


The association between markers of liver injury and clinical outcomes in patients with COVID-19 in Wuhan

Haijun Huang¹ | Shanshan Chen^{1,2} | Hong Li^{1,3} | Xian-Long Zhou⁴ | Yining Dai¹ | Jia Wu¹ | Jun Zhang¹ | Lina Shao¹ | Rong Yan¹ | Mingshan Wang¹ | Jiafeng Wang¹ | Yuexing Tu¹ | Minghua Ge¹ 

¹Hangzhou, China

²Bengbu, China

³Qingdao, China

⁴Wuhan, China

Correspondence

Minghua Ge and Yuexing Tu, Zhejiang Provincial People's Hospital Hangzhou, Hangzhou, China.
Emails: geminghua@hmc.edu.cn (M. G.) and tuyuexing1988@163.com (Y. T.)

Funding information

National Natural Science Foundation of China, Grant/Award Number: 81672115 and 81800507; Emergency Response Project of Hubei Science and Technology Department, Grant/Award Number: 2020FCA023

Summary

Background: The outbreak of coronavirus disease 2019 (COVID-19) is a critical challenge for public health. The effect of COVID-19 on liver injury has not been fully established.

Aims: To evaluate the dynamic changes in liver function and the relationship between liver damage and prognosis in patients with COVID-19.

Methods: Retrospective analysis of clinical data of 675 patients with COVID-19 in Zhongnan Hospital of Wuhan University from January 3 to March 8, 2020. Patients were classified as having normal or abnormal liver function and liver injury.

Results: Of 675 patients, 253 (37.5%) had abnormal liver function during hospitalisation, and 52 (7.7%) had liver injury. The dynamic changes of ALT and AST levels were more significant in patients with liver injury and in those who died. AST >3-fold upper limit of normal (ULN) had the highest risk of death and mechanical ventilation. Compared to patients with normal AST levels, mortality and risk of mechanical ventilation significantly increased 19.27-fold (95% confidence interval [CI], 4.89-75.97; $P < 0.0001$) and 116.72-fold (95% CI, 31.58-431.46; $P < 0.0001$), respectively, in patients with AST above 3-fold ULN. Increased leucocytes, decreased lymphocytes and female sex were independently associated with liver injury.

Conclusions: The dynamic changes in liver function may have a significant correlation with the severity and prognosis of COVID-19. Increased index of liver injury was closely related to mortality and need for mechanical ventilation. Therefore, these indicators should be closely monitored during hospitalisation.

[Correction added on August 28, 2020 after first online publication: The Aims section of the Summary was revised from "... the relationship between liver function damage and ...".]

[Correction added on August 14, 2020, after first online publication: The 6th author's name was corrected in the byline.]

Haijun Huang, Shanshan Chen, Hong Li and Xian-Long Zhou contributed equally to this work.

The Handling Editor for this article was Dr Stephen Ryder, and it was accepted for publication after full peer-review.

The complete list of authors' affiliation are listed in Appendix 1.

1 | INTRODUCTION

In December 2019, unexplained pneumonia cases emerged in Wuhan, Hubei Province, China,^{1,2} which spread rapidly throughout the country and became a public health emergency of international concern. On January 7, a novel coronavirus was detected in a swab sample of a patient by the China Center for Disease Control and Prevention (CDC). The disease was subsequently named the novel coronavirus disease 2019 (2019-nCoV).³

The pathogen of COVID-19 pneumonia is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),^{1,4} which mainly causes respiratory, intestinal, liver and nervous system diseases.^{5,6} A study showed that more than 50% of patients with COVID-19 have different degrees of liver injury.⁷ Some studies have reported the clinical characteristics of patients with coronavirus disease 2019 (COVID-19), including some factors that may lead to COVID-19-related liver damage and the relationship between liver function damage and disease prognosis.^{1,3,8-11} In these studies, different degrees of elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported.^{1,3,8,12} However, the effect of COVID-19 on liver injury has not been fully presented.

Liver injury is related to the severity and mortality of COVID-19.¹³⁻¹⁶ Cai et al systematically described the clinical characteristics of COVID-19 patients with liver injury and revealed that liver injury was related to disease severity.¹⁴ In addition, a study reported that liver injury was related to death in patients with COVID-19, and mortality was related to an increase in liver enzyme levels.¹³ However, mechanical ventilation, which is the main auxiliary treatment for critical patients and an important clinical outcome of COVID-19, was not involved. On the other hand, dynamic changes in liver functions may indicate a certain relationship between liver injury and mortality. There were few studies on the dynamic changes of liver functions in COVID-19-related liver injury.^{13,17} Nevertheless, the dynamic changes in liver function based on fatal and nonfatal individuals have never been reported. Moreover, there is little research on what abnormalities occur at what time and how those may relate to clinical outcomes. Therefore, we retrospectively analysed the clinical characteristics and dynamic changes in liver function based on different liver function levels at admission and different prognosis, in the purpose of finding out risk factors related to liver injury, and associations between markers of liver injury and clinical outcomes in COVID-19, including mortality and mechanical ventilation.

2 | MATERIALS AND METHODS

2.1 | Patients

From January 3 to March 8, 2020, the medical records of in-patients diagnosed with COVID-19 were analysed retrospectively at Zhongnan Hospital of Wuhan University. Information on epidemiological, demographic, clinical symptoms or physical signs and comorbidities was extracted from the electronic medical records.

