

Early-stage predictive markers of critically ill COVID-19 cases

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Abstract

Background: Severe cytokine storm syndrome (CSS) is considered as the cause of death among critically ill COVID-19 cases. Early identification of the high-risk severe cases is crucial to lower the fatality and healthcare costs.

Methods: In this study, we retrospectively analyzed the first and second-week serum levels of IL-6, IL-8, and IL-10 of 50 COVID-19 cases. We calculated the ratios of IL-6/IL-10 and IL-8/IL-10 at 3rd, 6th, 9th, and 12th days of hospitalization.

Results: We collected 50 COVID-19 cases (male 54%, mean age 51.2, range 18 - 86), including 39 mild cases (78%), 7 severe/recovered cases (14%), and 4 died cases (8%). The ratios of IL-6/IL-10 and IL-8/IL-10 among mild cases were below 27 (the highest, 26.9) along the 4 testing points of two week hospitalization, while we found that the IL-6/IL-10 and IL-8/IL-10 ratios were as high as 187.51 and 225.3 respectively in the death group on 3rd day with the highest IL-6/IL-10 ratio of 297.28 on the 6th day of hospitalization.

Conclusions: Our preliminary results suggest that the ratios of IL-6/IL-10 and IL-8/IL-10 at the early stage (the first two weeks) of COVID-19 could be a predictive marker for the disease prognosis, of which the cut-off lines were suggested below 50 for a mild and recoverable severe cases.

Background

COVID-19 pandemic has caused devastating damages to global economy and frightening human deaths worldwide. High transmissibility and fatality of COVID-19 has been an unprecedented challenge to global health. Even though over 80% of COVID-19 cases were mild, 20% of severe and critically ill cases has overburnt the healthcare system of countries with high epidemic. In the large number of death cases infected with COVID-19 virus, the cause of death is found to be due to immune disorders, manifested in immune impairment and cytokine storm production[1]. Early identification of the high-risk severe cases is crucial to lower the fatality and healthcare costs. In this study, we aimed to find a early-stage predictive markers of critically ill COVID-19 cases.

Methods

Participants and sample collection

In this study, we retrospectively analyzed the first and second-week serum levels of IL-6, IL-8, and IL-10 of 50 COVID-19 cases (male 54%, mean age 51.2, range 18 - 86), including 39 mild cases (78%), 7 severe/recovered cases (14%), and 4 died cases (8%). All patients were hospitalized within the first week of symptom onsets. The blood testing of each case was conducted at 3rd, 6th, 9th, and 12th days of hospitalization. We calculated the ratios of IL-6/IL-10 and IL-8/IL-10 among mild, severe/recovered and died cases.

Results

The ratios of IL-6/IL-10 and IL-8/IL-10 among mild cases were below 27 (the highest, 26.9) along the 4 testing points of two week hospitalization, while the severe/recovered cases had an up-then-down variation of IL-6/IL-10 and IL-8/IL-10 ratios with the highest ratio of 45.3 at the 9th day. Importantly, we found that the IL-6/IL-10 and IL-8/IL-10 ratios were as high as 187.51 and 225.3 respectively in the death group on 3rd day with the highest IL-6/IL-10 ratio of 297.28 on the 6th day of hospitalization. (Fig.1) The balance of pro and anti-inflammatory cytokines is crucial for human anti-virus immunity and prognosis of COVID-19 disease. Our preliminary results suggest that the ratios of IL-6/IL-10 and IL-8/IL-10 at the early stage (the first two weeks) of COVID-19 could be a predictive marker for the disease prognosis, of which the cut-off lines were suggested below 50 for a mild and recoverable severe cases.

Discussion

Severe cytokine storm syndrome (CSS) is considered the cause of death among critically ill COVID-19 cases [2]. IL-6 and IL-8 are the most important pro-inflammatory cytokines [3], while IL-10 is an anti-inflammatory cytokine [4-6]. This study suggest that the ratios of IL-6/IL-10 and IL-8/IL-10 at the early stage (the first two weeks) of COVID-19 could be a predictive marker for the disease prognosis.

