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Troponin I, a risk factor indicating more severe pneumonia among patients with novel coronavirus infected pneumonia

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A R T I C L E  I N F O

Article history:
Received 24 April 2020
Received in revised form 31 May 2020
Accepted 24 June 2020

Keywords:
Novel coronavirus infected pneumonia
Severe acute respiratory syndrome coronavirus 2
Troponin I
Myocardial damage

A B S T R A C T

Background: In December 2019, a novel communicable disease, novel coronavirus infected pneumonia (NCIP) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) broke out. We aimed to analyze the characteristics and severity of patients with myocardial damage in NCIP.

Methods: We enrolled 215 adult patients with NCIP from January 2020 to February 2020. Outcomes were followed up until March 1st, 2020.

Results: 28.37% of the total patients showed increased level of TnI (>0.040 ng/ml). Patients were older and had more cardiovascular complications in increased TnI group. Higher CRP, NT-proBNP, lower immune CD3, CD4 and CD8 cell account and more involved lobes detected by CT scan in the lung were observed in increased TnI group. Patients with elevated TnI had higher CURB-65 scores and were more likely given glucocorticoid therapy and mechanical ventilation than patients in normal TnI group.

Conclusions: Markers of cardiomyocyte injury were elevated not least in elderly males with pre-existing cardiovascular disease. Patients with elevated TnI presented more severe situation, leading to multiple organ dysfunction, which appeared as a pivotal feature of patients with NCIP that requires attention by clinicians in order to provide necessary treatment as soon as possible and improve patients’ outcomes.

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Introduction

In December 2019, a novel coronavirus infected pneumonia (NCIP), originating from the Huanan Seafood Market in Wuhan broke out. Being highly transmissible through mainly air droplets and contact, this epidemic has spread throughout the globe and has caused a total of over 1,500,000 infections outside China as of April 10, 2020. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for this infection was soon isolated and sequenced by Chinese Center for Disease Control and Prevention [1]. SARS-CoV-2 within the subgenus sarbecovirus, Orthocoronavirinae subfamily, turns out to be another coronavirus that infect human currently.

In The Lancet, there are two research reported the clinical characteristics of patients with SARS-CoV-2 infection [2,3]. Symptoms, CT features, treatment, mortality, and comparison between ICU patients and non-ICU patients were reported [4].

Aside from pulmonary edema and hyaline membrane formation observed in lung, the biopsy samples taken from heart tissue from a severe case of NCIP showed a few interstitial mononuclear infiltrates and indicated myocardial damage [5]. We also observed elevated myocardial enzymes in severe patients with NCIP. Therefore, we retrospectively analyzed the characteristics and severity of patients with myocardial damage in NCIP.

Methods

Study design and participants

From January 2020 to February 2020, patients with NCIP admitted to Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine in Shanghai and Tongji Hospital affiliated to Tongji Medical College of Hubei Province Medical College, Huazhong University of Science & Technology in Wuhan were enrolled in this study. The respiratory specimens including nasal and pharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspirates were collected and detected
by real-time RT-PCR methods to confirm the presence of SARS-CoV-2. All participants underwent chest CT scans. The study was approved by Ruijin Hospital Ethics Committee and Tongji Hospital Ethics Committee, respectively. Written informed consent was waived for emerging infectious diseases.

Patients were divided into four types following the standards set up by the Chinese Diagnosis and Treatment of Pneumonia Caused by New Coronavirus Infection (Fifth Version) as follows:

1. Mild type: patients with mild clinical symptoms and no radiological abnormality.
2. Common type: patients presented with fever, cough or other respiratory symptoms, positive radiological findings as pneumonia.
3. Severe type: if one of the following conditions was met:
   - (1) Respiratory distress, RR ≥ 30 per min;
   - (2) Finger oxygen saturation (SaO2) ≤ 93% in resting state;
   - (3) Partial pressure of arterial oxygen (PaO2)/concentration of oxygen inhaled (FiO2) ≤ 300 mmHg.
4. Critical type: if one of the following conditions was met:
   - (1) Respiratory failure occurs and mechanical ventilation is needed;
   - (2) Shock occurs;
   - (3) Patients with other organ dysfunction need intensive care unit (ICU) monitoring treatment.

Patients with incomplete data were excluded from this study.

