Hepatic Impairment Induced by Scrub Typhus is Associated with New Onset of Renal Dysfunction

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SUMMARY

Background: Scrub typhus is a potentially fatal infectious disease caused by Orientia tsutsugamushi. There is little attention given to hepatic impairment in the adults with scrub typhus. This study investigated the incidence and the prognostic implications of hepatic impairment in patients with scrub typhus.

Methods: We retrospectively reviewed a total of 143 adult patients with scrub typhus who were admitted between January 1999 and December 2010 in Guangdong province, China. The patients were divided into three groups, e.g., normal, mild, and moderate to severe groups based on the elevated serum ALT and/or total bilirubin levels. Furthermore, clinical characteristics and prognosis of the patient groups were compared.

Results: 109 patients (76.2%) had abnormal liver function. Among the patients with hepatic impairment 45 cases (31.4%), 54 cases (37.8%), and 10 cases (7.0%) had mild, moderate, and severe hepatic damage, respectively. The moderate to severe hepatic impairment group had higher levels of serum creatinine compared with that of normal hepatic function. The incidence of new onset of renal dysfunction - defined as peak serum creatinine ≥ 176 µmol/L during hospital stay with no evidence of renal disease prior hospitalization - was 0% in the mild hepatic impairment group, 8.9% in the moderate hepatic impairment group, and 21.9% in the severe hepatic impairment group, (p = 0.005 for trend). Additionally, the patients with hepatic impairment (n = 109) had higher incidences of episodes of thrombocytopenia (45.9% vs. 8.8%, p < 0.001), hypalbuminemia (50.5% vs. 11.8%, p < 0.001), new onset of renal dysfunction (16.5% vs. 0.0%, p = 0.011), and electrocardiogram abnormality (28.4% vs. 8.8%, p = 0.019) than the patients without hepatic impairment.

Conclusions: The degree of hepatic impairment induced by scrub typhus is associated with new onset of renal dysfunction.


KEY WORDS
hepatic impairment, renal dysfunction, complication, outcome, scrub typhus

LIST OF ABBREVIATIONS
ALT - alanine aminotransferase
AST - aspartate aminotransferase
Thil - total bilirubin
WBC - white blood cell
ECG - electrocardiogram

INTRODUCTION
Scrub typhus is an acute febrile disease caused by the organism Orientia tsutsugamushi. It is common in eastern and southern Asia, northern Australia, and the Pacific Islands [1]. Scrub typhus has been endemic in southern China including Guangdong province for...
many decades [2]. Clinical manifestations include fever, maculopapular rashes, eschar, and lymphadenopathy [3]. It is characterized by focal or disseminated vasculitis and perivasculitis, which may involve the lung, heart, liver, spleen, and central nervous system. Usually, the symptoms of this disease are mild and its clinical course is uneventful. However, scrub typhus may have severe and fatal outcomes (in up to 30% of cases) under certain circumstances [4]. Hepatic impairment is a common finding in critically ill patients and is a predictor of mortality [5,6]. However, the relationship between hepatic impairment and other organic damages has been given little attention in scrub typhus. Therefore, we investigated the incidence of abnormal liver function in scrub typhus and the significance of hepatic impairment on the outcome of patients with scrub typhus.

