Cancer patients/survivors, lymphocytes, and severe COVID-19

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*Wen-hua liang*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Cai-chen Li*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Jian-fu Li*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Shan Xiong*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Ran Zhong*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Bo Cheng*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Li-min Ou*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

*Zi-sheng Chen*
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

Qi-hua He
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

Zhan-hong Xie
Department of Respiratory Disease, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

Jian-xing He
Department of Thoracic Oncology and Surgery, China State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University

✉ drjianxing.he@gmail.com Corresponding Author

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- SARS-CoV-2, cancer survivors, cancer patients, decreased lymphocytes
Abstract
There is a heated debate on whether the cancer survivors have worse outcomes in coronavirus disease 2019 (COVID-19). This study showed that both cancer survivors and cancer patients have decreased lymphocytes, partially explaining why these patients were associated with poorer prognosis in severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2) in principle. Therefore, patients with cancer history, whether they are going active treatment or not, deserve special attention.

Introduction
The coronavirus disease 2019 (COVID–2019) has become a pandemic, causing 823,626 confirmed cases and 40,598 deaths according to WHO, as of Apr 1, 2020.¹ Previously we published a nationwide study in China indicating that cancer patients were associated with poorer outcomes during COVID–19 caused by SARS-CoV–2 infection.² Seventy-five percent (12/16) of COVID–19 patients in our study were cancer survivors who received no active treatments, which was similar to the proportion (58.3%, 7/12) reported recently by Yu et al.³ A considering number of scholars have proposed that cancer patients or cancer survivors receiving no active treatment might not have significant immune suppression, therefore, these patients are not predisposed to the higher susceptibility or poorer prognosis of COVID–19.³⁻⁵ Hence, we sought to investigate the immune level among these patients.

Results
In the healthy population, we observed a negative linear correlation between age and lymphocyte count ($r = -0.74, r^2 = 0.54, Figure S1$). The changes in lymphocyte count and NLR of each patient were summarized in Figure S2. The average lymphocyte count and NLR of each category were shown in Table S1 and were illustrated in Figure 1A–1C. We found that, within 6 months after surgery for lung cancer, lymphocytes decreased significantly, then recovered gradually, but lower than the preoperative levels. Similar trends were observed among patients with or without adjuvant chemotherapy. In contrast, there was no short-term decline in patients with benign pulmonary nodules after surgery.

By studying the 16 cases with cancer history in the nationwide cohort of COVID–19 (baseline features
shown in Table S2), we found that the cancer survivors had a high risk of critical illness after adjusting other confounders compared with patients with no cancer history, and had a prognosis closer to cancer patients rather than non-cancer patients (cancer survivors: HR 3.55, 95% CI, 1.43 to 8.82; cancer patients, HR 4.92, 95% CI 1.12–21.6; Figure 1D, Table 1).

Discussion
We have acknowledged that age was the most important determinant of prognosis among COVID-19 patients. In the healthy population, we observed a negative linear correlation between age and lymphocyte count, which provided an indirect support for using lymphocyte count to assess the risk of severe COVID-19.

The lymphocyte count from postoperative cancer survivors and from patients with advanced lung cancer were both lower than healthy people. This implied that the immunity of cancer survivors was compromised, which persisted over time, regardless of receiving adjuvant chemotherapy or not. The uncontrolled virus infection in immune-compromised patients will cause extensive cell damages and induce T cell exhaustion even cytokine storm, which are common reasons for critical illness. Some recent studies showed that the cytokines were negatively associated with lymphocyte count.6,7 Interestingly, there was no short-term decline in patients with benign pulmonary nodules after surgery, suggesting that this decline in immunity may not be related to the surgery per se. Taken together, we assumed that this was due to the interaction between cancer and surgical trauma, which warrants further investigation.

In summary, we showed that both cancer survivors and patients might have reduced lymphocytes, partially explaining why these patients were associated with poorer prognosis in SARS-CoV-2 infection in principle. Patients with cancer history who are not undergoing active treatment should also deserve special attention.

Methods
To study the immune level of patients in different status, we have collected the pre-and post-operative complete blood counts (CBCs) of patients who underwent resection for stage I to IIIA lung cancer (N = 4,313) or benign non-infection pulmonary nodules (N = 52) in our center from 2013 to
2018. In addition, CBCs from healthy patients (retrieved from annual checkup reports) (N = 144,983) and patients with advanced lung cancer before and after chemotherapy (N = 3,238) during the same period were used as controls. Postoperative CBCs tested after cancer recurrence were excluded. We analyzed the absolute lymphocyte count and neutrophil-to-lymphocyte ratio (NLR), which can be considered as one of the measures for immune status, because lymphocytes are essential to our defense against virus and cancer, and both lymphocyte count and NLR have been proved as important prognostic factors in patients with cancers or virus infection.8–11 In addition, to illustrate the prognosis of cancer survivors who had COVID–19, we collected and analyzed a nationwide cohort of 1,590 COVID–19 cases from 575 hospitals in China as of Jan 31st. Details in data collection and processing were provided in previous publication2 and the appendix (p1). A cox regression model was used to study the impact of cancer status on risk for critical illness with adjustment for age, other comorbidity, and smoking.

Declarations
Acknowledgements
We declare no competing interests. This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. Because this is a retrospective study, the ethical committee approved the study and waived the informed consent requirement. We sincerely thank all the hospital for providing data, on behalf of China Medical Treatment Expert Group for COVID–19. We thank Meng Shu in Janssen Research and Development, Qiang Lin and Wei Shen in Yitu Technology for the great support in processing the data. This study is supported by the China National Science Foundation (grant no 81871893) and the Key Project of Guangzhou Scientific Research Project (grant no 201804020030).

Author Contributions
H. J. and L. W. conceived of and designed the study. L. W., L. C. and L. J. developed the methodology. H. J., L. W., L. C., L. J., X. S., Z. R., C. B., O. L., C. Z., H. Q., X. Z. and L. J. acquired the data. L. W., L. C., L. J., and X. S. analyzed and interpreted the data. L. W., L. C., L. J. and X. S. wrote the manuscript.

Competing Interests statement
All authors declare no competing interests.
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Table
Table 1. Cox regression for risk factors of critically-ill COVID-19

| Variables                        | Hazard ratio | 95% confidence interval | P value |
|----------------------------------|--------------|--------------------------|---------|
| Cancer history                   |              |                          | 0.003   |
| No cancer (reference)            |              |                          |         |
| Cancer survivors                 | 3.548        | 1.426                    | 8.824   | 0.006   |
| Current cancer patients          | 4.917        | 1.119                    | 21.597  | 0.035   |
| Age                              | 1.039        | 1.025                    | 1.053   | 0       |
| Any other comorbidity (yes vs. no) | 1.978       | 1.335                    | 2.929   | 0.001   |
| Smoking (yes vs. no)             | 1.519        | 0.902                    | 2.559   | 0.116   |

*, other comorbidities include chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, coronary heart disease, cerebrovascular disease, viral hepatitis type B, chronic kidney disease and immunodeficiency.

Figures
Figure 1

A) lymphocyte count and B) NLR of healthy people, early-stage lung cancer patients at different perioperative timepoints and patients with advanced lung cancer; C) lymphocyte count of patients with benign nodules at different perioperative timepoints; D) risk for critically-ill COVID-19 of cancer patients, cancer survivors and non-cancer patients. Ad-chemo, adjuvant chemotherapy, OP, operation

Supplementary Files
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