This retrospective study was approved by the Research Ethics Commission of Zhongnan Hospital of Wuhan University and the Ethics Committee of Zhejiang Provincial People's Hospital. The requirement for informed consent was waived due to its retrospective design.

According to the diagnosis and treatment standard of COVID-19¹⁸ issued by the National Health Committee, the disease severity was divided into three groups: mild, severe and critical. Patients with mild type might have fever and respiratory symptoms, and pneumonia was revealed by imaging. Severe COVID-19 was defined when the patients met any of the following criteria: (a) respiratory distress (≥ 30 breaths/min); (b) resting oxygen saturation $\leq 93\%$; and (c) arterial blood oxygen partial pressure (PaO₂)/F_iO₂ ≤ 300 mm Hg. In the critical group, at least one of the following three diagnostic criteria should be met: (a) respiratory failure requiring mechanical oxygenation; (b) shock; and (c) the development of other organ failure that necessitated intensive care unit (ICU) care. We defined liver abnormalities as any parameter being greater than the upper limits of the normal (ULN) values of ALT (40 U/L), AST (40 U/L) and total bilirubin (TBIL) (21 μ mol/L). We defined liver injury as the level of serum ALT being at least 3-fold greater than the ULN.¹³

2.2 | Data collection

Clinical data of patients were collected: demographic (including age and gender), history of illness, clinical symptoms or signs and laboratory examination. Laboratory tests included blood routine, C-reactive protein (CRP), coagulation function, serum biochemical indicators (ALT, AST and alkaline phosphatase [AKP], gamma-glutamyl transpeptidase [GGT], TBIL and albumin, etc), lactate dehydrogenase, procalcitonin and other data as well as specific drug use. The clinical characteristics, disease severity and laboratory examinations of patients in the liver injury group, abnormal liver function and normal liver function groups were compared; the related factors and prognosis of liver injury were analysed.

2.3 | Statistical analysis

Statistical analyses of the data were performed with SPSS software (version 21.0, SPSS Inc, IBM). Classified variables were represented by frequency. Continuous variables were described as the median (interquartile range [IQR]). If the data were normally distributed, a *t* test was used to compare the continuous variables; otherwise, the Mann-Whitney test was used. The Chi-squared test was used to compare the proportion of classified variables. The proportions of categorical variables were compared by the Chi-squared test or Fisher's exact test. Dynamic changes in liver function based on different liver function levels at admission and different prognosis were presented using locally weighted scatterplot smoothing (LOESS). The mixed-effect Cox proportional risk regression model was used to study the relationship between liver enzyme level and mortality and

mechanical ventilation. The mixed-effect Cox model was adjusted for gender, age, smoking, chronic liver disease and comorbidities (including hypertension, diabetes mellitus, coronary heart disease and chronic obstructive pulmonary disease). To explore the factors associated with COVID-19-related liver injury, logistic regression analysis was performed. The variables with $P < 0.1$ in a univariate analysis were then included in a forward stepwise regression model. A two-sided P of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic and epidemiological characteristics

A total of 726 patients with confirmed COVID-19 were recruited in the study, and 51 patients were excluded because of incomplete relevant data and delayed admission from symptom onset. Ultimately, 675 patients with COVID-19 were included in the study (Figure 1). The clinical characteristics of patients grouped according to liver function upon admission are shown in Supplementary Table. There were 52 patients with liver injury, 25 of whom had liver injury at admission, while the other 27 developed liver injury during hospitalisation.

The baseline characteristics of patients grouped according to liver function during hospitalisation are shown in Table 1. Among the 675 patients, 370 (54.8%) patients had normal liver function, 253 (37.5%) patients had abnormal liver function and 52 (7.7%) patients had liver injury. In patients with liver injury, the median age was 51.50 (35.75-60.25), and the ratio of males to females was 4:1. The body mass index (BMI) of patients with liver injury was 24.66 (23.14-26.37), which was higher than that of patients with normal and abnormal liver function. The incidences of hypertension, diabetes mellitus (DM), coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD) were 12 (23.08%), 6 (11.54%), 6 (11.54%) and 1 (1.92%), respectively, in these patients with liver injury.

Among 52 patients with liver injury, 42 (80.77%) patients had fever, and 20 (38.46%) had dyspnoea, which were significantly higher

than those of patients without liver injury ($P < 0.001$). Twenty-eight (53.85%) patients with liver injury were in the mild group, 8 (15.38%) patients were in the severe group and 16 (30.77%) patients were in the critical group. The median values of ALT, AST and TBIL were 105.00 (49.25-159.50), 58.50 (45.00-90.50) and 12.55 (9.50-17.67), respectively, which were much higher than those of patients with normal and abnormal liver function ($P < 0.001$ for all). The number of lymphocytes in patients with liver injury was 1.08 (0.58-1.63), which was significantly lower than that in patients without liver injury.

3.2 | Dynamic changes in liver function in patients with COVID-19

Figure 2 depicts the dynamic changes of ALT, AST and TBIL in patients with normal, abnormal liver function and liver injury. The ALT, AST and TBIL levels in patients with normal liver function at admission were always within the normal range during hospitalisation. With regard to those with abnormal liver function at admission, the ALT and AST levels generally fluctuated in a range of 1-2 times of ULN. In the group of liver injury, ALT and AST levels increased gradually during the course of disease, reaching their peaks in the third week after symptom onset. Along with the conditions of COVID-19 improved, ALT and AST concentrations gradually returned to the levels at admission. Among the three groups, TBIL level fluctuated slightly within the normal range.