Data collection

We collected demographic data, symptoms, laboratory, radiological characteristics, severity, and treatment from patients’ electronic medical records. Two physicians reviewed the date collected to double check.

Results

Patient characteristics

Totally, there are 222 patients admitted in the hospital. Seven patients lack the measurement of TnI. Therefore these 7 patients were excluded from this study. The participation rate is 96.85%. The patients were divided into two groups as normal TnI group (0 – 0.040 ng/ml, n = 154) and increased TnI group (>0.040 ng/ml, n = 61) according to their TnI level on admission. The majority patients were men (53%). Patients in normal TnI group were about 13 years younger than those in increased TnI group (p = 0.001) (Table 1). 80% or so of study population allocated exposure history (Table 1). More patients had the complications of hypertension and coronary heart disease in increased TnI group than in normal TnI group (16.2% vs. 41.0% respectively; p < 0.001; 7.1% vs. 16.4%; p = 0.039) (Table 1).

Cases in increased TnI group had higher score of CURB-65 at admission than patients in normal TnI group (p < 0.001). Most patients had fever or cough (80.5% and 48.8%). The distribution of symptoms was similar between these two groups (Table 1).

Laboratory and radiologic findings

On admission, level of CRP, direct bilirubin, creatinine, myoglobin, NT-proBNP, procalcitonin and fibrinogen were higher in increased TnI group than those in normal TnI group (Table 2). Compared with normal TnI group, the patients with lymphocyte count less than 1*10^9/L and D-...
Table 2
Laboratory findings of patients with NCP on admission and comparison between normal Tnl group and increased Tnl group.

| Blood routine examination | Total population (n = 215) | Normal Tnl group (n = 154) | Increased Tnl group (n = 61) | P-value | Adjusted P-value |
|---------------------------|---------------------------|---------------------------|-----------------------------|---------|------------------|
| White blood cell count (10^9/L) | 4.85 (4.09–6.11) | 4.89 (4.09–6.11) | 4.64 (4.00–6.46) | NS      |                  |
| <4 | 47 (21.9%) | 32 (20.8%) | 15 (24.6%) | NS      |                  |
| >10 | 8 (3.7%) | 5 (3.2%) | 3 (4.9%) | NS      |                  |
| Neutrophil count (10^9/L) | 3.14 (2.48–4.06) | 3.22 (2.45–4.03) | 3.02 (2.57–4.45) | NS      |                  |
| Lymphocyte count (10^9/L) | 1.22 (0.77–1.49) | 1.14 (0.87–1.55) | 0.91 (0.64–1.31) | NS      |                  |
| <1.0 | 90 (41.9) | 57 (37.0%) | 33 (54.1%) | 0.022 | 0.026 |
| CRP (mg/L) | 11.8 (6.0–37.2) | 10.7 (7.0–28.8) | 19.5 (3.9–81.9) | <0.001 | 0.016 |
| Hemoglobin (g/L) | 135 (124–148) | 134 (124–148) | 136 (121–150) | NS      |                  |
| Platelet count (10^9/L) | 179 (143–220) | 178 (142–220) | 177 (144–213) | NS      |                  |
| <100 | 7 (3.3%) | 4 (2.6%) | 3 (4.9%) | NS      |                  |

| Blood biochemistry examination | | | | |
| ALT (U/L) | 22 (15–32) | 21 (15–32) | 23 (15–21) | NS      |                  |
| AST (U/L) | 24 (19–33) | 24 (19–32) | 26 (21–33) | NS      |                  |
| Total bilirubin (μmol/L) | 8.2 (6.3–10.4) | 8.0 (6.4–9.7) | 9.1 (6.3–13.2) | NS      |                  |
| Direct bilirubin (μmol/L) | 3.9 (2.9–5.0) | 3.7 (2.9–4.7) | 4.5 (3.3–6.7) | 0.001 | 0.005 |
| Albumin (g/L) | 41 (38–44) | 41 (38–43) | 39 (26–43) | NS      |                  |
| Urea nitrogen (mmol/L) | 4.56 (3.67–5.51) | 4.39 (3.15–4.52) | 4.94 (4.07–5.95) | NS      |                  |
| Creatinine (μmol/L) | 64 (52–77) | 63 (51–75) | 70 (55–87) | 0.001 | 0.012 |
| D-dimer (ng/mL) | 12 (5.6%) | 12 (5.6%) | 14 (5.6%) | <0.001 | 0.006 |
| Sodium (mmol/L) | 139 (137–141) | 139 (137–141) | 139 (137–141) | NS      |                  |
| Potassium (mmol/L) | 3.8 (3.5–4.1) | 3.8 (3.5–4.0) | 3.9 (3.6–4.1) | NS      |                  |