MATERIALS AND METHODS

Study population and design
We retrospectively reviewed a total of 143 cases (aged ≥ 18 years old) with scrub typhus who were admitted between January 1999 and December 2010 to three hospitals: the first Affiliated Hospital of Jinan University, the second People’s Hospital of Yuebei, and eighth People’s Hospital of Guangzhou, Guangdong province, southern China. The diagnosis of scrub typhus was confirmed with three and/or more of the following conditions [7,8]. Firstly, history of outdoor activities in vegetated areas. Secondly, acute-onset fever and eschar or ulcer. Thirdly, enlarged lymphnode, maculopapular skin rashes. Fourthly, a positive Weil-Felix test (an OX1 titer ≥ 1:160, a four-fold or a greater rise in titer). The patients with chronic liver disease, chronic renal failure and/or dysfunction, chronic heart disease, hematologic discomfort, skin rash, eschar, lymphadenopathy, and splenomegaly among groups except for nausea/vomiting (χ² = 6.415, p = 0.040) and hepatomegaly (χ² = 7.188, p = 0.027). The incidence of nausea/vomiting and hepatomegaly in group I and group II (χ² = 0.024, p = 0.878 and χ² = 0.011, p = 0.917, respectively) was no different and data were merged, while the incidence of nausea/vomiting and hepatomegaly in group III was higher than that of group I and group II (χ² = 6.251, p = 0.012; and χ² = 7.181, p = 0.007) as shown in table 1. A summary of initial laboratory findings at admission for groups I, II, and III is shown in table 2. The serum ALT and total bilirubin levels in group I, II, and III were 24.00 ± 9.33 IU/L and 0.75 ± 0.32 mg/dL, 68.96 ± 13.52 IU/L and 0.78 ± 0.31 mg/dL, and 168.53 ± 129.98 IU/L and 2.73 ± 4.30 mg/dL, respectively. The serum AST levels in groups I, II and III (41.94 ± 40.52 IU/L, and 194.61 ± 138.41 IU/L, respectively) were different among the groups (F = 33.22, p < 0.001, one-way ANOVA). The serum albumin levels were different among the groups (p < 0.001, one-way ANOVA) and were lower with less severe damage to the liver function. The serum creatinine levels were higher in group III compared with group I (p = 0.019), while there were no difference in group II compared with group I or group III (p > 0.05). Platelet count was significantly higher in group I compared with group II (p = 0.002) or group III (p < 0.001). The incidence of thrombocytopenia and hypoalbuminemia was lower in group I compared with group II (χ² = 8.587, p = 0.003; and χ² = 7.684, p = 0.006) or group III (χ² = 17.452, p <

RESULTS

In this study, the 143 patients revealed that the proportions of patients with the disease did not differ between the genders; 71 (49.7%) patients were male. Patient ages ranged from 18 to 77 years, with a median age of 48 years. 109 (76.2%) patients had abnormal liver function in which 45 cases (31.4%), 54 cases (37.8%), and 10 cases (7.0%), had mild, moderate, and severe hepatic impairment, respectively. There were no differences in age and gender among the three groups. There were no differences in clinical signs and symptoms such as fever, chill, headache, fatigue, anorexia, abdominal discomfort, skin rash, eschar, lymphadenopathy, and splenomegaly except for nausea/vomiting and hepatomegaly in group I and group II (χ² = 0.024, p = 0.878 and χ² = 0.011, p = 0.917, respectively) and hepatomegaly (χ² = 7.188, p = 0.027). The incidence of nausea/vomiting and hepatomegaly in group III was higher than that of group I and group II (χ² = 6.251, p = 0.012; and χ² = 7.181, p = 0.007) as shown in table 1. A summary of initial laboratory findings at admission for groups I, II, and III is shown in table 2. The serum ALT and total bilirubin levels in group I, II, and III were 24.00 ± 9.33 IU/L and 0.75 ± 0.32 mg/dL, 68.96 ± 13.52 IU/L and 0.78 ± 0.31 mg/dL, and 168.53 ± 129.98 IU/L and 2.73 ± 4.30 mg/dL, respectively. The serum AST levels in groups I, II and III were different among the groups (F = 33.22, p < 0.001, one-way ANOVA). The serum albumin levels were different among the groups (p < 0.001, one-way ANOVA) and were lower with less severe damage to the liver function. The serum creatinine levels were higher in group III compared with group I (p = 0.019), while there were no difference in group II compared with group I or group III (p > 0.05). Platelet count was significantly higher in group I compared with group II (p = 0.002) or group III (p < 0.001). The incidence of thrombocytopenia and hypoalbuminemia was lower in group I compared with group II (χ² = 8.587, p = 0.003; and χ² = 7.684, p = 0.006) or group III (χ² = 17.452, p <

hospital stay (176 μmol/L) [11,12]. Laboratory and clinical values were then compared among the three groups, and the correlation between the hepatic impairment and the clinical parameters representing severity of scrub typhus values was evaluated.

