

Clinical characteristics and mechanism of liver damage in patients with severe acute respiratory syndrome

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BACKGROUND: Abnormal liver function was found in patients with severe acute respiratory syndrome (SARS). This study was undertaken to explore the clinical characteristics and mechanisms of liver damage.

METHODS: The serial laboratory data of liver function test and hepatic histological examination from 168 patients with SARS were retrospectively analyzed.

RESULTS: The abnormalities of serum alanine aminotransferase (ALT) were 52.5%, 71.8%, 85.7% and 85.2%. The average levels of ALT of the patients were 56.07 ± 51.57 U/L, 86.46 ± 69.93 U/L, 106.69 ± 102.50 U/L and 111.32 ± 160.24 U/L, and the average levels of serum albumin were 37.25 ± 5.37 g/L, 35.82 ± 4.74 g/L, 34.49 ± 5.04 g/L, and 34.26 ± 4.70 g/L, at the day of admission, the first week, second week, and third week after hospitalization, respectively. Significant correlation was not shown among liver damage, blood oxygen saturation (SaO₂), degree of fever, and immune functional disorder in this study. Hepatic histological examination of 4 patients demonstrated that non-specific inflammation existed in the liver.

CONCLUSIONS: Liver damage of patients with SARS usually occurs in the early stage of the disease with a high occurrence rate and a prolonged profile, which can be characterized by early, obvious decrease of albumin levels and slightly abnormal levels of ALT. The liver damage induced by SARS seems to be caused by SARS virus directly rather than by low SaO₂ or high fever. Hepatotoxic drugs may play a role in increasing the severity of liver damage or prolonging the time of liver function recovery.

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KEY WORDS: severe acute respiratory syndrome;
liver damage;
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Introduction

Severe acute respiratory syndrome (SARS) is an infectious disease of humans, which has never been seen before 2002. Our understanding of this disease is still very limited. Clinical characteristics of SARS include fever, dry cough, persistent difficulty in breathing, and severe respiratory failure. Though the respiratory symptoms are the most predominant, most patients have concurrent liver damage. In this study, we studied retrospectively the clinical characteristics of liver damage in 168 patients with SARS who had been hospitalized from February 2003 to March 2003 and the results of serial liver function tests and pathological examinations of liver tissues from 4 SARS patients were evaluated in an attempt to explore the mechanisms of liver damage.

Methods

Patients

Following the *Guidelines for the Diagnosis and Treatment of SARS*, which was issued by the Center for Disease Control of the Ministry of Health, China,^[1] we treated a total of 168 patients with SARS, including 96 women and 72 men from February 2 to March 20, 2003. Their average age was 42.8 ± 18.6 years.

Clinical characteristics

The average time from onset of the disease to hospitalization was 4.4 ± 2.1 days. All the patients had fever and changes in chest X-ray films. The average recovery time from fever was 7.4 ± 4.1 days and that for clearance of lung opacities was 11.9 ± 3.57 days. Ninety of the 168 patients were subjected to test of hepatitis B virus. Twelve patients were HBsAg positive (13.3%) and 5 were HBeAg positive. In the 168 patients, 77 (45%) were treated with antibiotics for 2-3 days before hospitalization. Quinolones and macrolides including ofloxacin, roxithromycin were the commonest drugs used.

Liver function tests and oxygen saturation

During hospitalization, liver function tests relating to total bilirubin (TBil), albumin (Alb), globulin (Glb), albumin: globulin ratio (A/G), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were performed once a week including the first day of hospitalization. Oxygen saturation (SaO₂) was measured as or when required.

Pathological examination of the liver

Samples were collected by needle aspiration, fixed in 10% formalin, paraffinized, sliced to 5 micron thickness, stained with hematoxylin and eosin, and examined under a light microscope.

Use of antibiotics

According to the *Guidelines*, quinolones, macrolides and tetracycline were used for the suspected patients for 5-7 days (ciprofloxacin 0.8 g/day orally or azithromycin 0.1-0.2 g/day intravenously or doxycycline 0.2 g/day orally).

Statistical analysis

The SPSS 6.0 software was used to perform the chi-square test, paired *t* test and regression analysis.

