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Immunological alternation in COVID-19 patients with cancer and its implications on mortality

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ABSTRACT

Patients with malignancy were reportedly more susceptible and vulnerable to Coronavirus Disease 2019 (COVID-19), and witnessed a greater mortality risk in COVID-19 infection than noncancerous patients. But the role of immune dysregulation of malignant patients on poor prognosis of COVID-19 has remained insufficiently investigated. Here we conducted a retrospective cohort study that included 2,052 patients hospitalized with COVID-19 (Cancer, n = 93; Non-cancer, n = 1,959), and compared the immunological characteristics of both cohorts. We used stratification analysis, multivariate regressions, and propensity-score matching to evaluate the effect of immunological indices. In result, COVID-19 patients with cancer had ongoing and significantly elevated inflammatory factors and cytokines (high-sensitivity C-reactive protein, procalcitonin, interleukin (IL)-2 receptor, IL-6, IL-8), as well as decreased immune cells (CD8 + T cells, CD4 + T cells, B cells, NK cells, Th and Ts cells) than those without cancer. The mortality rate was significantly higher in cancer cohort (24.7%) than non-cancer cohort (10.8%). By stratification analysis, COVID-19 patients with immune dysregulation had poorer prognosis than those with the relatively normal immune system both in cancer and non-cancer cohort. By logistic regression, Cox regression, and propensity-score matching, we found that prior to adjustment for immunological indices, cancer history was associated with an increased mortality risk of COVID-19 ($p < .05$); after adjustment for immunological indices, cancer history was no longer an independent risk factor for poor prognosis of COVID-19 ($p > .30$). In conclusion, COVID-19 patients with cancer had more severely dysregulated immune responses than noncancerous patients, which might account for their poorer prognosis.

Clinical Trial: This study has been registered on the Chinese Clinical Trial Registry (No. ChiCTR2000032161).

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Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global public health problem.[1] Compared with the general population, patients with cancer have been found to have a significantly higher mortality risk from COVID-19 infection.[2,3] However, the underlying pathophysiology of this increased risk of mortality is not completely understood.

Immune response mediates both viral control and host toxicity during severe COVID-19.[4] Recent studies have confirmed that the levels of inflammatory cytokines (e.g., IL-6) and lymphocytes (e.g., CD8 + T cell) in the peripheral blood are dynamically correlated with the severity of COVID-19.[5–8] Patients with cancer tend to have a more dysregulated immune response, either for the cancer itself or for anti-tumor treatments.[9,10] Further impairment of the immune system by COVID-19 may potentially lead to worse outcomes in these patients. Previous studies have characterized the immunological indices (such as tumor necrosis factor α (TNF-α) and CD4 + T cells) associated with the poorer prognosis of COVID-19 among cancer patients.[3,11–16] However, the longitudinal course of inflammatory cytokines and the role of disrupted immune response in COVID-19 deterioration of cancer patients remain unclear.

In this multicenter retrospective closed cohort study, we aimed to compare the longitudinal immunological characteristics in COVID-19 patients with and without cancer, and

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AbbreviationsCOVID-19: Coronavirus Disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; hsCRP: high-sensitivity C-reactive protein; PCT: procalcitonin; IL-1β: interleukin-β; IL-2R: interleukin-2R; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumor necrosis factor alpha; Th cells: T-helper cells; Ts cells: T-suppressor cells; NK cells: natural killer cells; COPD: chronic obstructive pulmonary diseases; K-M curves: Kaplan-Meier curves; OR: odds ratio; HR: hazard ratio; IQR: interquartile range; 95% CI: 95% confidence interval

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analyze the impact of dysregulated immune response on the prognosis of cancer patients with COVID-19 compared with non-cancer ones. These findings may provide additional insights into potential mechanisms causing higher mortality risk among cancer patients with COVID-19.

Methods

Study design and participants

This is a multi-center, retrospective, cohort study that included 2,425 consecutive patients admitted between February 4 and March 31, 2020, in two branches of Tongji hospital (Optical Valley Branch and Sino-French New City Branch). Of all patients, 78 were excluded for insufficient diagnosis according to the 7th edition of the Diagnosis and Treatment Protocol of COVID-19[17] by the National Health Commission, 205 were excluded because they were transferred from mobile cabin hospitals for the requirement of isolation, 31 were excluded due to death within 24 hours of admission, 35 were excluded given under 18 years old, five were excluded due to unknown cancer history, and 19 were excluded for inaccessible survival time. Overall, 2,052 patients were included in this study, including 93 patients with cancer and 1,959 without cancer.

To study the role of immune dysregulation in the poorer prognosis of cancer patients with COVID-19, we conducted a propensity-score matched analysis in patients with and without cancer. Propensity-score matching 1 matched clinical confounding factors including sex, age, symptoms, and comorbidities, in which 93 patients with cancer and 930 patients without cancer were included. Propensity-score matching 2 added immunological indices (high-sensitivity C-reactive protein (hsCRP), procalcitonin (PCT), ferritin, interleukin (IL)-1β, IL-2 R, IL-6, IL-8, IL-10, tumor necrosis factor α (TNF-α), and total lymphocytes) into matching on the basis of propensity-score matching 1. Eventually, 49 patients with cancer with matched 490 without cancer were included in later analysis. The flowchart of the study design is presented in Figure 1.

In this study, we conducted the following analyses: (1) described the longitudinal immunologic characteristics in cancer cohort and non-cancer cohort during the first 6 weeks since COVID-19 onset; (2) analyzed the association between immune dysregulation and worse prognosis in cancer patients by a) stratification analysis, b) multivariate logistic and Cox regression, and c) propensity-score matching.

This study was approved by the Ethical Committee of Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20200406), and registered on the Chinese Clinical Trial Registry (No. ChiCTR202003212161). The requirement for informed consent was waived, and the study carried out following the rules of the Declaration of Helsinki.