Figure 3 illustrated the trajectories of ALT, AST and TBIL in the nonfatal and fatal groups. The models showed significant differences between the ALT, AST and TBIL of the two groups, as the rangeability was significantly greater, and most of the time, the values were higher in the fatal group. In the first week, both the fatal and nonfatal groups had a normal range of ALT levels. Subsequently, the ALT rose rapidly until it peaked and exceeded the ULN at the third week in the fatal group. In addition, slightly elevated ALT levels occurred during the 2-3 weeks after the onset of fever in the nonfatal groups. Figure 3B illustrated the slight elevation of AST on the first day of symptom onset in the fatal group, which was maintained at

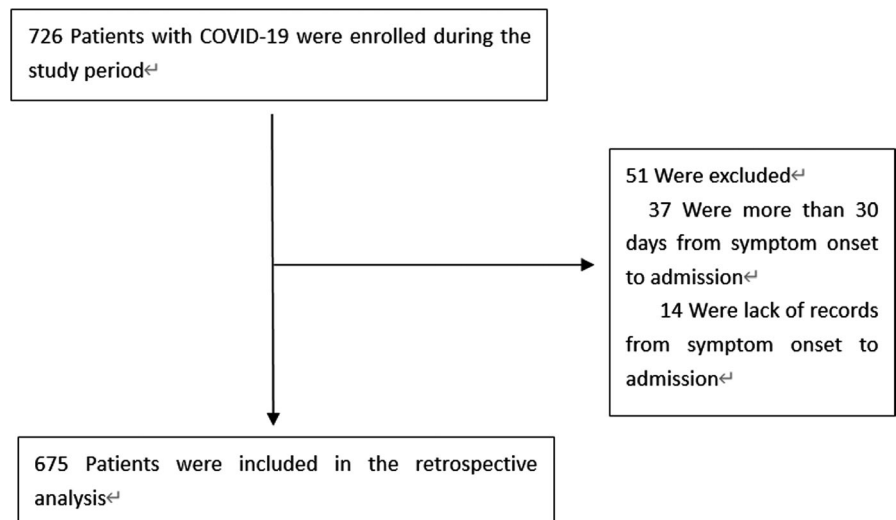


FIGURE 1 Flow diagram of the exclusion criteria. COVID-19, coronavirus disease 2019

TABLE 1 Clinical Characteristics of COVID-19 Patients with normal, abnormal and injury liver function during hospitalisation

| Characteristics | Liver function | | | P value |
|-----------------------------------|------------------------|------------------------|------------------------|---------|
| | Normal | Abnormal | Injury | |
| Number (%) | 370 (54.8%) | 253 (37.5%) | 52 (7.7%) | |
| Age (y) | 53.50 (37.00-64.00) | 58.00 (47.00-67.00) | 51.50 (35.75-60.25) | <0.001 |
| Males (%) | 122 (32.97%) | 149 (58.89%) | 42 (80.77%) | <0.001 |
| BMI (kg/m ²) | 23.44 (21.30-25.25) | 24.22 (22.31-26.17) | 24.66 (23.14-26.37) | 0.025 |
| Comorbidities (%) | | | | |
| Hypertension | 78 (21.08%) | 71 (28.06%) | 12 (23.08%) | 0.132 |
| DM | 36 (9.73%) | 25 (9.88%) | 6 (11.54%) | 0.92 |
| CHD | 19 (5.14%) | 15 (5.93%) | 6 (11.54%) | 0.187 |
| COPD | 10 (2.70%) | 4 (1.58%) | 1 (1.92%) | 0.64 |
| Chronic liver disease | 10(2.70%) | 14(5.53%) | 3(5.77%) | 0.131 |
| Symptom (%) | | | | |
| Fever | 233 (62.97%) | 192 (75.89%) | 42 (80.77%) | <0.001 |
| Cough | 192 (51.89%) | 134 (52.96%) | 27 (51.92%) | 0.964 |
| Dyspnoea | 45 (12.16%) | 62 (24.51%) | 20 (38.46%) | <0.001 |
| Muscle ache | 42 (11.57%) | 33 (13.47%) | 7 (14.89%) | 0.69 |
| Hypodynamic | 113 (30.54%) | 92 (36.36%) | 19 (36.54%) | 0.275 |
| Chest distress | 67 (18.11%) | 70 (27.67%) | 18 (34.62%) | 0.002 |
| Blood biochemistry | | | | |
| ALT (U/L) | 18.00 (13.00-26.00) | 42.00 (24.00-58.00) | 105.00 (49.25-159.50) | <0.001 |
| AST (U/L) | 20.00 (16.00-24.00) | 34.00 (24.00-48.00) | 58.50 (45.00-90.50) | <0.001 |
| TBIL (μmol/L) | 10.60 (8.50-13.30) | 13.00 (9.80-18.90) | 12.55 (9.50-17.67) | <0.001 |
| ALP (U/L) | 81.00 (65.00-102.00) | 81.00 (64.00-106.00) | 81.50 (65.00-103.75) | 0.56 |
| GGT (U/L) | 21.00 (14.00-31.00) | 35.00 (23.00-63.00) | 53.50 (32.75-85.25) | <0.001 |
| Disease severity (%) | | | | |
| Mild | 322 (87.03%) | 173 (68.38%) | 28 (53.85%) | <0.001 |
| Severe | 43 (11.62%) | 48 (18.97%) | 8 (15.38%) | |
| Critical | 5 (1.35%) | 32 (12.65%) | 16 (30.77%) | |
| Blood tests | | | | |
| WBC (×10 ⁹ /L) | 5.20 (4.13-6.23) | 5.66 (4.48-7.09) | 6.08 (4.91-7.88) | <0.001 |
| Lymphocytes (×10 ⁹ /L) | 1.39 (1.02-1.68) | 1.23 (0.78-1.72) | 1.08 (0.58-1.63) | 0.002 |
| HB (g/L) | 127.70 (117.40-136.65) | 132.60 (122.30-142.60) | 139.00 (125.85-150.00) | <0.001 |
| PLT (×10 ⁹ /L) | 201.00 (169.00-244.00) | 196.00 (155.00-240.00) | 196.50 (142.00-236.25) | 0.451 |
| CRP (mg/L) | 2.62 (1.27-9.63) | 11.60 (2.10-56.05) | 25.22 (2.12-74.18) | <0.001 |
| IL-6 (pg/mL) | 1.60 (0.00-4.53) | 3.70 (0.30-18.93) | 7.89 (0.10-47.98) | 0.774 |