Other
LDH (U/L) | 232 (192–299) | 220 (189–276) | 269 (209–339) | NS      |                  |
Creatine kinase (U/L) | 80 (56–125) | 76 (52–113) | 93 (64–170) | NS      |                  |
CK-MB (U/L) | 12 (10–15) | 12 (9–14) | 13 (11–16) | NS      |                  |
Myoglobin (μg/L) | 7.6 (3.2–17.4) | 5.4 (3.0–12.7) | 11.6 (5.1–37.0) | 0.001 | 0.016 |
Procalcitonin (pg/mL) | 0.03 (0.02–0.07) | 0.03 (0.02–0.06) | 0.04 (0.02–0.08) | 0.032 | 0.048 |
Hemoglobin (g/L) | 139 (137–141) | 139 (137–141) | 139 (137–141) | NS      |                  |
Potassium (mmol/L) | 3.8 (3.5–4.1) | 3.8 (3.5–4.0) | 3.9 (3.6–4.1) | NS      |                  |

Arterial blood gas analysis
PH | 7.40 (7.37–7.43) | 7.40 (7.38–7.43) | 7.39 (7.37–7.42) | NS      |                  |
PаCO2 (kPa) | 12.3 (10.1–14.8) | 12.6 (10.4–15.4) | 11.8 (9.8–14.2) | NS      |                  |
PаCO2 (kPa) | 5.24 (4.80–5.64) | 5.25 (4.85–5.64) | 5.21 (4.73–5.66) | NS      |                  |
Oxygen saturation (%) | 97.6 (96.1–98.7) | 97.6 (96.2–98.8) | 97.4 (95.7–98.5) | NS      |                  |
Standard bicarbonate (mmol/L) | 23.8 (22.7–25.1) | 24.0 (22.8–25.1) | 23.5 (22.5–24.7) | NS      |                  |
Base excess | –0.9 (–2.4–0.8) | –0.6 (–2.3–0.8) | –1.4 (–2.8–0.3) | NS      |                  |
Lactate (mmol/L) | 1.4 (1.0–2.1) | 1.4 (0.9–2.0) | 1.3 (1.0–2.15) | NS      |                  |

Immune status
CD3 count | 721 (491–1041) | 779 (505–1085) | 629 (328–913) | 0.006 | 0.008 |
CD4 count | 85 (39.5%) | 50 (32.5%) | 35 (57.4%) | <0.001 | <0.001 |
CD8 count | 425 (297–650) | 450 (307–680) | 395 (173–607) | 0.017 | 0.019 |
GALT | 74 (34.8%) | 42 (37.3%) | 32 (52.5%) | <0.001 | 0.015 |
GALT | 246 (154–389) | 270 (161–409) | 215 (133–321) | 0.031 | 0.046 |
IGM | 11.7 (10.1–13.6) | 11.7 (9.9–13.4) | 11.8 (10.6–13.8) | NS      |                  |
IgA | 22.8 (1.76–3.05) | 22.6 (1.71–2.97) | 2.36 (1.90–3.27) | NS      |                  |
IgM | 0.94 (0.70–1.22) | 0.95 (0.70–1.21) | 0.86 (0.69–1.28) | NS      |                  |

Tnl, troponin I; CRP, C reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK-MB, creatine kinase MB; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal - pro hormone BNP.

Data were shown as number (percentage) or median (IQR). P-values between two groups were calculated by Fisher’s exact test, Chi-square test, or Mann–Whitney U test. Adjusted P-values were calculated by covariance analysis after adjusting age, sex. These numbers in bold indicate they are less than 0.05.
dimer more than 0.5 μg/L was more in increased TnI group (37.0% vs. 54.1%, 31.2% vs. 50.8% in normal TnI group and increased TnI group respectively; p = 0.022, p = 0.007) (Table 2). Arterial blood gas between the two groups showed no significant differences. Compared with cases in increased TnI group, patients in normal TnI group presented higher level in CD3 count, CD4 count and CD8 count than those in increased TnI group, while their level of antibodies (IgG, IgA, IgM) were similar (Table 2).