Results

Correlation of abnormal biochemical indices of liver function with disease course

At the time of hospitalization, the percentage of patients with abnormal ALT was 52.5%, which increased to an average of 70% assessed on the values recorded at different time points (Table 1). There was a significant difference between the time of hospitalization and the point time of testing, suggesting that the respiratory symptoms were always accompanied with liver damage.

Correlation of average biochemical indices of liver function with disease course

The level of serum albumin at the first week of hospitalization was low apparently and continued to decrease at the 2nd and 3rd week. The average level of serum albumin for the 3 weeks was significantly different from that at hospitalization. The level of ALT was also increased moderately during the period of hospitalization, but AST level appeared to be slightly abnormal. The average level of serum total bilirubin was within the normal range. Nevertheless, the low serum albumin levels could not be correlated with the other indices (Table 2).

Comparison of incidence of high fever (> 39 °C) with rate of abnormal ALT levels

The percentage of patients with high fever decreased rapidly with the prolonging of the disease. But

Table 1. The correlation between abnormalities of biochemical levels of liver function and disease course (%)

	ALT	AST	Alb	A/G	Glb
W ₀	52.5	41.0	25.6	78.0	7.3
W ₁	71.8 *	53.6	32.3	90.8	16.9
W ₂	85.7 *	46.5	39.0	90.2	9.8
W ₃	85.2	45.0	52.6	94.7	15.8

W₀: the day of hospitalization; W₁: week 1 of hospitalization. *: as compared to W₀ levels; $\chi^2=7.398, P<0.01$; $\chi^2=14.540, P<0.01$, respectively.

Table 2. Average biochemical levels of liver function and disease course (%)

	ALT	AST	Alb	A/G	TBil
W ₀	56.07±51.57	47.42±43.14	37.25±5.37	1.28±0.27	9.81±4.80
W ₁	86.46±69.93 *	57.36±47.41	35.82±4.74▲	1.20±0.28	10.41±6.68
W ₂	106.69±102.50 *	49.33±33.17	34.49±5.04▲	1.16±0.25	9.44±4.68
W ₃	111.32±160.24	48.95±45.45	34.26±4.70	1.16±0.26	10.41±6.18

*: compared to W₀, $t=4.936, P<0.01$; $t=2.97, P<0.01$, respectively; ▲: compared to W₀, $t=2.705, P<0.01$; $t=2.326, P<0.01$, respectively.

Table 3. Comparison of high fever incidence with abnormal ALT levels (%)

Variables	W ₀	W ₁	W ₂	W ₃
High fever	42.4	16.9	5.4	0.6
Abnormal ALT	52.5	71.8	85.7	85.2

Table 4. Comparison of oxygen saturation with average level of ALT

Variables	W ₀	W ₁	W ₂	W ₃
SaO ₂ (%)	86.55±18.33	92.34±12.75	91.37±13.08	92.58±11.51
ALT level(U/L)	56.07±51.57	86.46±69.93	106.69±102.50	111.32±160.24

The analysis of correlation between increased ALT levels and decreased SaO₂, $r=-0.44, P>0.05$, $r=0.11, P>0.05$, $r=0.079, P>0.05$ and $r=0.52, P>0.05$, at the time of hospitalization and at the 1st, 2nd and 3rd week after hospitalization, respectively.

the abnormal level of ATL did not decrease. No correlation of fever with abnormal ATL level was observed, suggesting that high fever is not the direct cause of liver damage (Table 3).

Comparison of oxygen saturation with average value of ALT

The correlation of the levels of oxygen saturation with ALT levels at different time points was not significantly different. When the level of SaO₂ was low, high ALT levels suggested that low oxygen saturation is not the cause of liver damage (Table 4).