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; GGT, glutamyl transpeptidase; HB, haemoglobin; IL-6, interleukin-6; PLT, platelet count; TBIL, total bilirubin; ULN, upper limit of normal; WBC, white blood cell.

high levels. Furthermore, the AST increased rapidly in the fatal group until it peaked and exceeded the 3ULN value at the third week. In contrast, the change in AST levels in the nonfatal group remained in the normal range for 30 days. Figure 3C depicted that the fluctuation in TBIL levels was mild and normal in the nonfatal group, and the TBIL levels increased much more slowly than the ALT and AST in the fatal group. Nevertheless, TBIL continued to rise slowly until it surpassed the ULN at the third week.

3.3 | Associations between liver function and clinical outcomes

Kaplan-Meier survival curves were used to evaluate the survival probability and mechanical ventilation-free survival probability during hospitalisation in patients of COVID-19 with different levels of ALT, AST and TBIL. Among these indexes of liver function, AST over 3-fold ULN had the highest risks of death and mechanical

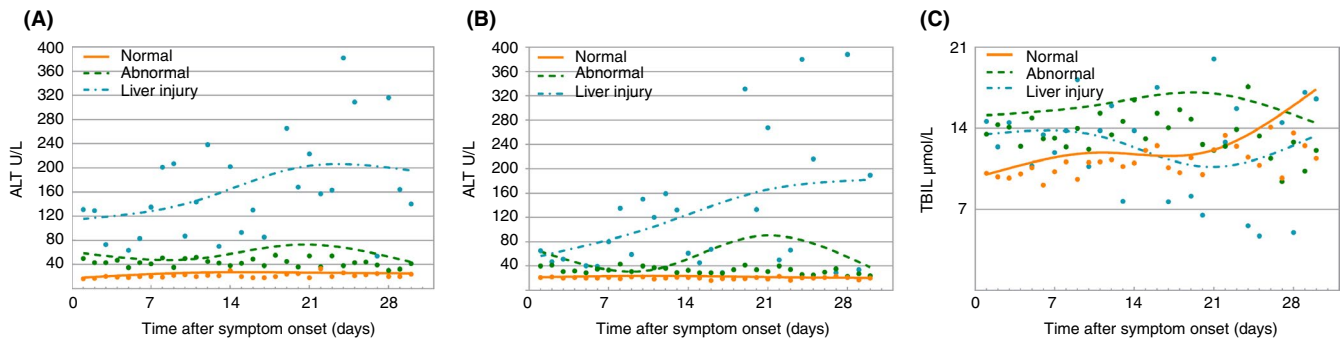


FIGURE 2 Smooth trajectories and scatter represent the median values (A) ALT; (B) AST; and (C) TBIL in the normal liver function, abnormal liver function and liver injury groups

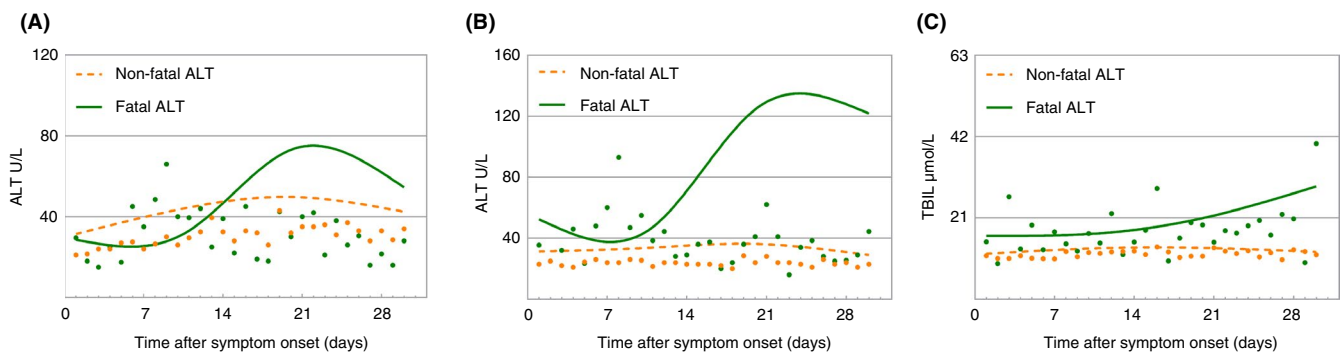


FIGURE 3 Smooth trajectories and scatter represent the median values (A) ALT; (B) AST; and (C) TBIL in the fatal and nonfatal groups

