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

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**Research Article**

# Abstract

There is a heated debate on whether the cancer survivors have worse outcomes in corona virus disease 2019 (COVID-2019). 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 publication[2] 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

## 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 |
| --- | --- | --- | --- | --- |
| | | lower | upper | |
| 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.
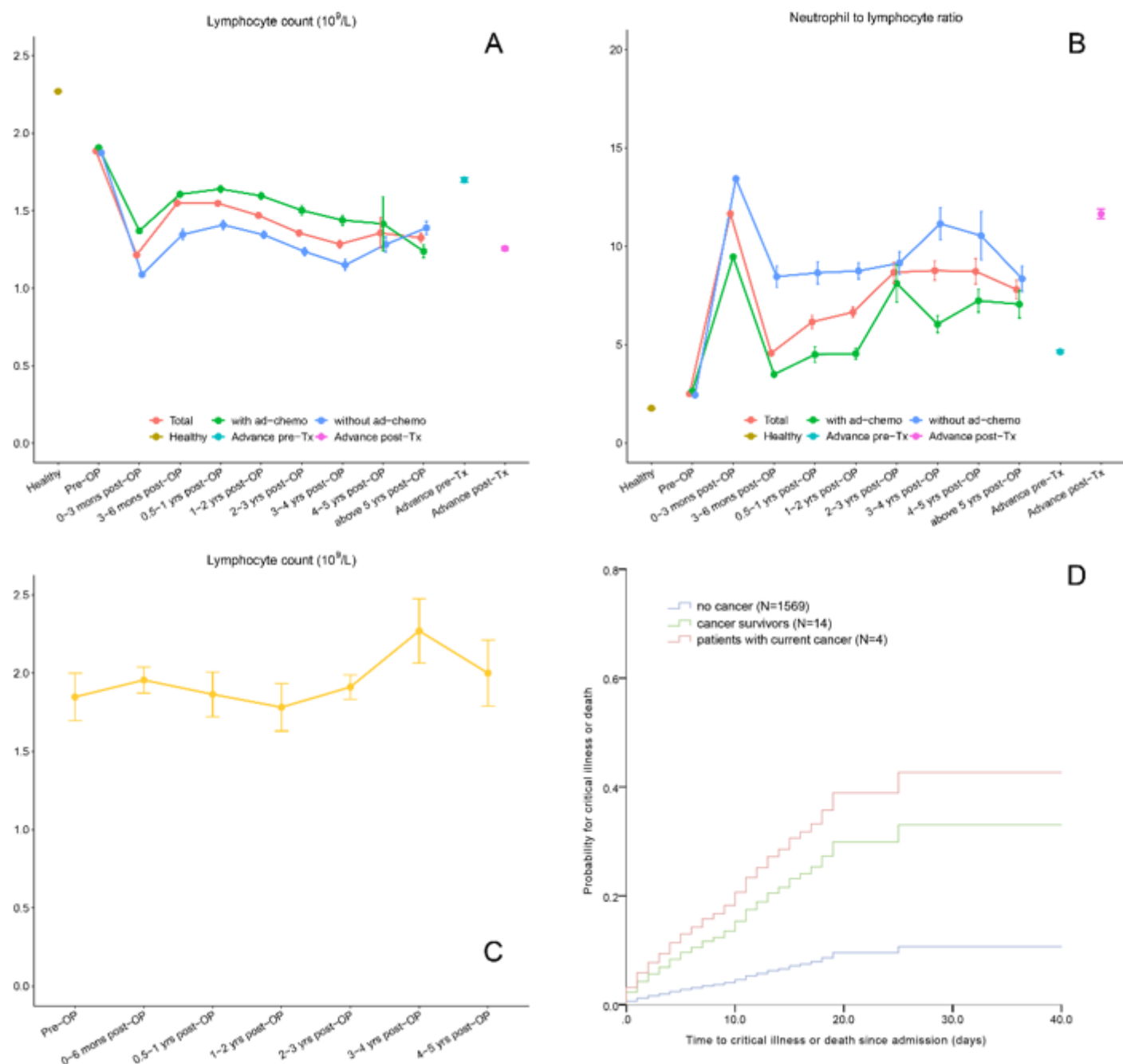
# Figures

**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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