Data collection

Data were collected by review of electronic medical records for demographic, clinical, immunological, and survival information. A standardized form was employed during data collection, and every fragment of data was cross-checked by two

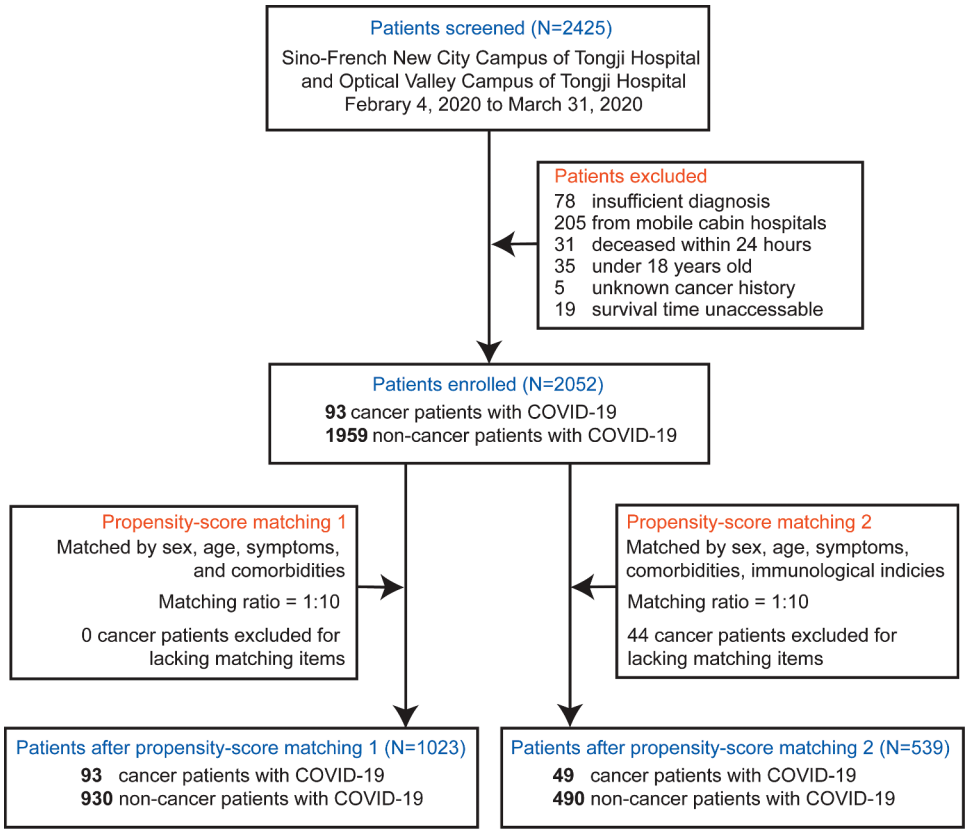

Figure 1. Flowchart of study design.

authors. Death or discharge was used as the clinical outcome of the study. Survival time was defined as the time interval from COVID-19 onset to death or discharge. Fever was defined as the axillary temperature of at least 37.3°C. The abnormal value range for immunologic indices and corresponding population statistics are shown in Table 1. The severity of COVID-19 was graded according to the 7th edition of the Diagnosis and Treatment Protocol of COVID-19.[17]

Statistical analysis

For descriptive analysis, median (IQR) and frequencies (%) were assessed for continuous and categorical variables, respectively. All the continuous variables were compared between the two cohorts by the Mann-Whitney U test. All the categorical variables were compared by the chi-square test or Fisher's exact test, as appropriate. Kaplan-Meier curves (K-M curves) with log-rank test was used in the survival analysis. The propensity-score matching was achieved with the *MatchIt* package of R, using the method of "nearest".[18] The odds ratio (OR) from logistic regression and hazard ratio (HR) from Cox regression together with the corresponding 95% confidence interval (95% CI) were calculated to determine the correlation between cancer status and the outcome. The significant level was set at a two-sided p value below 0.05. All analysis was achieved using SPSS (Version 23) or R (Version 3. 6. 3).

Results

Demographic and clinical characteristics

The baseline characteristics of the population are shown in Table 1 and Table S2. There were 93 patients with an accompanying cancer diagnosis (93 of 2,052 patients, 4.53%) who were diagnosed and admitted with COVID-19. The sex distribution (male, cancer vs. non-cancer, 44 (47.3%) vs. 954 (48.7%), p = .877) was similar among both cohorts (patients with and without cancer). Patients with cancer had a larger median age (median [IQR] age, cancer vs. non-cancer, 65 years [56–71] vs. 62 [51–70], p = .089) compared with those without cancer. The clinical symptomatology on admission and comorbidities except cancer history were largely similar between both cohorts as well. Despite the similarity in the baseline characteristics, patients with cancer were more likely to have critical status of illness (43.0% vs. 17.9%) than the non-cancer cohort. The mortality rate was significantly higher in cancer cohort (24.7%) than non-cancer cohort (10.8%), and the median time

Table 1. Demographic, clinical, and immunological characteristics of the total population.