ventilation. In addition, abnormal levels of ALT and TBIL were also significantly associated with the risk of death and mechanical ventilation (Figures 4 and 5). The relationship between impaired liver function, mortality and mechanical ventilation was evaluated by a mixed-effect Cox model adjusted for age, gender, smoking, chronic liver disease and comorbidities, with the hazard ratios of ALT, AST and TBIL to mortality and the risk of mechanical ventilation showed in Table 2. Compared with patients with normal AST, the risks of death and mechanical ventilation increased by 19.27-fold (95% confidence interval [CI], 4.89-75.97; $P < 0.0001$) and 116.72-fold (95% CI, 31.58-431.46; $P < 0.0001$), respectively, in patients with AST above 3-fold ULN.

3.4 | Predictors of liver injury in COVID-19

Logistic regression analysis of the influencing factors of liver injury, such as epidemiological and clinical characteristics, and laboratory variables was performed to select the predictor parameters of COVID-19 patients. Factors significantly associated with liver injury were increased leucocytes, decreased lymphocytes and female (Table 3).

4 | DISCUSSION

In this study, we retrospectively and systematically analysed the clinical characteristics of patients with normal, abnormal liver

function and liver injury in 675 patients with COVID-19 in Wuhan. It demonstrated that the dynamic changes of ALT and AST levels were more significant in patients with liver injury and in the fatal group. The AST levels had the highest correlation with mortality and mechanical ventilation, and mortality and risk of mechanical ventilation were the highest when the AST level >3 times of the ULN. Moreover, the predictors of liver injury included female, an increased level of leucocytes and a decreased level of lymphocytes.

There were few studies on the dynamic changes of liver functions in COVID-19-related liver injury.^{13,17} One study had suggested that the dynamic changes in liver enzyme levels in severe patients were more significant, and AST was the parameter most correlated with mortality.¹³ Another study indicated that the pattern of liver biochemical was consistent with the damage of hepatocytes, especially AST. The correlation between AST and ALT was very strong on admission and throughout the hospitalisation. This suggested that liver injury was the predominant source of aminotransferase elevation.¹⁷ It is in agreement with our findings. In our study, the dynamic changes of ALT and AST levels were more significant in patients with liver injury and in the fatal group. Moreover, AST over 3-fold ULN had the highest risks of death and mechanical ventilation.

In the group of patients with liver injury, ALT and AST levels increased gradually with the course of disease, reaching their peaks in the third week after symptom onset and decreased gradually when patients are getting better. Furthermore, this group