Results of histopathological examination of liver tissues

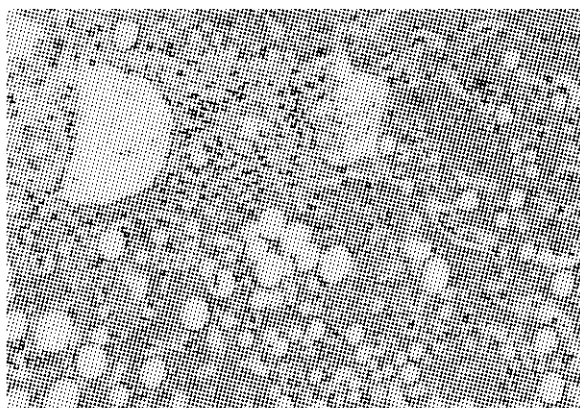


Fig. 1. A 64-year-old woman. Hydropic degeneration, generalized steatosis and slight canalicular cholestasis. Multiple areas of spotty or focal necrosis in parenchyma, with no enlarged portal tracts and no interface hepatitis (HE, original magnification $\times 100$).

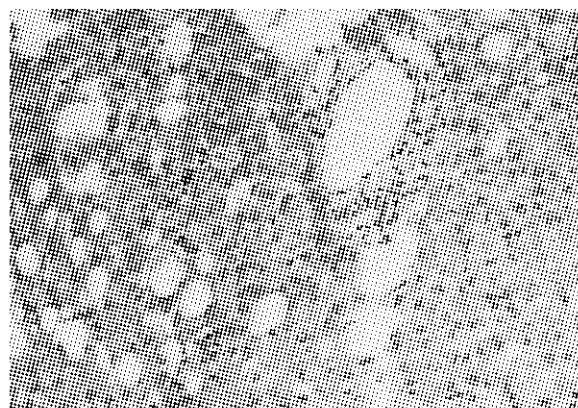


Fig. 2. A 41-year-old man. Hydropic degeneration, generalized steatosis and few areas of spotty or focal necrosis in parenchyma, with no enlarged portal tracts and no interface hepatitis (HE, original magnification $\times 100$).

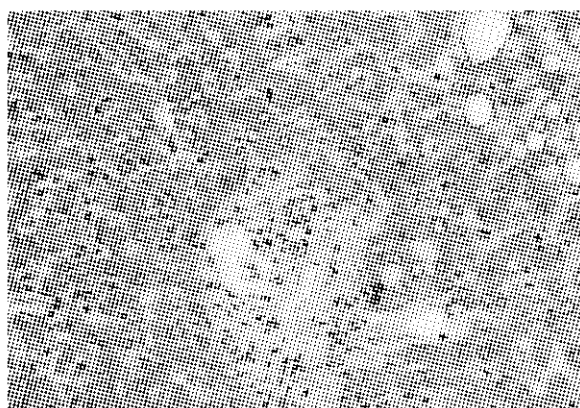


Fig. 3. A 69-year-old woman. Steatosis and acidophilic degeneration with few areas of spotty or focal necrosis in parenchyma, but no enlarged portal tracts and interface hepatitis (HE, original magnification $\times 100$).

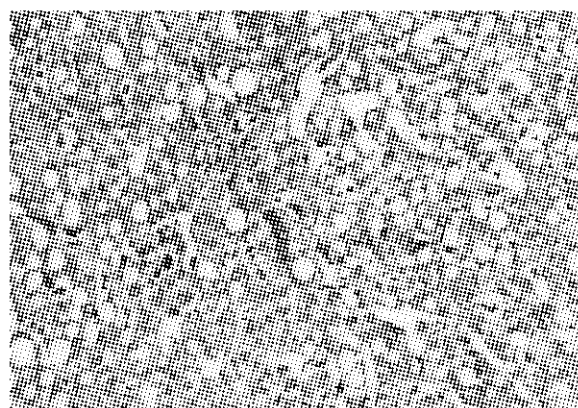


Fig. 4. A 72-year-old woman. Generalized steatosis with canalicular cholestasis and few enlarged portal tracts and fibrotic tissue (HE, original magnification $\times 100$).

Pathological results of liver tissues showed hydropic degeneration and steatosis in liver cells as well as in some patchy and focal necrotic areas. Enlarged portal tract and interface hepatitis were not observed (Figs. 1-4).

