used. Finally, for the comparison of qualitative data, Chi-square test was used with 95% confidence interval ($p<0.05$).

RESULTS

The mean age of patients was 43.11±15.44; 226 patients (56.8%) were males and 87 were cirrhotics. Of those cirrhotics, 18 (20.7%) were HCV positive, 37 (42.5%) were HBV positive and 12 (13.8%) were negative for viral markers.

With Mann Whitney U test and Spearman's correlation analysis, serum AST values emerged as the most important predictive variable of hepatic fibrosis ($r:0.311$; $p<0.01$). A correlation was found between AST values and histological activity ($r:0.295$; $p<0.01$) On the other hand, serum ALT values did not correlate with the extent of hepatic fibrosis ($r:0.094$; $p>0.05$) but correlated weakly with histological activity ($r:0.242$; $p<0.01$) (Figures 3, 4). There were no significant correlations between age, gender or AST/ALT ratio and the extent of histological activity or fibrosis. (Table 1).

In cirrhotics vs noncirrhotics, there was no significant difference for median (25-75%) serum ALT levels [64 (42-115) vs 61 (40-115,5) units/L)], but a significant difference was found for serum AST levels [65 (43-124) vs 46 (32-73,5) units/L] (Figure 5).

When subgroups were considered, serum ALT values did not correlate with the extent of hepatic fibrosis in HCV positive cases ($r: 0.113$; $p> 0.05$). But this result was not significant although there was a positive correlation between ALT values and modified HAI score ($r:0.247$; $p>0.05$)

Additionally, there was a weak and statistically insignificant correlation between AST levels and fibrosis ($r:0.220$; $p>0.05$). On the other hand, a positive correlation was observed between AST values and modified HAI scores ($r:0.340$; $p<0.05$).

Although there was no correlation between ALT levels and fibrosis in HBV positive cases ($r:0.078$; $p>0.05$), a statistically significant positive correlation was observed between modified HAI score and ALT levels ($r:0.347$; $p<0.01$).

There was a statistically significant correlation between AST levels and both fibrosis ($r:0.200$; $p<0.05$) and modified HAI ($r:0.449$; $p<0.0$).

There was a statistically significant correlation between ALT levels and both fibrosis ($r:0,302$; $p<0.01$) and modified HAI ($r:0.413$; $p<0.01$) in steatohepatitis group. Moreover, both fibrosis ($r:0.302$; $p<0.01$) and HAI scores ($r:0.389$; $p<0.01$) were correlated significantly with ALT levels (Table 2).

DISCUSSION

Liver biopsy has been considered as the gold standard for evaluation of necro-inflammatory activity grading and fibrosis staging. Furthermore, it allows identifying suspected or unexpected cofactors and comorbidities. On the other hand, liver biopsy has a number of limitations that have to be taken into account. In addition, liver biopsy may be in fact a risky procedure for some patients, particularly for those with more advanced liver fibrosis. Significant complications of liver biopsy, which are defined as those requiring hospital admission or prolonged hospital stay occur in 1-5% of patients with a mortality rate ranging between 1: 1000 and 1: 10 000.[2] A French survey which interviewed 1177 general practioners concluded that liver biopsy may be refused by up to 59 % of patients with chronic hepatitis C and that 22 % of the physicians share the same concern for this invasive procedure.[6]

Several studies have investigated relationship between the aminotransferase profile and the histological activity or fibrosis. A statistically signifi-