Statistical analysis
The results were analyzed using SPSS v15.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared by Fisher’s exact test or chi-square test and continuous variables were compared by the ANOVA. A difference was considered statistically significant if the p value was less than 0.05.
HEPATIC IMPAIRMENT AND RENAL DYSFUNCTION IN SCRUB TYPHUS

Table 1. Demographic and clinical characteristics of 143 patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 34)</th>
<th>Group II (n = 45)</th>
<th>Group III (n = 64)</th>
<th>t - or χ² - value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>44.3 ± 18.2</td>
<td>47.1 ± 13.6</td>
<td>45.5 ± 14.0</td>
<td>0.349</td>
<td>0.706</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>13 (38.2%)</td>
<td>24 (53.3%)</td>
<td>34 (53.1%)</td>
<td>2.325</td>
<td>0.313</td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>33 (97.1%)</td>
<td>44 (97.8%)</td>
<td>63 (98.4%)</td>
<td>0.734</td>
<td>1.000</td>
</tr>
<tr>
<td>Chill, n (%)</td>
<td>21 (61.8%)</td>
<td>25 (55.6%)</td>
<td>39 (60.9%)</td>
<td>0.417</td>
<td>0.812</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>23 (67.6%)</td>
<td>30 (66.7%)</td>
<td>52 (81.3%)</td>
<td>3.644</td>
<td>0.162</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td>28 (82.4%)</td>
<td>37 (82.2%)</td>
<td>60 (93.8%)</td>
<td>4.229</td>
<td>0.121</td>
</tr>
<tr>
<td>Anorexia, n (%)</td>
<td>20 (58.8%)</td>
<td>30 (66.7%)</td>
<td>49 (76.6%)</td>
<td>3.483</td>
<td>0.175</td>
</tr>
<tr>
<td>Nausea/Vomiting, n (%)</td>
<td>4 (11.8%)</td>
<td>7 (15.6%)</td>
<td>20 (31.3%)*</td>
<td>6.415</td>
<td>0.040</td>
</tr>
<tr>
<td>Abdominal discomfort, n (%)</td>
<td>2 (5.9%)</td>
<td>7 (15.6%)</td>
<td>11 (17.2%)</td>
<td>2.493</td>
<td>0.287</td>
</tr>
<tr>
<td>Skin rash, n (%)</td>
<td>11 (32.4%)</td>
<td>14 (31.1%)</td>
<td>17 (26.6%)</td>
<td>0.455</td>
<td>0.797</td>
</tr>
<tr>
<td>Eschar, n (%)</td>
<td>18 (52.9%)</td>
<td>33 (73.3%)</td>
<td>47 (73.4%)</td>
<td>5.027</td>
<td>0.081</td>
</tr>
<tr>
<td>Lymphadenopathy, n (%)</td>
<td>17 (50%)</td>
<td>27 (60%)</td>
<td>35 (54.7%)</td>
<td>0.798</td>
<td>0.671</td>
</tr>
<tr>
<td>Hepatomegaly, n (%)</td>
<td>5 (14.7%)</td>
<td>7 (15.6%)</td>
<td>22 (34.4%)*</td>
<td>7.188</td>
<td>0.027</td>
</tr>
<tr>
<td>Splenomegaly, n (%)</td>
<td>5 (14.7%)</td>
<td>7 (15.6%)</td>
<td>16 (25%)</td>
<td>2.170</td>
<td>0.338</td>
</tr>
</tbody>
</table>

* The incidence of nausea/vomiting and hepatomegaly in group III was higher than that of group I and group II (p = 0.012 and p = 0.007, respectively).