	Total population			
	All (n = 2052)	Non-cancer (n = 1959)	Cancer (n = 93)	p-Value
Sex				0.877
Male	998/2052 (48.6)	954/1959 (48.7)	44/93 (47.3)	
Female	1054/2052 (51.4)	1005/1959 (51.3)	49/93 (52.7)	
Age, years	63 [51–70]; n = 2052	62 [51–70]; n = 1959	65 [56–71]; n = 93	0.089
Inflammatory factors and cytokines				
hsCRP, mg/L	1.8 [0.78–16.35]; n = 2016	1.8 [0.7–15.8]; n = 1925	10.2 [0.8–36.45]; n = 91	0.053
>10	694/2016 (34.4)	647/1925 (33.6)	47/91 (51.6)	0.001
Procalcitonin, ng/mL	0.06 [0.04–0.14]; n = 1775	0.06 [0.04–0.13]; n = 1696	0.12 [0.05–0.49]; n = 79	<0.001
>0.5	209/1775 (11.8)	189/1696 (11.1)	20/79 (25.3)	<0.001
Ferritin, ug/L	590.0 [325.22–902.77]; n = 1186	582.6 [324.75–889.35]; n = 1131	741.6 [341.95–1356.6]; n = 55	0.013
>400	803/1186 (67.7)	764/1131 (67.6)	39/55 (70.9)	0.710
IL-2 R, pg/mL	568 [378–811.5]; n = 1688	565 [372–801]; n = 1611	641 [472–940]; n = 77	0.004
>710	575/1688 (34.1)	540/1611 (33.5)	35/77 (45.5)	0.042
IL-6, pg/mL	5.37 [2.30–19.42]; n = 1705	5.25 [2.26–19.02]; n = 1627	8.39 [4.31–36.06]; n = 78	0.001
≥7	719/347 (42.2)	671/1627 (41.2)	48/78 (61.5)	0.001
IL-8, pg/mL	8.8 [5.82–17.98]; n = 1690	8.8 [5.8–17.7]; n = 1613	9.4 [6.7–30.7]; n = 77	0.042
≥62	146/1690 (8.6)	132/1613 (8.2)	14/77 (18.2)	0.004
IL-10, pg/mL	5.0 [5.0–5.9]; n = 1689	5.0 [5.0–5.8]; n = 1613	5.0 [5.0–8.33]; n = 76	<0.001
≥9.1	176/1689 (10.4)	164/1613 (10.2)	12/76 (15.8)	0.169
TNF-α, pg/mL	7.9 [6.1–9.6]; n = 1690	7.9 [6.1–9.6]; n = 1613	8.7 [6.7–9.9]; n = 77	0.074
≥8.1	814/1690 (48.2)	772/1613 (47.9)	42/77 (54.5)	0.303
Immune cells				
Lymphocytes, $*10^9$ per L	1.65 [1.27–2.07]; n = 2052	1.65 [1.28–2.08]; n = 429	1.45 [1.05–1.93]; n = 93	0.001
<1.10	335/2052 (16.3)	307/429 (15.7)	28/93 (30.1)	<0.001
CD8 + T cells, per μL	348.5 [225.75–479]; n = 466	355 [240–491]; n = 429	234 [158–363]; n = 37	0.005
<320	196/466 (42.1)	172/429 (40.1)	24/37 (64.9)	0.006
CD4 + T cells, per μL	635.5 [449–824.5]; n = 466	641 [469–840]; n = 429	392 [149–633]; n = 37	<0.001
<550	176/466 (37.8)	150/429 (35.0)	26/37 (70.3)	<0.001
Total T cells, per μL	1000 [726–1365.25]; n = 466	1042 [783–1379]; n = 429	707 [494–904]; n = 37	<0.001
<955	209/466 (44.8)	181/429 (42.2)	28/37 (75.7)	<0.001
B cells, per μL	164[101.25–259.75]; n = 466	169 [113–263]; n = 429	92 [56–174]; n = 37	<0.001
<90	95/466 (20.4)	77/429 (17.9)	18/37 (48.6)	<0.001
NK cells, per μL	201[112.25–295.25]; n = 466	203 [114–300]; n = 429	178 [74–261]; n = 37	0.102
<150	163/466 (35.0)	148/429 (34.5)	15/37 (40.5)	0.576
Death	235/2052 (11.5)	212/1959 (10.8)	23/93 (24.7)	<0.001
Time from illness onset to death or discharge, days	34 [26–43]; n = 2052	34 [26–42]; n = 1959	36 [25–52]; n = 93	0.024

Data are median (IQR) or n/N (%). p-Values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. The value conducted the statistics with the largest distance from the normal range for immunological indices. The value conducted the statistics with the largest distance from the normal range for immunological indices. hsCRP = high-sensitivity C-reactive protein. IL-2 R = interleukin-2 R. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10. TNF-α = tumor necrosis factor alpha. NK cells = natural killer cells.

from illness onset to death or discharge was 36 days [25–52] for cancer cohort versus 34 days [26–42] for non-cancer cohort.

Thyroid cancer (15%, 14 patients), breast cancer (14%, 13 patients), and lung cancer (13%, 12 patients) were the most common cancer types, whereas esophageal cancer (67%, two of three patients), hematologic cancer (56%, five of nine patients), and bladder cancer (50%, four of eight patients) had the highest mortality (Figure S1). Among all 93 COVID-19 patients with cancer, 18 (19.4%) had a cancer diagnosis at a late stage, 7 (7.5%) got recurrence. Thirteen (14.0%) patients with cancer received anti-cancer treatment within 40 days before COVID-19 onset, in which 2 (2.15%) had surgery, 9 (9.7%) had chemotherapy, 4 (4.3%) had radiotherapy, 2 (2.2%) had targeted therapy, 1 (1.1%) had immunotherapy (Table S4).

Comparison of the immunological characteristics

The immunological indices are presented in Table 1 and Table S2. Compared with non-cancer patients, cancer patients had markedly higher level of inflammatory factors and cytokines after infection of COVID-19, including hsCRP, PCT, ferritin, IL-2 R, IL-6, IL-8, IL-10, and TNF-α. Patients with cancer had a twice percentage of elevated procalcitonin than those without cancer (cancer vs. non-cancer, 25.3% vs 11.1%, $p < .001$). 61.5% of cancer patients got an IL-6 above the normal range during hospitalization, by contrast with 41.2% for non-cancer patients ($p < .001$). The proportion of patients with an abnormal value of all immunologic factors and cytokines except complement C4 in cancer cohort exceeded that in the non-cancer cohort. In terms of the immune cells, the decline in the number of total lymphocytes, CD8 + T cells, CD4 + T cells, T helper and T suppressor (Th and Ts) cells, total T cells, and B cells was more significant in patients with cancer. Notably, over 50% of patients with cancer had a decrease in CD8 + T cells or CD4 + T cells, which was significantly more than non-cancer ones.