Discussion

The first case of SARS was found in November 2002 in a small town in Guangdong province, China, and the disease soon spread in this province. The disease is characterized by such typical clinical features as severe and acute lung damage, thus named SARS.^[2] As a new disease, it has still not been well understood. Current research has found that a new strain of coronavirus may be the etiopathological agent.^[3] Since multiple organs can be the targets of coronaviruses,^[4] it is essential to examine the functions of other organs besides the lung in the study of the disease.

In this study, liver function tests of the 168 SARS patients showed that SARS-related liver damage took place early with a high occurrence rate in the course of the disease. At the time of hospitalization, 52.5% patients showed abnormal ALT levels. The percentage consistently increased in the following 3 weeks. The percentage of patients with abnormal ALT levels reached 85.7% in the second week and maintained at that level even at the end of the third week. These data suggest that respiratory symptoms can be accompanied with liver damage throughout the course of the disease. Biochemical indices of liver function also demonstrate that the major characteristic of SARS-related liver damage is the lowered levels of serum albumin. The level is decreased in early stage of the disease, and continues to decrease throughout the course of the disease. The decreased serum globulin level may be one of the causes for pulmonary edema and worsening of respiratory symptoms. It is

not correlated with the degree of liver damage.

The liver was usually not damaged badly in this group. Observation for a 3-week period in this study showed that the level of total bilirubin was within the normal range. The slightly increased levels of AST were indicated mild damage to the liver tissues. Histologically the liver tissues from 4 patients revealed multiple localized, dotted areas of necrosis with some inflammatory exudates in hepatocytes. We consider that the type of inflammation is non-specific and the result is correlated with the results of liver function tests. Since liver damage is mild, most patients do not show typical symptoms of hepatic failure. In this study, the 12 patients who were HBsAg positive did not show any serious damage to the liver. This suggests that hepatitis B virus does not influence or enhance the damage caused by SARS virus.

The mechanism for SARS-related liver damage is not completely clear. The data obtained in this study may provide some valuable information about it. Liver damage is common in many diseases and can be induced by different factors. The existence of high fever associated with low oxygen saturation may cause liver damage to some extent. The data of our study, however, have clearly demonstrated that there is a slight association between liver damage, high fever and low oxygen saturation. The percentage of patients with high fever was 5.4%, while 85.7% patients in the same group were complicated by liver damage during the second week. The correlation of fever with liver damage was evident at the third week (Table 3). Although prolonged abnormal levels of ALT were associated with low oxygen saturation during the same period, this correlation was not statistically significant (Table 4). The correlation coefficient (r) for the increased level of ALT and decreased level of oxygen saturation was -0.44, 0.11, 0.079 and 0.52 before hospitalization, and at the 1st week, 2nd week and 3rd week after hospitalization, respectively. These data suggested that high fever and oxygen saturation may not be the direct cause of liver damage.

Hepatotoxic drugs are one of the commonest causes of liver damage. Before and during hospitalization, most of the SARS patients of this group were treated with antibiotics known for their potential to cause liver damage including steatosis, ballooning degeneration, spotty and focal necrosis.^[5] These typical morphological changes were observed in the 4 SARS patients in this study. Nevertheless, they were not the direct cause of SARS-related liver damage since 52.5% of the patients had abnormal results of liver function tests at the time of hospitalization. Drugs usually doesn't cause hepatitis early,

but they may increase the severity of liver damage or prolong the recovery of the liver.

The dysfunction of the immune system is another factor causing liver damage. In this study, we did not find any evidence of association between dysfunction of the immune system and liver damage. Liver damage appeared early and the levels of globulin were unchanged (Table 1), suggesting that liver damage is not related to the dysfunction of the immune system in SARS patients. We speculate that liver damage in SARS patients may be caused by the virus itself and the liver might be a direct target of the virus. It has been reported that the coronavirus causes cellular damage,^[4] which is consistent with our clinical findings.

In conclusion, SARS-related liver damage takes place early with a high rate, which can be characterized by early, obviously decreased albumin levels and slightly, moderately decreased abnormal ALT levels. These features coexist with respiratory symptoms throughout the course of the disease. In most patients, there is slight non-specific inflammation in the liver, which is not related to hepatitis B virus infection. Our data suggest that the liver may be a direct target for the SARS virus, while the lowered level of globulin because of liver damage might be responsible for pulmonary edema.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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