Table 2. Laboratory tests of 143 patients with scrub typhus at admission.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 34)</th>
<th>Group II (n = 45)</th>
<th>Group III (n = 64)</th>
<th>t - or χ² - value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10³/μL)</td>
<td>7.81 ± 4.84</td>
<td>8.84 ± 5.41</td>
<td>8.35 ± 4.38</td>
<td>0.439</td>
<td>0.645</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.24 ± 5.38</td>
<td>35.61 ± 5.85</td>
<td>33.36 ± 5.42</td>
<td>2.172</td>
<td>0.118</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.26 ± 1.65</td>
<td>12.09 ± 2.06</td>
<td>11.52 ± 2.40</td>
<td>1.605</td>
<td>0.205</td>
</tr>
<tr>
<td>Platelet (x 10³/mm³)</td>
<td>188.71 ± 108.27</td>
<td>129.55 ± 81.39</td>
<td>112.07 ± 69.69</td>
<td>9.454</td>
<td>0.000</td>
</tr>
<tr>
<td>Thrombocytopenia, n (%)</td>
<td>3 (8.82%)</td>
<td>17 (37.77%)</td>
<td>33 (51.56%)</td>
<td>17.402</td>
<td>0.000</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>24.00 ± 9.33</td>
<td>68.96 ± 13.52</td>
<td>168.53 ± 129.98</td>
<td>35.10</td>
<td>0.000</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>41.94 ± 34.50</td>
<td>82.44 ± 40.52</td>
<td>194.61 ± 138.41</td>
<td>33.22</td>
<td>0.000</td>
</tr>
<tr>
<td>Tbil (mg/dL)</td>
<td>0.75 ± 0.32</td>
<td>0.78 ± 0.31</td>
<td>2.73 ± 4.30</td>
<td>8.158</td>
<td>0.000</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.50 ± 0.59</td>
<td>3.14 ± 0.80α</td>
<td>2.83 ± 0.64</td>
<td>10.709</td>
<td>0.000</td>
</tr>
<tr>
<td>Hipoalbuminemia, n (%)</td>
<td>4 (11.76%)</td>
<td>18 (40%)</td>
<td>37 (57.81%)</td>
<td>19.469</td>
<td>0.000</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>83.78 ± 30.66³</td>
<td>88.88 ± 35.47</td>
<td>120.29 ± 95.64</td>
<td>4.272</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Values are mean ± SD. WBC = white blood cell; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin. Thrombocytopenia: platelet count < 100 x 10³/mm³; Hipoalbuminemia: serum albumin < 3.0 g/dL. * Group I vs. group II, p < 0.05; † group I vs. group III, p < 0.05; § group II vs. group III, p < 0.05.

0.001; and χ² = 19.348, p < 0.001). On the other hand, there were no statistical differences in WBC, hematocrit, or hemoglobin between the three groups. Three cases had electrocardiogram abnormalities in group I, including one case of sinus tachycardia, one case of sinus tachycardia with occasional premature ventricular contractions, and one case of sinus bradycardia. Eleven cases had electrocardiogram abnormalities in group II, including four cases of sinus tachycardia, one case of premature ventricular contractions, one case of first-degree atrioventricular block and five cases of ST segment/T wave changes. Twenty cases had electrocardiogram abnormalities in group III, including five cases of sinus tachycardia, seven cases of ST segment/T wave...
Table 3. Complications and outcomes of scrub typhus in 143 patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 34)</th>
<th>Group II (n = 45)</th>
<th>Group III (n = 64)</th>
<th>t- or $\chi^2$- value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>4 (6.3)</td>
<td>2.148</td>
<td>0.313</td>
</tr>
<tr>
<td>Hospitalization, days</td>
<td>9.50 ± 4.60</td>
<td>9.46 ± 4.60</td>
<td>11.56 ± 6.92</td>
<td>2.307</td>
<td>0.103</td>
</tr>
<tr>
<td>Pneumonitis, n (%)</td>
<td>7 (20.6)</td>
<td>13 (28.9)</td>
<td>26 (40.6)</td>
<td>4.409</td>
<td>0.110</td>
</tr>
<tr>
<td>New onset renal dysfunction, n (%)</td>
<td>0 (0)$^\dagger$</td>
<td>4 (8.9)</td>
<td>14 (21.9)</td>
<td>10.473</td>
<td>0.005</td>
</tr>
<tr>
<td>ECG abnormalities, n (%)</td>
<td>3 (8.8)$^\ddagger$</td>
<td>11 (24.4)</td>
<td>20 (31.3)</td>
<td>6.178</td>
<td>0.046</td>
</tr>
<tr>
<td>Myocarditis, n (%)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>6 (9.4)</td>
<td>4.182</td>
<td>0.102</td>
</tr>
<tr>
<td>Meningitis/meningoencephalitis, n (%)</td>
<td>2 (5.9)</td>
<td>1 (2.2)</td>
<td>4 (6.3)</td>
<td>1.014</td>
<td>0.602</td>
</tr>
</tbody>
</table>

Values are mean ± SD. $^\dagger$ group I vs. group II and group III, p < 0.05.
ECG = electrocardiogram; Renal dysfunction: serum creatinine ≥ 176 µmol/L.

