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Journal of Infection 82 (2021) e5–e7

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

The potential indicators for pulmonary fibrosis in survivors of severe COVID-19

Dear editor,

We read great interest in the risk factors of critical or mortal COVID-19 cases, recently reported by Ye et al. in this journal.[1] Here we paid more attention about the long-term lung sequelae among survivors of severe COVID-19. With more than 21 million people worldwide recovered from COVID-19, early analysis suggested a high rate of patients had residual abnormal lung function and fibrotic remodeling on CT, especially in survivors of severe SARS-CoV-2 associated pneumonia.[2,3] These might contribute to long-term impairment of lung function or even lung transplants. The early identification of patients at higher risk of lung injury and fibrotic damage is critical.[4] Therefore, we performed an observational cohort study that compared fibrosis and non-fibrosis group to investigate the potential indicators for post-fibrosis.

The two-center retrospective study was approved by the institutional review board of Xianning Central Hospital and Huangshi Central Hospital, both in Hubei Province. The informed consent was waived. From December 19, 2019 to March 5, 2020, a total of 430 consecutive patients with positive RT-PCR were reviewed. Finally 81 survivors who recovered from severe COVID-19 pneumonia were enrolled. The median hospitalization was 26 days; all had at least three follow-up CT scans after discharge, and the median period between the discharge and the latest CT scan was 58 days (IQR: 25–46). Pulmonary fibrosis was diagnosed based on the extensive and persistent fibrotic changes, including parenchymal bands, irregular interfaces, reticular opacities, and traction bronchiectasis with or without honeycombing on the follow-up CT scans. CT scores were evaluated by two experienced cardiothoracic radiologists independently, and quantified by the percentage of high attenuation area using thresholds with pixels between 0 and −700 HU via Chest Imaging Platform (http://chestimagingplatform.org/). Fibrosis grouping was reached by consensus. Comparative analysis were performed with R software, covering age, sex, prior medical history, signs and symptoms, laboratory data, oxygen supply, ICU admission, and treatments. The statistical difference was assessed with the unpaired, 2-tailed chi-square test for categorical variables and *t*-test or Mann-Whitney for continuous variables. $P<0.05$ indicated a statistically significant difference.

All patients were divided into two groups: fibrosis ($N=42$) and non-fibrosis ($N=39$). Fibrosis cases were older ($p<0.001$), disproportionately male ($p=0.036$), with more underlying diseases (Any [78% vs. 41%]; diabetes [31% vs. 23%]; hypertension [40% vs. 23%]; chronic pulmonary disease [21% vs. 7%]; chronic liver disease [19% vs. 13%]; cardiovascular and cerebrovascular diseases [29% vs. 15%]) than non-fibrosis cases. It is worth stressing that fibrosis group had much higher rate of fever ($p=0.034$), long prehospital duration of fever ($p=0.001$), and shortness of breath ($p=0.024$) on admission. Abnormal parameters including leucocytosis, neutrophilia, lymphopenia, eosinopenia, elevated CRP and D-dimer, had significant difference between groups (Fig. 1A). Details were provided in Supplementary Table.

Importantly, the longitudinal analysis demonstrated distinct features (Fig. 1B). In fibrosis group, we noticed that the levels of neutrophils, NLR, CRP and LDH were markedly above the normal range within 4 weeks, while CRP dramatically elevated unlike other parameters declining in the next 4 weeks. Conversely, in non-fibrosis group, CRP and LDH elevated within 2 weeks, then sharply dropped back to normal. Lymphopenia and eosinopenia occurred in most patients on admission. Note that the sustained low values of lymphocytes and the continuous absence of eosinophil early in-hospital showed a statistically significant difference. Fibrosis group suffered from more severe complications, resulting in higher rates of ICU admission and more intensive treatments to control the disease progression (Fig. 1C).

To date, available data indicate that more than a third of recovered patients develop fibrotic abnormalities on discharge.[2,5] Additionally, 47% of patients had impaired DLCO and 25% had reduced TLC.[2] It seems even worse in severe survivors. In our study, all survivors had varying degrees of fibrotic damage, ranging from subtle linear opacities to diffuse distribution of crazy-paving pattern (Fig. 1D); 52% (42/81) of patients showed extensive and unimproved fibrosis in a longitudinal analysis of CT findings. The radiographical abnormalities strongly correlated with long-term impairment of lung function.[6] It remains unclear why certain individuals are able to recover from lung injury, whereas others develop into fibrotic damage.[7] Several markers associated with mortality risk, including age, illness severity, length of ICU stay, mechanical ventilation and hyper-inflammatory markers, might be the potential predictors for pulmonary fibrosis.[8]

The highlight here reported a series of early indicators after tracing backwards to the features of disease progression between fibrosis and non-fibrosis group. Other than common factors of advancing age, male and underlying diseases, that had been well described,[9] it should be noted that the dynamic evolution of inflammatory markers within two weeks of hospitalization might point to fibrosis. More importantly, the long prehospital duration of fever, the rapid and shallow breathing, and the ab-

Abbreviations: COVID-19, Coronavirus disease 2019; CT, Computed tomography; SARS-CoV, Severe acute respiratory syndrome coronavirus; IQR, interquartile range; RT-PCR, Realtime Polymerase chain reaction; NLR, Neutrophil to lymphocyte ratio; CRP, C-reactive protein; LDH, Lactate dehydrogenase; ICU, Intensive care unit; DLCO, Diffusing Capacity of the lungs for carbon monoxide; TLC, total lung capacity.