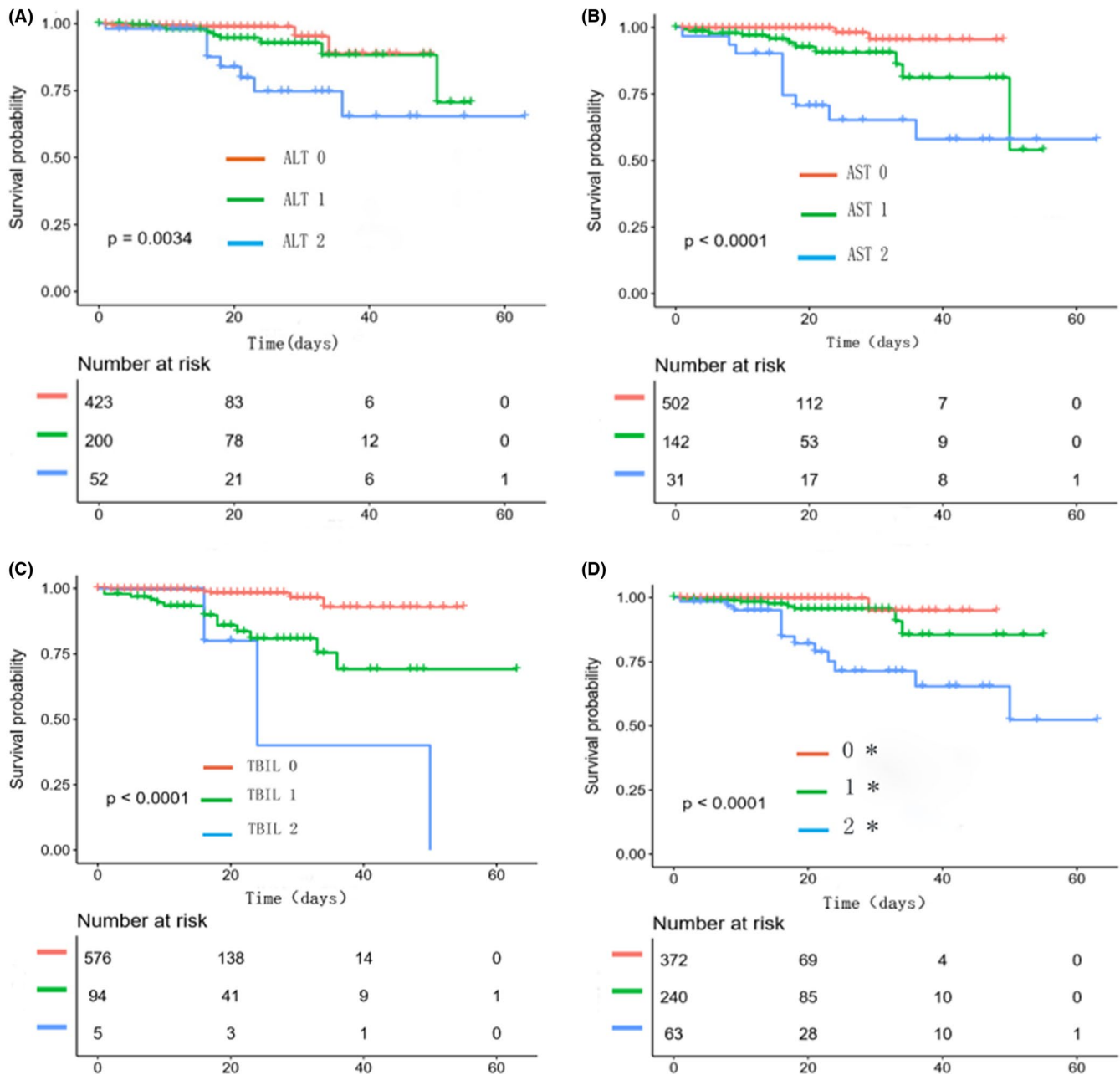


FIGURE 4 Kaplan-Meier curves for survival probability of COVID-19 during hospitalisation in patients with different levels of (A) ALT, (B) AST and (C) TBIL. ALT 0: ALT \leq 40 U/L; ALT 1: 40-120 U/L; ALT 2: \geq 120 U/L. AST 0: AST \leq 40 U/L; AST 1: 40-120 U/L; AST 2: \geq 120 U/L. TBIL 0: \leq 21 μ mol/L; TBIL 1: 21-63 μ mol/L; TBIL 2: \geq 63 μ mol/L. 0*: ALT or AST or TBIL \leq ULN; 1*: ALT or AST or TBIL: ULN-3ULN; 2*: ALT or AST or TBIL \geq 3ULN

of patients had liver injury in the early stage of disease, before the use of any antiviral agents, which excluded the possibility of drug-induced liver injury. A previous study indicated that SARS-CoV-2 might enter hepatocytes, then propagate and damage the hepatocytes, so it is presumed that early liver injury might be a result of direct attack of viruses.¹⁹ Further research is needed to verify this hypothesis.

To our knowledge, this is the first study to fully elucidate the dynamic changes in liver function among fatal and nonfatal groups in COVID-19, and the association between liver function

and mechanical ventilation. It demonstrated that the dynamic changes of markers of liver injury in the fatal and nonfatal groups were significantly different, especially the AST level in the fatal group, which indicated a relationship between impaired liver function, especially the AST levels, and severity of COVID-19 disease. The slight increase of AST levels in the early stage of disease may be related to immune-mediated inflammation in the liver.¹³ On the other hand, a multicentre study has reported that the incidence of increased TBIL in COVID-19 was 10%.¹² In our study, level of TBIL increased only in the later stage of