To describe the longitudinal immunological difference in the two cohorts, inflammatory factors, cytokines, and immune cells were tracked since illness onset (Figure 2). hsCRP, PCT, ferritin, IL-2 R, IL-6, IL-8, and TNF-α in cancer patients were consistently higher compared with non-cancer patients for at least 5 weeks of their COVID-19 illness. Among cancer patients, hsCRP, PCT, ferritin, IL-6, and TNF-α remained above the normal range during the whole disease course, and reached a second peak at week four or five which coincided with the peak of time from illness onset to death or discharge (Figure S2). For non-cancer patients, however, after the first 3 weeks, all the immunological parameters returned toward the normal range. There was no visible trend change in IL-10 (Figure 2g) and IL-1β (Figure S3) between two cohorts.

The difference between the patients with and without cancer was even more remarkable in the analysis of the immune cells (Figure 2i-n, Figure S3). Compared to patients without cancer, patients with cancer had a sustained decrease not only in the total lymphocytes, but also in CD8 + T cells, CD4 + T cells, Th and Ts cells, Total T cells, B cells, and NK cells. Besides, the ratio of Th and Ts (Th/Ts) remained lower in cancer cohorts. These results suggested a more immunosuppressed status of cancer patients than non-cancer patients after COVID-19 infection. The two cohorts had similar changing tendencies on the counts of different immune cells, which reached a minimum at week one or two, and then displayed an increasing trend in the following time. Finally, the immune cell counts in non-cancer cohort recovered to the normal range in week three. In the cancer cohort, B cells and NK cells also went back to the normal range after 5 weeks, whereas T cells, especially CD8 + T cells, and CD4 + T cells, continued to be within the lower limit of normal.

Immune dysregulation and its prognostic implications

The K-M curve in Figure 5a showed that patients with cancer had higher mortality risk than those without cancer ($p = .002$). Stratified by cancer history and survival outcome, we found that deceased patients had significantly more severe immune dysregulation compared with discharged patients both in the cancer cohort and non-cancer cohort, including an elevation of hsCRP, PCT, ferritin, IL-2 R, IL-6, IL-8, IL-10, and TNF-α, and a decrease of lymphocytes, CD8 + T cells, CD4 + T cells, Th and Ts cells, total T cells, B cells, and NK cells, while the difference in immunological indices between cancer cohort and non-cancer cohort with same survival outcome was not that huge (Figure 3, Figure S4).

Next, we stratified all included patients in the cancer cohort and non-cancer cohort separately according to the immunological indices (Figure 4). The stratification criteria of immunological indices were displayed in Table S1. The K-M curves indicated that inflammatory factors, cytokines, and immune cells could distinguish the prognosis of patients both in cancer and non-cancer cohort, but cancer patients did not have an adverse effect on survival under the same level of immunological indices. Among all the analyzed indices, patients with the abnormal values of procalcitonin and lymphocytes had the shortest estimated median survival time (cancer vs. non-cancer: procalcitonin, 35 vs. 29 days; lymphocytes, 32 vs. 33 days), which could be the potential biomarker for prognosis.

Logistic regression and Cox regression were used in the further assessment of the correlation between the dysregulated immune systems and the worse prognosis of cancer patients (Table 2). Compared with non-cancer patients, patients with cancer had an odds ratio (OR) of 2.708 [95% CI: 1.655–4.429; $p < .001$] in the univariate logistic regression model and 2.640 [95% CI: 1.498–4.654; $p = .001$] in the multivariate logistic regression model 1 (adjusted for sex, age, symptoms, and comorbidities), whereas there was no significant difference in mortality risk between cancer patients and non-cancer patients (OR: 1.931, 95% CI: 0.498–7.493, $p = .341$) after adding immunological indices into model adjustment (multivariate logistic regression model 2 which was adjusted for sex, age, symptoms, comorbidities, immune indices including hsCRP, PCT, ferritin, TNF-α, IL-1β, IL-2 R, IL-6, IL-8, IL-10, lymphocytes). Complement C3, C4, and immune cell subsets except lymphocytes were not considered in the multivariate logistic regression model 2 because over half the population did not receive these tests during hospitalization. Similarly, hazard ratio (HR) for patients with cancer compared to those without cancer were significant in the univariate Cox regression model (HR: 1.995, 95% CI: 1.280–3.108, $p = .002$) and in the multivariate Cox