In the terms of CT examination, ground-glass opacities (94.9%) and pleural thickening (59.1%) were the most common manifestations (Table 3). Images suggested more patients with 4–5 lobes involved in increased TnI group (52.00% vs. 75.4% in normal TnI group and increased TnI group respectively; p = 0.006) (Table 3).

**Severity and treatment**

The proportion of severe and critical illness in increased TnI group was significantly higher than those in normal TnI group (11.9% vs. 14.8%, 2.8% vs. 11.5% in normal TnI group and increased TnI group respectively; p = 0.014) (Table 4). Regarding therapy situation, subjects in increased TnI group were more likely given glucocorticoid therapy and mechanical ventilation than patients in normal TnI group (Table 4).

**Discussion**

Coronavirus could result in severe respiratory syndrome [6]. However, myocardial lesions and the elevation of myocardial enzymes in coronavirus infections are limited. Our study found that SARS-CoV-2 induced elevated myocardial enzymes and myocardial injury. From the present study, 28.37% of the total patients showed increased level of TnI. Elevated TnI usually indicates myocardial damage. Previous study reported increased serum troponin concentration might be a biomarker to stratify risk in subjects with pneumonia [7]. Troponin elevation in sufferers with COVID-19 is likely to be due to multifactorial non-ischemic causes, and less likely to be on account of atherothrombotic coronary occlusion [8]. Biopsy heart specimens of a patient with SARS-CoV-2 showed a few interstitial mononuclear inflammatory infiltrates [5]. SARS-CoV-2 was reported to use the same cell entry receptor as SARS-CoV (human angiotensin-converting enzyme 2 [hACE2]) [9]. As a homolog of the key enzyme of renin-angiotensin system, ACE2 is highly expressed in arterial and venous endothelial cells and arterial smooth muscle cells aside from lungs, which account for myocardium’s susceptibility of SARS-CoV-2 [10–12]. Previous study suggested SARS-CoV mediated myocardial inflammation and damage through down-regulating myocardial ACE2 system, which might serve as the mechanism of SARS-CoV-2 impairing heart as well [13].

On the one hand novel coronavirus directly invades the myocardium and results in myocardial damage. On the other hand, previous cardiovascular complications aggravate this process. Pneumonia and cardiac disease frequently coexist in the same patients [14]. New-onset or worsening cardiac complications, not least atrial fibrillation are well-characterized complications of acute pneumonia [15]. Researchers have showed during the course of community-acquired pneumonia, a high incidence of cardiac complications, was independently associated with increased short-term mortality [7]. Consistent with previous study [2,16], the comparison of baseline characteristics indicated elderly male with comorbidities including hypertension and coronary heart disease were more likely to present a high level of TnI. A prospective study of elderly persons reported pre-existing heart failure figures as a risk factor for the development of pneumonia and as well increased the risk of pneumonia-related death [17]. This phenomenon suggests that patients with underlying cardiovascular disease have less robust cardiac reserve function, therefore their cardiac systolic and diastolic dysfunction are more vulnerable when virus attacks the myocardium. Hypoxia caused by pneumonia leads to an increase in heart rate, which induces the shortening diastolic time and insufficient coronary perfusion, thereby aggravating myocardial ischemia and hypoxia, ultimately causing instability and even collapse of the circulatory system. In our research, that patients with elevated myocardial enzymes had higher CURB-65 scores and higher NT-proBNP- a biomarker of cardiac function confirm the above theory from another aspect.

With regard to laboratory tests and CT scan results, higher CRP, lower immune CD3, CD4 and CD8 cell account and more involved lobes in the lung were observed in increased TnI group indicating higher virus load and more severe inflammatory response, also known as cytokine storm, a phenomenon associated with a wide variety of infectious and noninfectious diseases [18]. The storm of inflammatory factors can further cause disorders in multiple organs and systems as patients in increased TnI group showed elevating bilirubin, creatinine and D-dimer. Creatinine is the product of muscle metabolism in the human body and is mainly excreted by the glomerular filtration. Increased creatinine concentration indicates kidney damage. As a specific degradation product of fibrin, D-dimer increase when hypercoagulability and secondary fibrinolysis take place in the body. Figuring as a biomarker of liver function, bilirubin elevates if liver damage happens. Aforementioned multiple organ disorders along with myocardial damage exacerbated patients’ condition.