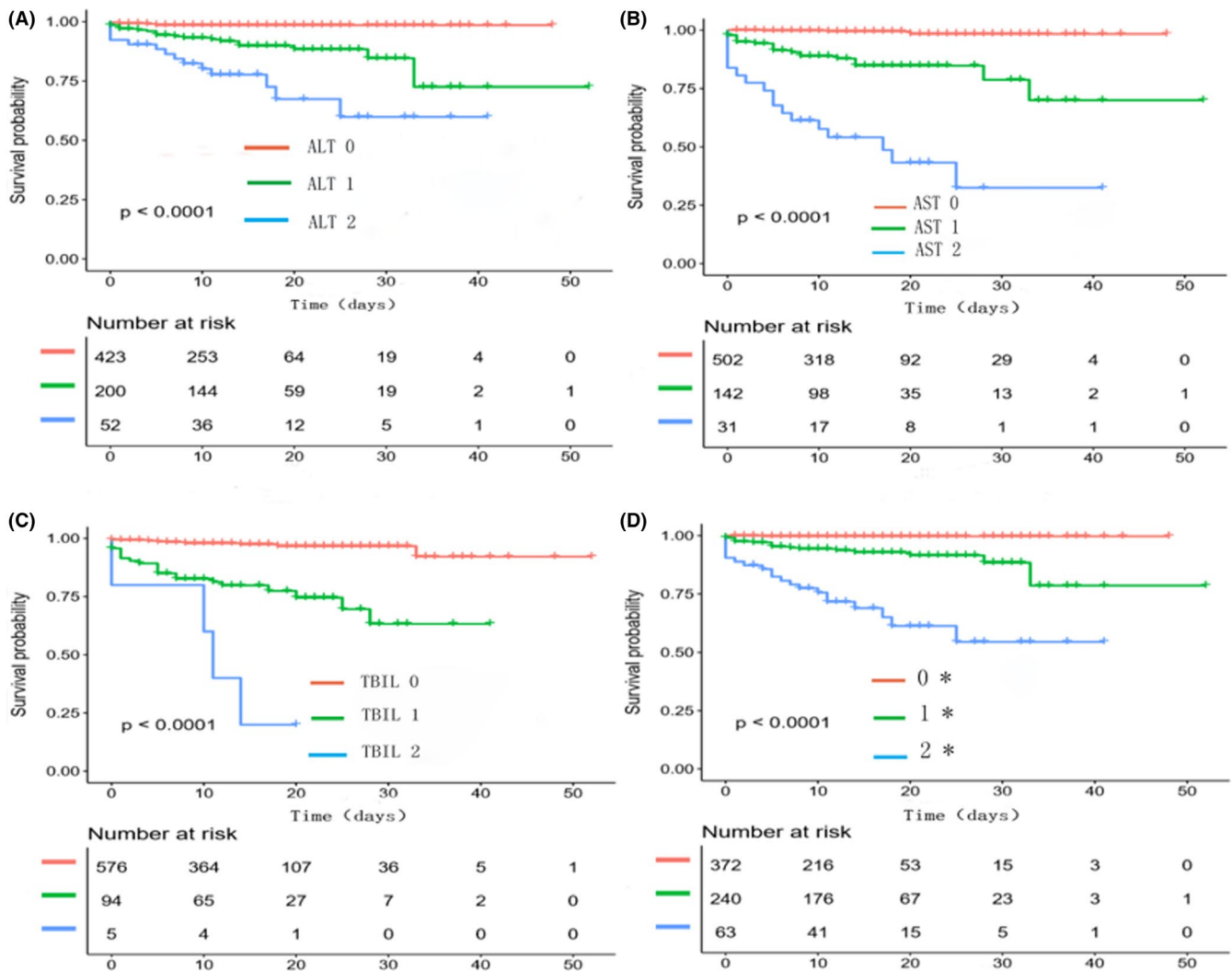


FIGURE 5 Kaplan-Meier curves for mechanical ventilation-free survival probability during hospitalisation in patients with different levels of (A) ALT, (B) AST and (C) TBIL. ALT 0: ALT ≤ 40 U/L; ALT 1: 40-120 U/L; ALT 2: ≥ 120 U/L. AST 0: AST ≤ 40 U/L; AST 1: 40-120 U/L; AST 2: ≥ 120 U/L. TBIL 0: ≤ 21 $\mu\text{mol/L}$; TBIL 1: 21-63 $\mu\text{mol/L}$; TBIL 2: ≥ 63 $\mu\text{mol/L}$. 0*: ALT or AST or TBIL \leq ULN; 1*: ALT or AST or TBIL: ULN-3ULN; 2*: ALT or AST or TBIL ≥ 3 ULN

disease in the fatal group, and this might be a result of multiple organ failure. Severe immune response leads to the release of a large amount of inflammatory cytokines, resulting in systemic inflammatory response syndrome, with hepatic ischaemia and hypoxia, and further hepatic cell damage and necrosis.²⁰ In the nonfatal group, ALT increased slightly with the course of disease and then returned to normal, while AST and TBIL levels were almost within the normal range, which suggested that elevated ALT might be related to liver injury caused by the virus itself.¹⁴ Further analysis suggested that AST over 3-fold ULN, along with abnormal ALT and TBIL, was correlated with the highest risk of death as well as mechanical ventilation. Therefore, it is necessary to monitor the dynamic changes of liver function closely, especially in patients with severe COVID-19, and liver protective agents should be given ahead of time in patients with mechanical ventilation.

Increased leucocytes and decreased lymphocytes were proved to be risk factors for liver injury.²¹⁻²³ This occurred because of inflammatory response having some effect on the occurrence of COVID-19-related liver injury.²³ A study has showed that lymphopenia may be a key factor related to disease severity and mortality,²⁴ and this is consistent with the conclusion of our research.

The study has several limitations. Firstly, this is a retrospective study. The data are not able to assess the causality of COVID-19-related liver injury and poor clinical outcomes. Secondly, some cases did not have enough clinical data on past liver injury. Thirdly, the sample size of this study is small. A large cohort study is needed to clarify the association of dynamic changes in liver function and clinical outcomes.

In conclusion, the dynamic changes in the markers of liver injury have a significant correlation with severity and prognosis of COVID-19. Elevated liver function was closely related to mortality and risk of

| | Mixed Cox (crude) | | | Mixed Cox (adjusted) | | |
|-------------------------------|-------------------|--------------|---------|----------------------|--------------|---------|
| Mortality | | | | | | |
| ALT | HR | 95% CI | P value | HR | 95% CI | P value |
| 0-40 U/L | Ref | | | Ref | | |
| 40-120 U/L | 2.17 | 0.78-6.08 | 0.1385 | 3.18 | 1.05-9.67 | 0.0412 |
| >120 U/L | 5.57 | 1.88-16.55 | 0.002 | 10.50 | 2.94-37.48 | 0.0003 |
| AST | | | | | | |
| 0-40 U/L | Ref | | | Ref | | |
| 40-120 U/L | 9.00 | 2.49-32.55 | 0.0008 | 9.16 | 2.40-34.92 | 0.0012 |
| >120 U/L | 23.86 | 6.34-89.87 | <0.0001 | 19.27 | 4.89-75.97 | <0.0001 |
| TBIL | | | | | | |
| 0-21 µmol/L | Ref | | | Ref | | |
| 21-63 µmol/L | 7.91 | 3.15-19.86 | <0.0001 | 5.29 | 2.00-14.01 | 0.0008 |
| >63 µmol/L | 20.03 | 4.86-82.64 | <0.0001 | 7.01 | 1.24-39.63 | 0.0275 |
| Mechanical ventilation | | | | | | |
| ALT | | | | | | |
| 0-40 U/L | Ref | | | Ref | | |
| 40-120 U/L | 6.31 | 2.53-15.75 | <0.0001 | 7.02 | 2.74-18.02 | <0.0001 |
| >120 U/L | 17.54 | 6.73-45.72 | <0.0001 | 24.52 | 8.86-67.90 | <0.0001 |
| AST | | | | | | |
| 0-40 U/L | Ref | | | Ref | | |
| 40-120 U/L | 22.44 | 6.66-75.58 | <0.0001 | 25.68 | 7.49-88.07 | <0.0001 |
| >120 U/L | 99.65 | 29.17-340.43 | <0.0001 | 116.72 | 31.58-431.46 | <0.0001 |
| TBIL | | | | | | |
| 0-21 µmol/L | Ref | | | Ref | | |
| 21-63 µmol/L | 9.27 | 4.74-18.15 | <0.0001 | 8.18 | 4.03-16.61 | <0.0001 |
| >63 µmol/L | 38.03 | 12.47-116.01 | <0.0001 | 19.56 | 5.21-73.44 | <0.0001 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; TBIL, total bilirubin.