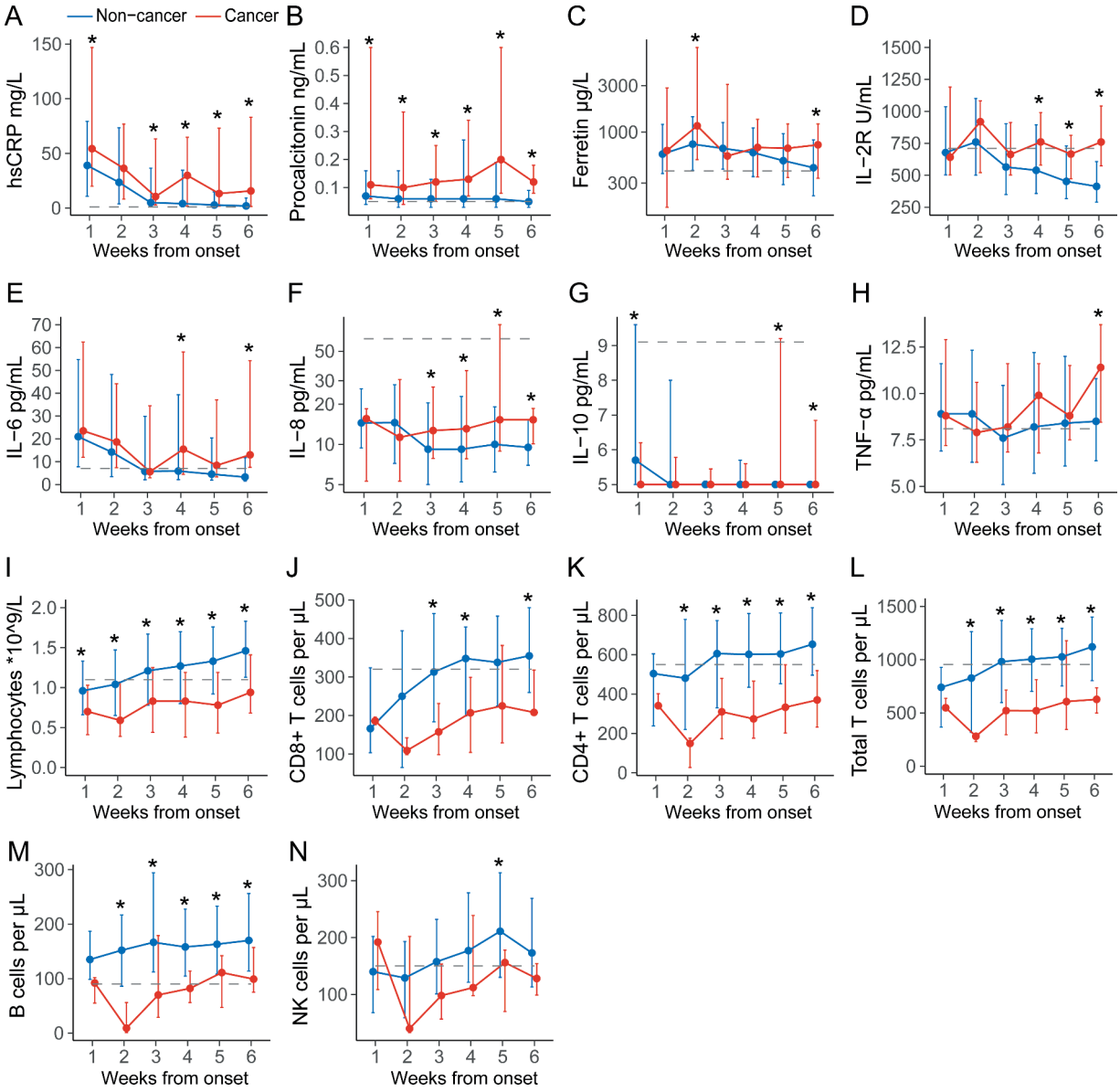

Figure 2. Longitudinal changes in immunological indices in 6 weeks from COVID-19 onset. Grey dashed lines represent the limit of the normal range of every index. Time points with * indicated statistically significant differences between the cancer cohort and non-cancer cohort. hsCRP = high-sensitivity C-reactive protein. IL-2 R = interleukin-2 receptor. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10. TNF-α = tumor necrosis factor α. NK cells = natural killer cells.

regression model 1 (adjusted items were the same as multivariate logistic regression model 2) (HR: 2.023, 95% CI: 1.296–3.159, p = .002), but not significant in the multivariate Cox regression model 2 (adjusted items were the same as multivariate logistic regression model 2) (HR: 0.778, 95% CI: 0.404–1.496, p = .451).

Moreover, we conducted propensity-score matching to validate the effects of immune disorder and other confounding factors (Table 3, Table S3, Figure 5). The baseline characteristics of the population after matching are shown in Table 3, Table S3. The mortality rate after propensity-score matching 1 was 24.7% for the cancer group and 13.5% for non-cancer group, p = .006. In population of propensity-score matching 1, the statistical analysis before adjustment of immunological indices (log-rank test, univariate logistic regression, multivariate logistic regression 1, univariate Cox regression, multivariate Cox regression 1) all showed a significant difference between cancer and non-cancer patients, while the difference was no more significant after adjustment of immunological indices (multivariate logistic regression 2, multivariate Cox regression 2). Comparing the analysis of the total population and propensity-score matching 1, the results of the two populations were similar, suggesting clinical factors contributed little to the high mortality risk of cancer patients (Table 2).

In population of propensity-score matching 2, we found all statistical analysis showed no significant difference in mortality of patients with and without cancer. By comparing results of propensity-score matching 1 and propensity-score matching 2, we found after adding immunological indices into matching, the significant difference in crude mortality rate (cancer vs. non-cancer, 24.5% vs. 25.3%, p = 1.000) between two cohorts disappeared (Table 3). In the K-M curves of the population after propensity-score