In this study, all patients were hospitalized within the first week of symptom onsets. Therefore, these three indicators can accurately reflect the inflammation and anti-inflammatory in patients. In the mild group, we found the ratio of IL-8/IL-10 was higher than IL-6/IL-10 along the 4 testing. However, IL-6/IL-10 levels were higher in the severe group. Study[7] has shown that the IL-6 level in mild patients was always very low, while IL-6 was drastically increased in severe patients. Interestingly, as IL-6, IL-8 stayed at a relatively stable levels within two weeks, and then went up on day 15-20 followed by a decline back to the initial level. This result is consistent with the present study.

In this study we found the cut-off lines, which were suggested below 50 for a mild and recoverable severe cases. However, the ratios of IL-6/IL-10 and IL-8/IL-10 were higher at the early stage in the died group. This early-stage predictive markers may indicate a poor prognosis. The study[8] of SARS found that the ratio of IL-6/IL-10 at 2th was 4, while the ratios of IL-6/IL-10 was below 2 at the 9th day among the died group. The difference between COVID-19 and SARS virus is that the body can cause varying degrees of inflammation in the critical group. So the conclusion is that in early-stage the increasingly in the ratio of pro and anti-inflammatory cytokines (above 50) indicates an enhanced collective inflammatory response, indicate a poor prognosis. Due to the limited number of cases included in this study, further studies are needed to validate our findings.

Conclusions

We showed that, the ratios of IL-6/IL-10 and IL-8/IL-10 at the early stage (the first two weeks) of COVID-19 could be a predictive marker for the disease prognosis, of which the cut-off lines were suggested below

50 for a mild and recoverable severe cases.

Abbreviations

CSS: Severe cytokine storm syndrome; SARS: Severe Acute Respiratory Syndromes

Declarations

All participates/patients were consented orally to participate our study.

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Author contributions

XM and ZZ had full access to all the data in the study, who took responsibility for the integrity of the data and the accuracy of the data analysis. ZZ and JX contributed to acquisition of data. SWY, JX and ZZ contributed to analysis and interpretation of data. Deng contributed to critical revision of the manuscript for important intellectual content. ZZ, SWY and JX contributed equally and shared first authorship.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Ethics Commission of Shandong Provincial Chest Hospital (2020XKYYEC-03).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

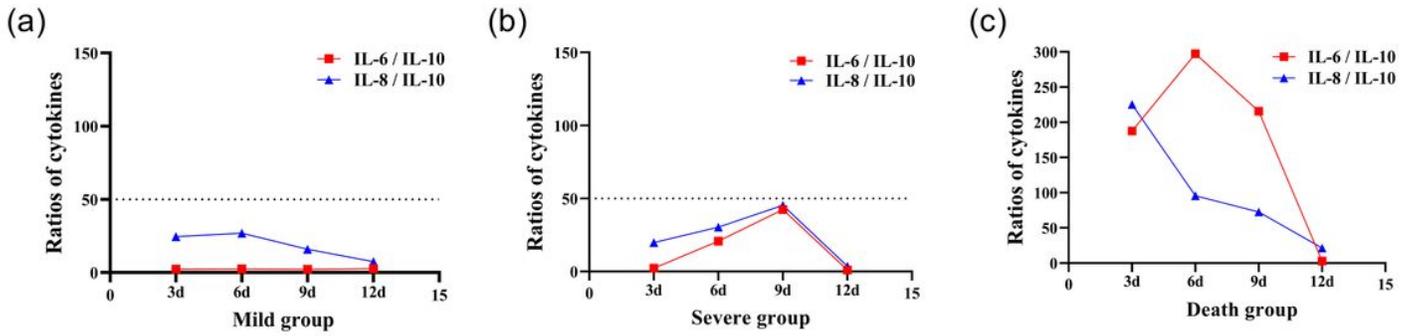


Figure 1

Ratios of serum pro and anti-inflammatory cytokines among COVID-19 patients. (a) 39 mild cases; (b) 7 severe/recovered cases; (c) 4 died cases