https://doi.org/10.1016/j.jinf.2020.09.027

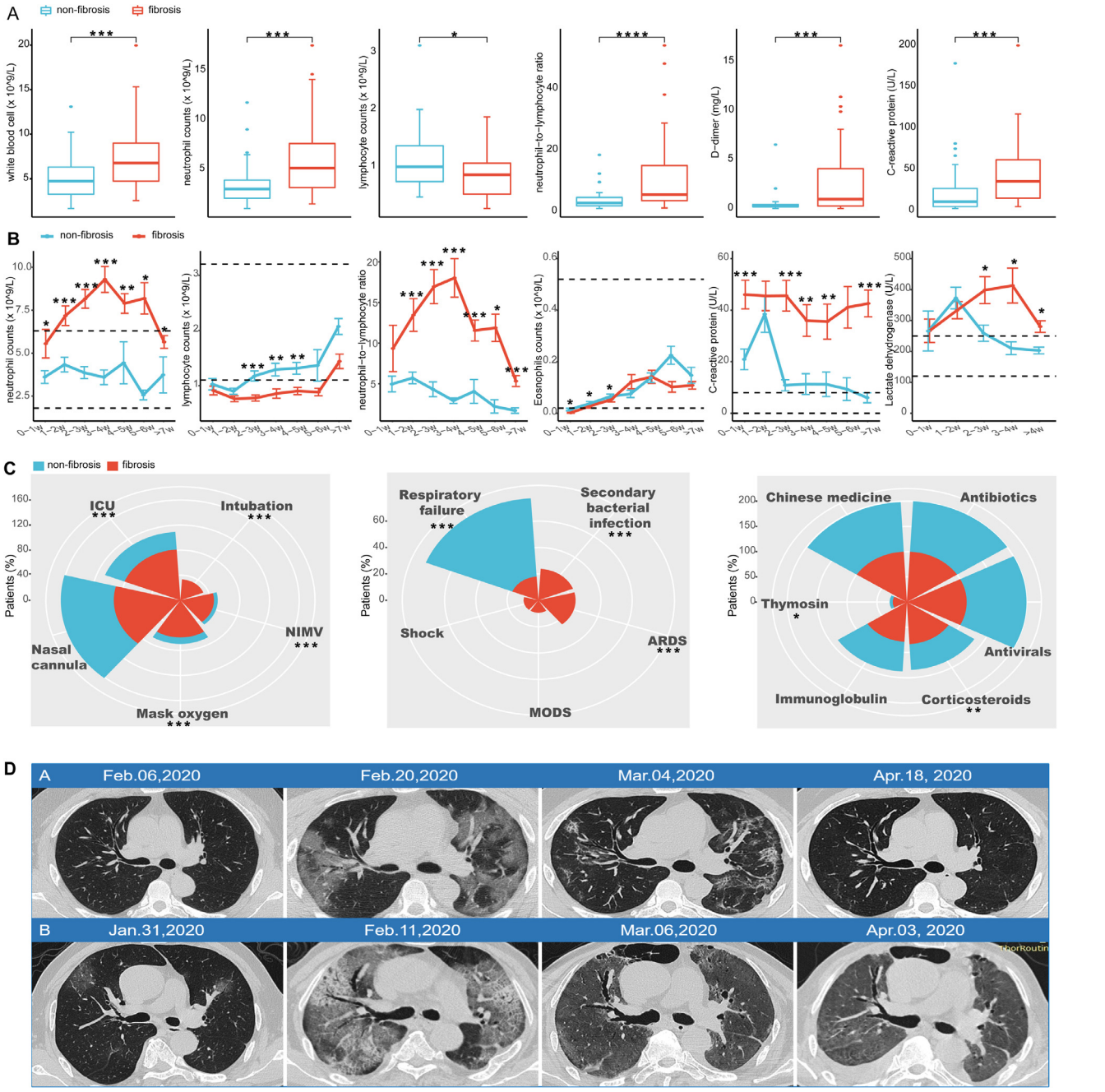

Fig. 1. The clinical course and the temporal changes of follow-up CT in fibrosis and non-fibrosis groups. (A) A series of indexes on admission showed significant difference between two groups. (B) Dynamic changes of inflammatory markers including neutrophils, lymphocytes, neutrophil-to-lymphocytes ratio, eosinophils, c-reactive protein, and lactate dehydrogenase showed distinct features between two groups. (C) Oxygen supply, ICU admission, complications and treatment during hospitalization were included for comparative analysis. ***, $p<0.001$; **, $p<0.01$; *, $p<0.05$. (D) Temporal changes in axial chest CT images of two survivors indicated the distinct evolutions of lung involvement. a) A 33-year-old male with critical pneumonia who undergone both ARDS and mechanical ventilation, discharged at March 5, 2020 with subtle linear opacities on follow-up CT. b) A 69-year-old male with critical pneumonia, undergone both ARDS and mechanical ventilation and discharged at March 1, 2020 with fibrotic pulmonary remodeling on follow-up CT. ARDS indicates acute distress respiratory syndrome.

sence of eosinophil on admission might be a combination of early indicators. All these can be readily obtained in clinical practice; thus, it holds great promise for large-scale use in a catastrophic pandemic.

Certain limitations and potential biases may exist in our study. Firstly, due to the relatively short-term of clinical follow-up, a large cohort of prospective and long-term analysis should be performed for more evidence. Secondly, only survivors of severe or critical COVID-19 with a high likelihood of lung injury were enrolled in our study, when all resources were stretched in a pandemic. The patients with mild or moderate infection would be added for analysis in our further study.

Acknowledgment

This two-center study was approved by the ethics committee, with a waiver of informed consent. Great thanks for the Xianning Central Hospital and Huangshi Central Hospital, both in Hubei

Province. Thanks for all the valuable cases presented by these hospitals. We are grateful to all members of the frontline for their contribution to the SARS-CoV-2 outbreak.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.09.027.

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