Figure 1. Renal dysfunction in groups. $^\dagger$ p < 0.005, group I vs. group II and group III.

Changes, four cases of premature ventricular contractions, two cases of sinus bradycardia and sinus arrhythmia, one case of sinus arrhythmia, and one case of complete right bundle branch block. The incidence of renal dysfunction and electrocardiogram abnormality was no different in group II and group III ($\chi^2 = 3.232$, p = 0.072; and $\chi^2 = 0.601$, p = 0.438) and the data were merged. The merged data was higher than that of group I ($\chi^2 = 6.423$, p = 0.011; and $\chi^2 = 5.503$, p = 0.019, respectively) as shown in figure 1 and 2. However, there was no difference in hospital stay, mortality, and complications such as pneumonitis, myocarditis, meningitis/meningoencephalitis between the three groups (p > 0.05) as shown in table 2 and 3. We also compared these clinical factors between patients with and without hepatic impairment. The patients with hepatic impairment (n = 109) had higher incidences of episodes of thrombocytopenia (45.9% vs. 8.82%, $\chi^2 = 17.25$, p < 0.001), hypoalbuminemia (50.5% vs. 11.8%, $\chi^2 = 10.01$, p = 0.000), renal dysfunction (16.5% vs. 0.0%, $\chi^2 = 6.42$, p = 0.011), and electrocardiogram abnormality (28.4% vs. 8.82%, $\chi^2 = 5.50$, p = 0.019) than the patients without hepatic impairment (n = 34).
DISCUSSION

Scrub typhus is an acute febrile disease caused by infection with Orientia tsutsugamushi and characterized by fever, an eschar at the chigger bite site, regional lymphadenopathy, and a maculopapular rash. Hepatic impairment is frequently observed but overlooked in the acute stage of scrub typhus [13,14]. In this study, 76.2% scrub typhus patients had abnormal liver function tests (31.4%, 37.8%, and 7.0% for mild, moderate, and severe hepatic impairment, respectively), and the degree of hepatic impairment was mainly mild or moderate, similar to the results of previous studies [15,16]. Regarding hepatitis-like manifestations, nausea/vomiting and hepatomegaly occurred more frequently in the patients with moderate to severe hepatic impairment. Therefore, if patients are found with fever of unknown origin, varying degrees of hepatic impairment, even severe hepatic impairment, and skin lesions (including eschar and maculopapular rash) in endemic areas, we should take scrub typhus into consideration. The mechanism of hepatic impairment is unknown so far. It might be a result of direct invasion of Orientia tsutsugamushi [17,18], and cellular immunity may be attributed to the pathogenesis of the hepatic injury [19].

In the current study, thrombocytopenia and hypoalbuminemia were more severe in the group with hepatic impairment (group II and group III). Thrombocytopenia is one of the most common laboratory abnormalities in critically ill patients and likely a marker of disease severity [20,21]. Generally, hypoalbuminemia is known to be associated with complications and mortality in patients with acute infectious disease [22]. In scrub typhus, about 34.1% ~ 69.2% of patients presented hypoalbuminemia [23,24]. Hypoalbuminemia in scrub typhus is related to the frequency of various complications. Lee et al. [23] reported hypoalbuminemia, as a criterion, was an important marker of clinical outcome in this patient population. Although the mechanism of hypoalbuminemia in patients with scrub typhus is still not well known, it is considered to be associated with plasma protein leakage from the blood vessels due to increased vascular permeability [25]. Moreover, the patients with hepatic impairment (group II and group III) tended to have a greater incidence of renal dysfunction and electrocardiogram abnormalities than the patients without hepatic impairment (group I). Renal complications may prolong its morbidity and even lead to death, and an elevated creatinine level was found to be an independent predictor of mortality [26].

The finding that we did not observe any differences with regard to hospital stay or even mortality among groups is due to the fact that our study is underpowered for these hard clinical endpoints.

In conclusion, our study indicated that the degree of hepatic impairment in patients with scrub typhus is related to signs of cardiac damage as indicated by ECG abnormalities and in particular the likelihood for acute kidney failure.

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Declaration of Interest:
There is no conflict of interest for any of the authors.

References:

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