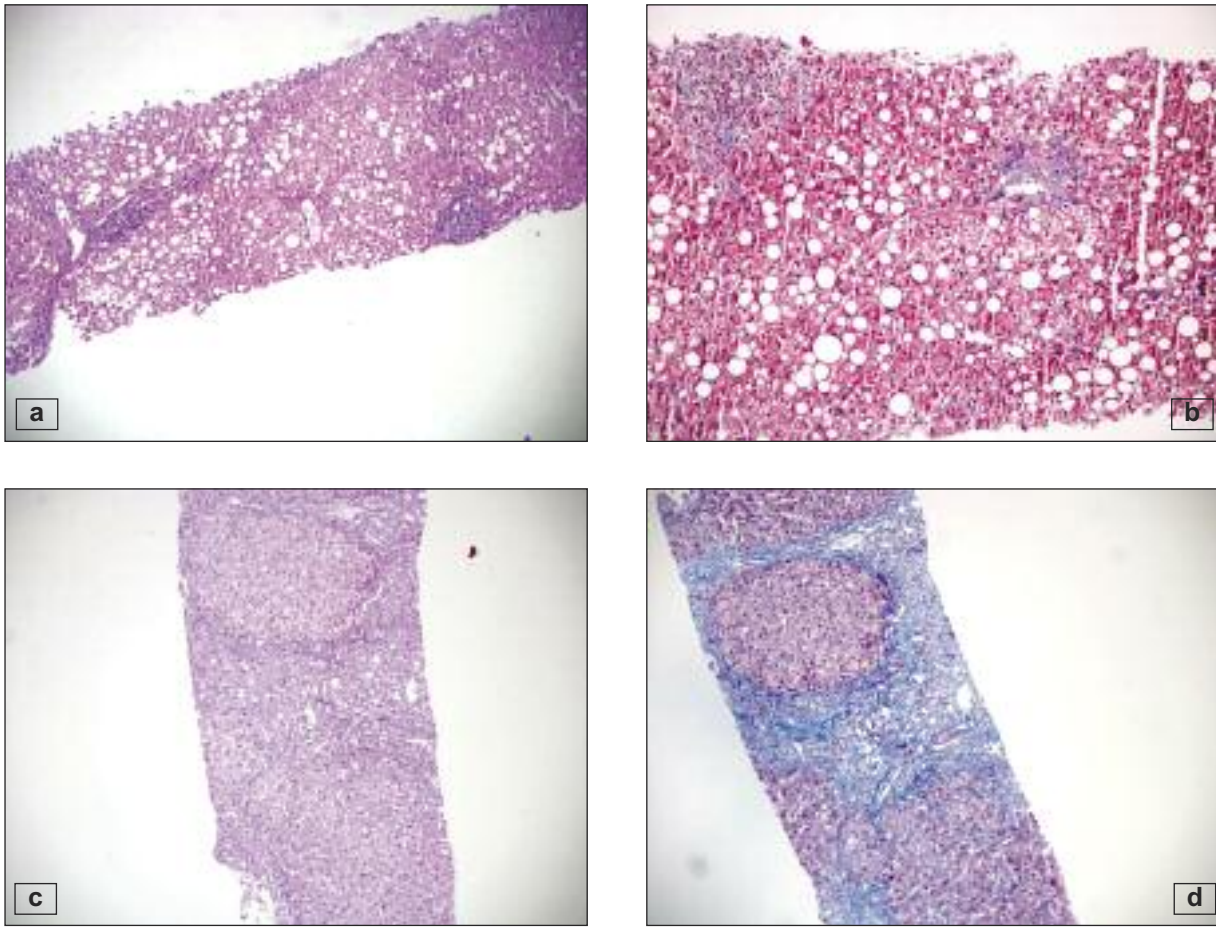


FIGURE 2: a) Steatohepatitis with midly portal lymphocytic inflammation, macrovesicular fatty change (H&E x 40) and centrilobular fibrosis. **b)** masson's trichrome stain x200). **c)** Nodulation of the liver in micronodular cirrhosis (H&E x 100) **d)** Fibrous bands subdividing the liver into regenerative nodules (masson's trichrome stain x100).

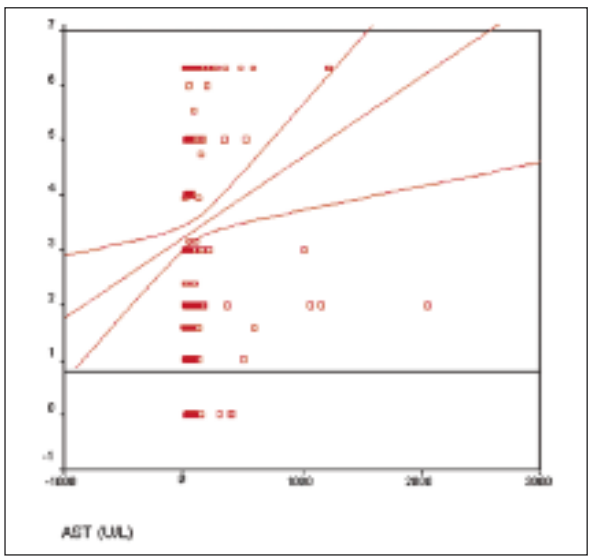


FIGURE 3: Correlation between the extent of fibrosis and AST levels.
AST: Aspartate aminotransferase.