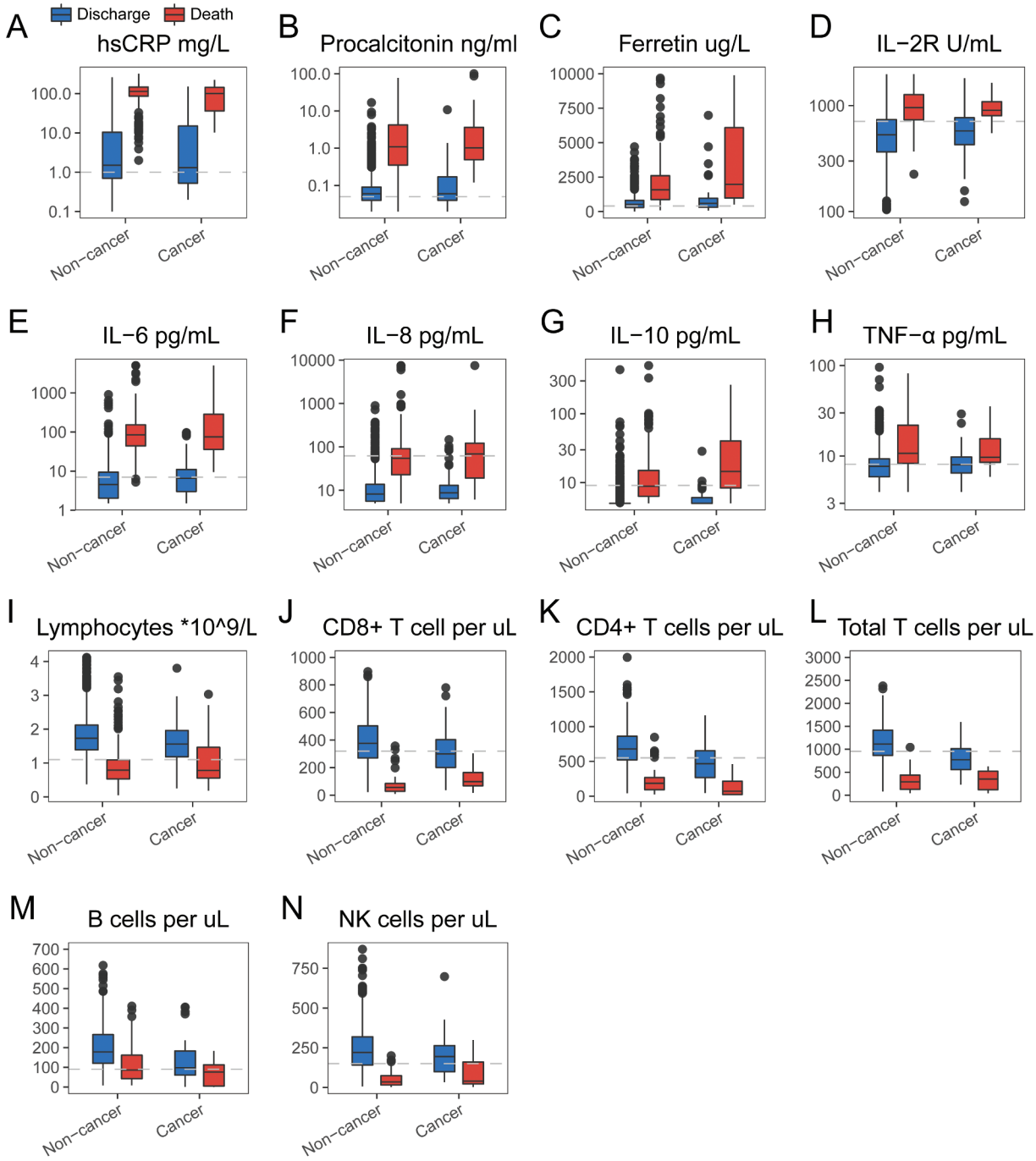

Figure 3. Comparison of immunological indices between groups stratified by history of cancer and survival outcome. Grey dashed lines represent the limit of the normal range of every immunological index. In all immunological indices, deceased patients had a significantly higher level of the immune disorder compared with discharged patients both in the cancer cohort and non-cancer cohort (Mann-Whitney U test, $p < .05$). hsCRP = high-sensitivity C-reactive protein. IL-2 R = interleukin-2 receptor. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10. TNF-α = tumor necrosis factor α. NK cells = natural killer cells.

matching 2 and propensity-score matching 1, it was found that patients with cancer no longer had a poorer prognosis than those without cancer after matching immunological indices (p = .600) (Figure 5). The OR of cancer history in logistic regression models and HR in corresponding Cox regression models all showed no significance in propensity-score matching 1 and propensity-score matching 2 (Table 2). These results indicated the level of immunological indices was associated with the poor prognosis of cancer patients after infection of COVID-19.

Subgroup analysis based on cancer status and anti-cancer treatments

Subgroup analyses were conducted based on cancer stage, recurrence, and recent anti-cancer treatments (within 40 days before COVID-19 onset). No matter what the cancer status was and what anti-cancer treatments patients received, subgroups of cancer patients had relatively higher inflammatory factors as well as lower immune cell counts than non-cancer patients (PCT, lymphocytes, CD8 + T cells, CD4 + T cells, total T cells, and B cells) (Table S5, Figure S5).