**Table 4**

| Treatment | Total population | Normal TnI group | Increased TnI group | P-value | Adjusted P-value |
|-----------|-----------------|-----------------|--------------------|---------|------------------|
| Antibiotics | 101/200 | 70/143 | 31/57 | NS | |
| Glucocorticoids | 41/215 | 24/154 | 17/61 | 0.039 | NS |
| Assisted ventilation | 34/205 | 18/154 | 16/61 | 0.008 | 0.047 |
| Severity in hospital | | | | | |
| Mild + common | 164/201 | 122/143 | 42/58 | 0.021 | 0.036 |
| Severe | 26/201 | 17/143 | 9/58 | (14.8%) | |
| Critically severe | 11/201 | 4/143 | 7/58 | (11.5%) | |

TnI, troponin I. Data were shown as number/total numbers (percentage). P-values between two groups were calculated by Fisher’s exact test, or Chi-square test. Adjusted P-values were calculated by covariance analysis after adjusting age, sex. These numbers in bold indicate they are less than 0.05.

**Table 3**

| Abnormalities on chest CT | Total population (n = 215) | Normal TnI group (n = 154) | Increased TnI group (n = 61) |
|---------------------------|---------------------------|---------------------------|---------------------------|
| Pleural effusion | 15 (7.0%) | 9 (5.8%) | 6 (9.8%) | NS |
| Pleural thickening | 127 (59.1%) | 90 (58.4%) | 37 (60.7%) | NS |
| Ground-glass opacity | 204 (94.9%) | 145 (94.2%) | 59 (96.7%) | NS |
| Fibrous stripes | 42 (19.5%) | 33 (21.4%) | 9 (14.8%) | NS |
| Consolidation | 62 (28.8%) | 50 (32.5%) | 12 (19.7%) | NS |
| Numbers of involved lung lobes | | | | |
| 0-1 | 30 (14.0%) | 26 (16.9%) | 4 (6.8%) | 0.006 | 0.014 |
| 2-3 | 59 (27.4%) | 48 (31.1%) | 11 (18%) | |
| 4-5 | 126 (58.6%) | 80 (52.0%) | 46 (75.4%) | |

TnI, troponin I; CT, computed tomography. P-values between two groups were calculated by Fisher’s exact test, or Chi-square test. Adjusted P-values were calculated by covariance analysis after adjusting age, sex. These numbers in bold indicate they are less than 0.05.
Our study suffers from three limitations: 1. As a cross-sectional study, we have not included data of dynamic changes in myocardial enzymes, echocardiography and not evaluated diastolic function and ejection fraction of heart. The relationship between heart damage and NCIP pneumonia could be better assessed if aforementioned data could be included. 2. The data in this study was from 2 centers and incomplete data has been excluded, possibly resulting in a certain degree of selection bias. 3. For part of patients were still hospitalized as of press, we failed to know their eventual prognosis. Nevertheless, this retrospective study suggested myocardial damage is not ought to be ignored in the diagnosis and treatment of patients with NCIP.

Conclusion

Myocardial enzymes were elevated in a significant proportion of patients with NCIP, not least in elderly males with pre-existing cardiovascular disease. Patients with elevated myocardial enzymes presented a stronger immune and inflammatory response, leading to multiple organ dysfunctions including heart, liver and kidney which appeared as a pivotal feature of patients with NCIP that requires attention by clinicians in order to provide necessary treatment as soon as possible and improve patients’ outcomes.

Acknowledgements

Thanks for all medical staff and patients involve in this study.

Funding

This work was supported by the National Key Research and Development Project (sq2018yghb000345); National Natural Science Foundation of China (81870041); and Shanghai Key Discipline for Respiratory Diseases (2017ZZ02014). This work was also funded in part by a grant from Innovative Research Team of High-Level Local Universities in Shanghai.

Authors’ contributions

W Chen is a member of the first batch of medical teams from Shanghai to support Hubei. Conception or design of the work: JMQ and DL. Data collection: WC, YF, YSX, HHL and JYY. Data analysis and interpretation: WPH, HC and DL. Draft of the article: DL, QYY. Critical revision of the article: JMQ and DL.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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