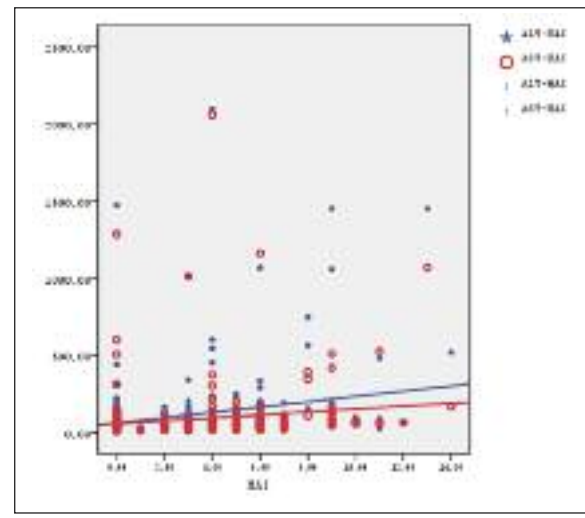
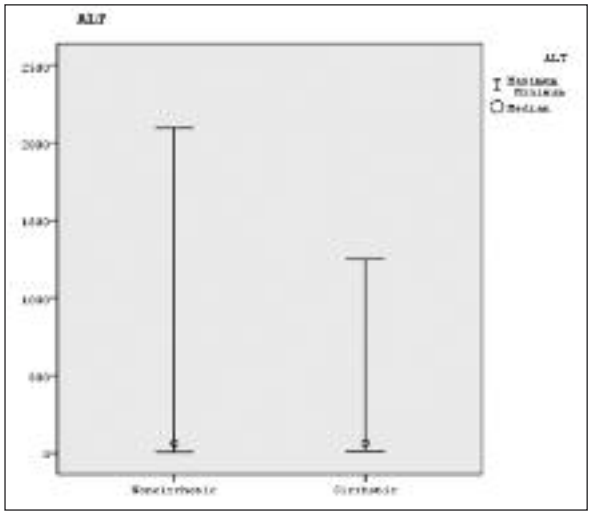


FIGURE 4: Correlation between overall HAI and AST, ALT score.
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
HAI : Histological activity index.



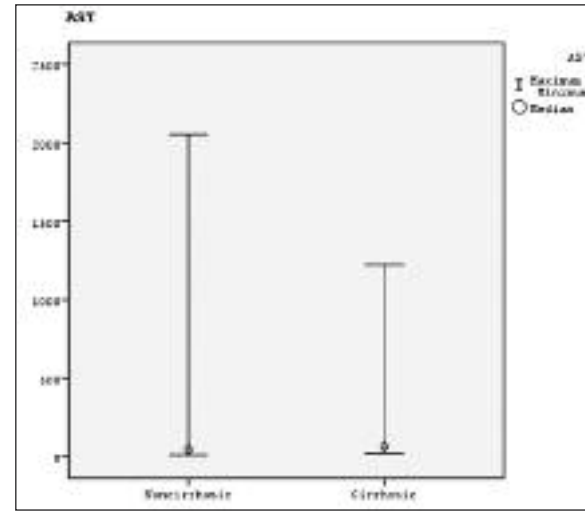


FIGURE 5: Correlation between overall HAI and AST, ALT score.
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
HAI : Histological activity index.

cant correlation was found between biochemical tests and histological findings in some of these studies, though not in others.[7-18]

ALT is considered as a liver-specific enzyme and normally found largely only in the liver. Elevations in serum ALT levels are associated with reversible or irreversible damage to the hepatocyte plasma membrane. Increased serum ALT level has the highest sensitivity (80 % to 100 %) for inflammation, necrosis, vacuolar hepatopathy and primary neoplasia.[19]

Compared with ALT, AST is more sensitive but less specific for detection of hepatic disease. AST is normally found in a diversity of tissues including liver, heart, muscle, kidney, and brain. It is released into serum when any of these tissues is damaged. Therefore, it can not be accepted as a sole indicator of liver injury. Increased serum AST level, in the absence of increased ALT level, indicates an extrahepatic source, most likely muscle injury. However, AST can be found in both cytosol and mitochondria of liver tissue. The cytosolic isozyme is released with reversible or irreversible damage to hepatocyte plasma membranes and its level usually increases as parallel to the levels of ALT. For example, it was shown in rat liver that, ischemic cells with minimal loss of integrity, resulting in the formation of

TABLE 1: Serum transaminase levels and AST/ALT ratios by fibrosis and HAI.