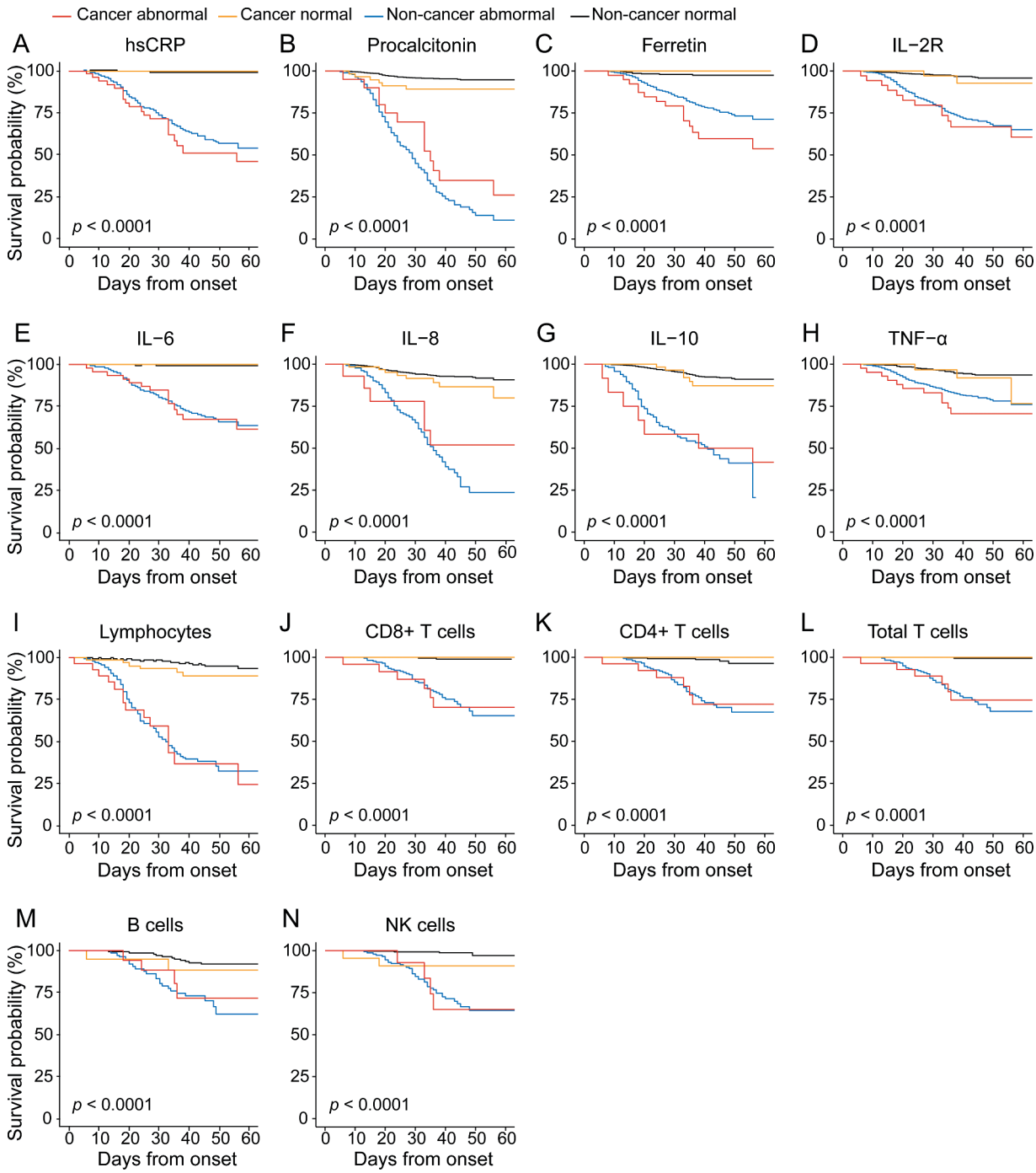

Figure 4. Kaplan-Meier survival plots according to different immunological indices stratified by the normal range. Log-rank test showed that stratification of immunological indices could distinguish the prognosis both in cancer and non-cancer cohort. hsCRP = high-sensitivity C-reactive protein. IL-2 R = interleukin-2 receptor. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10. TNF-α = tumor necrosis factor α. NK cells = natural killer cells.

Moreover, cancer patients at an early stage had comparable immunological indices with those at a late stage after COVID-19 onset, while the recurrent patients showed more serious immune dysregulation (higher PCT and less immune cells) than those who had never got a recurrence (Table S5, Figure S5 A-F). Cancer patients receiving chemotherapy, radiotherapy, and targeted therapy in 40 days went through more serious lymphopenia and higher level of IL-6 than patients without those treatments during the 6 weeks since COVID-19 onset (Table S5, Figure S5 J-R). Surgery seemed to influence little on immunological indices (Table S5, Figure S5 G-I). Compared with patients without immunotherapy, patients with immunotherapy had lower level of immune cells, but the inflammatory factors did not show a clear trend. In survival analysis, cancer stage, recurrence, and all recent anti-cancer treatments did not have a significant influence on mortality risk of cancer patients after COVID-19 infection by logistic regression and Cox regression (Table S6).

Discussion

In this multicenter retrospective study, we provide a comprehensive longitudinal assessment of the immunological

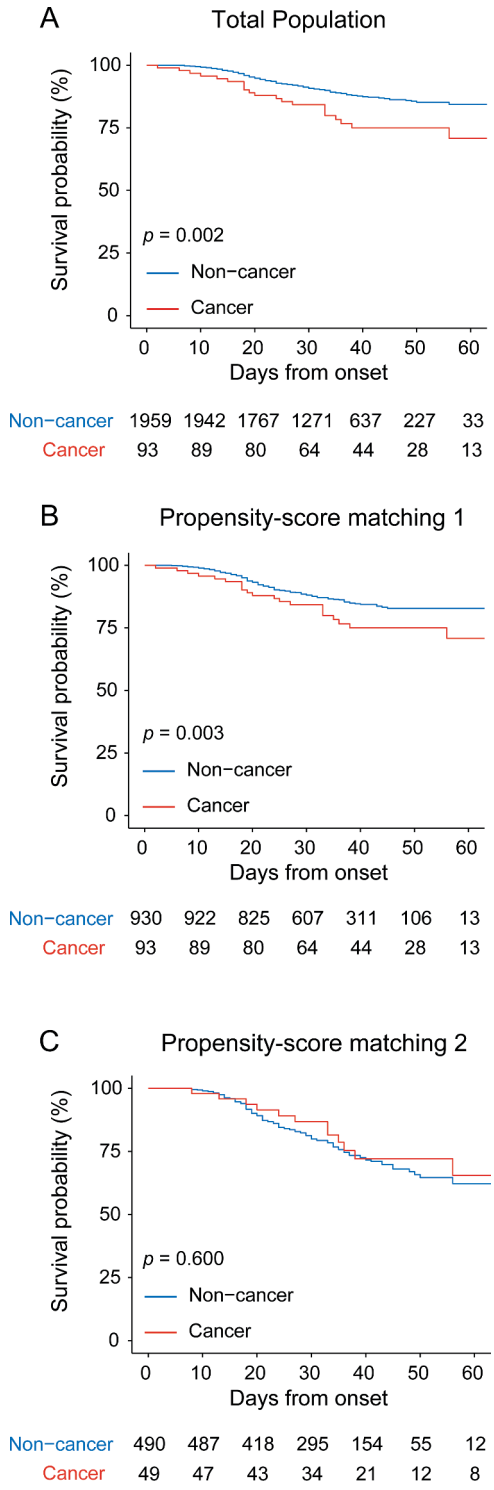

Figure 5. Kaplan-Meier survival plots for the whole included population (a), population after propensity-score matching 1 (b), and population after propensity-score matching 2 (c). Matching items of propensity-score matching 1 consisted of sex, age, symptoms, and comorbidities. Matching items of propensity-score matching 2 consisted of sex, age, symptoms, comorbidities, and immune indices including hsCRP, PCT, ferritin, TNF-α, IL-1β, IL-2 R, IL-6, IL-8, IL-10, lymphocytes. The prognosis was compared between cancer and non-cancer cohort with log-rank test.

characteristics of patients with and without cancer diagnosed with COVID-19. Persistent immune dysregulation as indicated by elevated inflammatory factors and cytokines as well as decreased immune cells among the cancer cohort was found during the entire course of COVID-19 illness. Later, the association between immune dysregulation and the poorer prognosis of cancer patients compared to the non-cancer ones after COVID-19 infection was demonstrated by stratification analyses, multivariate regressions, and propensity-score matching. In conclusion, our study revealed that immune dysregulation was an important feature in cancer patients with COVID-19, and indicated that the more severe immune dysregulation might be an important reason for the poorer prognosis of patients with cancer than those without cancer.