TABLE 3 Multivariate analysis of factors significantly associated with liver injury for the COVID-19 patients

| Risk factors | OR | 95% CI | P value |
|--------------|---------|-----------------|----------|
| Female sex | 0.1045 | 0.03513-0.3109 | 0.000049 |
| WBC | 1.1052 | 1.02099-1.19635 | 0.013371 |
| Lymphocytes | 0.50872 | 0.26006-0.99514 | 0.048357 |

Abbreviations: CI, confidence interval; OR, odds ratio; WBC, white blood cell.

mechanical ventilation. Therefore, these indicators should be closely monitored and evaluated during hospitalisation.

ACKNOWLEDGEMENTS

The study was supported by the National Natural Science Foundation of China (No. 81672115 and 81800507), the Emergency Response Project of Hubei Science and Technology Department (2020FCA023).

Declaration of personal interests: None.

TABLE 2 Determining associations between liver function and clinical outcomes

AUTHORSHIP

Guarantor of the article: Minghua Ge.

Author contributions: Ge Minghua and Tu Yuexing designed the study and revised the manuscript, Huang haijun and Zhou xianlong analysed data and prepared the manuscript, Chen shanshan analysed data and performed manuscript drafting; Hong Li arranges and filters data; Yining Dai performed manuscript drafting; Wu Jia and Jun Zhang searched the literature and analysed the data; Lina Shao, Rong Yan, Mingshan Wang and Jiafeng Wang collected data; Huang Haijun reviewed the results and made critical comments on the manuscript.

ORCID

Minghua Ge  <https://orcid.org/0000-0001-6726-6418>

REFERENCES

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.

2. Wu F, Zhao SU, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579:265-269.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
4. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20:425-434.
5. Weiss SR, Leibowitz JL. Coronavirus pathogenesis. *Adv Virus Res*. 2011;81:85-164.
6. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733.
7. Chau T-N, Lee K-C, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology*. 2004;39:302-310.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020:1061-1069.
9. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020; 1-12.
10. Yang W, Cao Q, Qin LE, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect*. 2020;80:388-393.
11. Tian S, Hu N, Lou J, et al. Characteristics of COVID-19 infection in Beijing. *J Infect*. 2020;80:401-406.
12. Guan W-J, Ni Z-Y, Hu YU, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.
13. Lei F, Liu Y-M, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology*. 2020.
14. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol*. 2020; 1-9.
15. Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcome of COVID-19 patients with liver injury. *J Hepatol*. 2020:1-4.
16. Praktijnjo M, Monteiro S, Grandt J, et al. Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure. *Liver Int*. 2020;40:1457-1466.
17. Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver biochemistries in hospitalized patients with COVID-19. *Hepatology*. 2020.
18. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*. 2020;7:4.
19. Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol*. 2020.
20. Guan GW, Gao L, Wang JW, et al. [Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia]. *Zhonghua Gan Zang Bing Za Zhi*. 2020;28:100-106.
21. Chen G, Wu DI, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130:2620-2629.
22. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020.
23. Chen P, Zhou B. Clinical Characteristics of COVID-19 in patients with liver injury. *Clin Gastroenterol Hepatol*. 2020.
24. Chan J-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395:514-523.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Huang H, Chen S, Li H, et al. The association between markers of liver injury and clinical outcomes in patients with COVID-19 in Wuhan. *Aliment Pharmacol Ther*. 2020;52:1051-1059. <https://doi.org/10.1111/apt.15962>

APPENDIX 1

THE AUTHORS' COMPLETE AFFILIATION LIST

Haijun Huang, Yining Dai, Rong Yan and Mingshan Wang: Department of Infectious Disease, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Shanshan Chen: Department of Infectious Disease, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China; Graduate School of Clinical Medicine, Bengbu Medical College, Bengbu, Anhui Province, China. Hong Li: Department of Infectious Disease, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China; Medical College of Qingdao University, Qingdao, Shandong, China. Xian-Long Zhou: Emergency Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China; Hubei Clinical Research Center for Emergency and Resuscitation, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China. Wu Jia: Department of Hepatobiliary and Pancreatic Surgery & Minimally Invasive Surgery, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Jun Zhang: Department of Orthopaedic Surgery, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Lina Shao: Department of Nephrology, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Jiafeng Wang: Department of Head, Neck and Thyroid Surgery, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Yuexing Tu: Department of Intensive Care Unit, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China. Minghua Ge: Department of Head, Neck and Thyroid Surgery, Zhejiang Provincial People's Hospital & People's Hospital affiliated of Hangzhou Medical College, Hangzhou, Zhejiang, China.