	ALT	AST	AST/ALT ratio
	r, p	r, p	r, p
Fibrosis	0.094; 0.001**	0.080 -0.346.	0.311; 0.001**
Modified HAI	0.242; 0.001**	0.001** 0.071;	0.295; 0.199

** p<0,01 *p<0,05
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
HAI : Histological activity index.

membrane blebs only, do not lose mitochondrial AST.[19] In fact, ischemic liver does not lose mitochondrial AST (mAST) until almost all cytosolic AST (cAST) is lost. Marked elevations in AST activity are suggestive of more severe hepatocelluler damage and irreversible hepatocyte injury with release of mAST stores. Moreover, plasma AST clearance is mainly accomplished by liver sinusoidal cells. Thus, while advancing fibrosis injures the sinusoidal cells, it may result in an additional AST increase.[19-22]

The mechanism of increase in AST levels due to hepatocyte injury is partially understood. Most of the AST in hepatocytes is located in mitochondria, whereas ALT is exclusively located in cytop-

TABLE 2: Relationship between the ALT, AST levels, AST/ALT ratio and fibrosis and modified HAI index in HCV, HBV, and Steatohepatitis

	ALT	AST	AST/ALT ratio
	r, p	r, p	r, p
HCV (+) (n=55)			
Fibrosis	0.113;	0.413	0.220;
	0.107	-0.268;	0.048*
Modified HAI	0.247;	0.07	0.340;
	0.011*	-0.149;	0.278
HBV (+)(n=135)			
Fibrosis	0.078;	0.366	0.200;
	0.020*	-0.132;	0.128
Modified HAI	0.347;	0.001**	0.449;
	0.001**	-0.136;	0.117
STEATOHEPATITIS(n=89)			
Fibrosis	0.302;	0.004**	0.515;
	0.001**	-0.269;	0.011*
Modified HAI	0.413;	0.001**	0.389;
	0.001**	0.053;	0.624

*p<0,05 **P<0,01
AST: Aspartate aminotransferase.
ALT: Alanine aminotransferase.
HAI : Histological activity index.

lasm. AST is released from the hepatocyte mitochondrial AST compartments as a consequence of more severe hepatocellular damage. Moreover, the fact that the plasma clearance of AST is modulated by sinusoidal liver cells and that the development of fibrosis or cirrhosis can provoke impairment in sinusoidal function may result in an additional AST increase. It is possible that the evolution of liver damage is accompanied by a progressive increase in AST release only in the presence of severe fibrosis or cirrhosis.[20-22]

Serum aminotransferase level is determined both by the amount of aminotransferases released by hepatocytes and by plasma clearance.[4,20] It is an indirect marker of hepatocellular damage and fibrosis. Determining serum aminotransferase activity is a simple, economical and immediate option. On the other hand, numerous studies conducted showed that its accuracy was higly variable.[3,4,7-18]

In our study, the only significant correlation was found between serum AST levels and HAI in hepatitis C. On the other hand, in hepatitis B, serum AST levels showed correlation both with fibrosis and HAI. Furthermore, a positive correlation was also seen between serum ALT levels and HAI in hepatitis B cases. In steatohepatitis cases, both AST and ALT levels showed significant correlations with fibrosis degree as well as HAI index. When all cases were considered, serum AST values emerged as the most important predictive variable for hepatic fibrosis. A significant correlation between AST values and histological activity was found. In addition, our study suggests that AST values may correlate with histological activity, extending to hepatic fibrosis.

CONCLUSION

In conclusion, our results demonstrated a correlation between the histological parameters and aminotransferase values statistically, and a stronger correlation between the AST values and fibrosis. Therefore, our study suggested that serum AST values correlated with histological parameters of disease severity. In clinical practice, our findings support that use of AST profile is a useful, noninvasive marker of liver damage progression.

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