Table 2. Results of logistic and Cox regression in patients with COVID-19 with different adjustment factors.

Model		Total population	Propensity-score matching 1	Propensity-score matching 2
Logistic regression				
Univariate logistic regression model	OR	2.708	2.907	0.862
	95% CI	1.655–4.429	1.263–3.481	0.436–1.702
	p-value	<0.001	0.004	0.668
Multivariate logistic regression model 1 †	OR	2.640	2.468	0.867
	95% CI	1.498–4.654	1.388–4.388	0.403–1.866
	p-value	0.001	0.004	0.715
Multivariate logistic regression model 2 §	OR	1.931	0.716	1.115
	95% CI	0.498–7.493	0.127–4.028	0.277–4.485
	p-value	0.341	0.704	0.878
Cox regression				
Univariate Cox regression model	HR	1.995	1.648	0.786
	95% CI	1.280–3.108	1.044–2.603	0.435–1.423
	p-value	0.002	0.032	0.427
Multivariate Cox regression model 1 †	HR	2.023	1.965	0.972
	95% CI	1.296–3.159	1.239–3.117	0.532–1.779
	p-value	0.002	0.004	0.928
Multivariate Cox regression model 2 §	HR	0.778	1.442	0.513
	95% CI	0.404–1.496	0.724–2.872	0.419–1.545
	p-value	0.451	0.298	0.804

OR and HR were used as the estimated effect of cancer. Propensity-score matching 1: matching sex, age, symptoms, and comorbidities. Propensity-score matching 2: matching sex, age, symptoms, comorbidities, and immune indices (hsCRP, PCT, ferritin, IL-1β, IL-2 R, IL-6, IL-8, IL-10, TNF-α, lymphocytes). † Adjusted for sex, age, symptoms, and comorbidities. §Adjusted for sex, age, symptoms, comorbidities, and immune indices (hsCRP, PCT, ferritin, IL-1β, IL-2 R, IL-6, IL-8, IL-10, TNF-α, lymphocytes). OR = odds ratio. HR = hazard ratio. 95% CI = 95% confidence interval. hsCRP = high-sensitivity C-reactive protein. PCT = procalcitonin. TNFα = tumor necrosis factor α. IL-1β = interleukin-1β. IL-2 R = interleukin-2 receptor. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10.

The percentage of cancer patients (4.53%) in the total COVID-19 cohort was higher than the reported prevalence of cancer in patients with COVID-19 (around 2%).[19,20] This might be because all the patients in the cohort were from the hospitals designated to serve those with severe and critical COVID-19. The mortality rate of cancer patients with COVID-19 in our cohort was 24.7%, compared to previous reports ranging from 13% to 33%.[2,14,21–23]

Our study not only found that cancer patients had higher levels of inflammatory factors, cytokines, and lower levels of immune cells as reported previously, [15] but also confirmed that this immune dysregulation lasted for the entire course of COVID-19 illness in patients with cancer, regardless of cancer stage, recurrence and anti-cancer therapy (Figure 2, Figure S5). We found that hsCRP, PCT, ferritin, IL-6, and TNF-α reached a second peak at week four or five of the COVID-19 onset for cancer patients, which coincided with the peak of the time interval from illness onset to death or discharge (Figure S2, Table 1). These findings provide substantial proof of principle to the concept of the prolonged and dysregulated immune response to SARS-CoV-2 infection in patients with cancer.

Immune dysregulation has been proposed to play an important role in the immunopathology of COVID-19.[24–27] Evidence indicated that innate and adaptive immune response were crucial for antiviral defense on the one hand, and mediated toxic inflammation on the other hand.[4] Previous investigations have reported that the severity and fatal outcome of COVID-19 correlated with infection-induced cytokine storm and lymphopenia, including an increase of IL-2 R, IL-6, IL-10, and TNF-α, and a decrease of lymphocytes and T cell subsets, [9,10,24] which are similar to the immunological characteristics of patients with cancer. Thus, we studied the reasonable hypothesis that immune disorder contributed to the worse prognosis of cancer patients. In this study, more than verifying that cancer patients had a significantly poorer prognosis than non-cancer patients, we utilized stratification by immunological indices, multivariate regressions, and propensity-score matching to detect the actual difference in mortality risk between cancer and non-cancer. Our study provides evidence that cancer and non-cancer patients with same level of immunological indices had similar prognosis, while patients with dysregulated immune system had poorer prognosis than those with relatively normal immune system whether they had cancer history or not. Since cancer patients had a higher level of dysregulated immune response than non-cancer ones, they were more likely to develop a worse prognosis. In the subgroup analysis, patients with recurrence, recent chemotherapy, radiotherapy, targeted therapy, and immunotherapy performed more serious immune disorder than those without, but no statistical difference was reached in terms of the survival of COVID-19 patients with cancer. Considering the number of patients in some subgroups was limited, larger population is needed to explore the influence of cancer status and anti-cancer treatments on the survival of cancer patients infected with COVID-19.

IL-6 is a central mediator of innate immune response. SARS-CoV infected mice models have revealed that elevated IL-6 and IL-1β released by the accumulated inflammatory monocyte-macrophages (IMMs) are responsible for exaggerated virological responses and inflammation.[28] Similar to SARS-CoV, the higher level of IL-6 in cancer patients after the infection of SARS-CoV-2 led to more recruitment of neutrophils and CD8 + T cells.[29] The leukotrienes and reactive oxygen species produced by activated neutrophils could cause the endothelial injury in persistent COVID-19 infection. IL-6 elevation occurred in over half of the cancer patients during hospitalization, and kept above the normal range during 6 weeks since COVID-19 onset.

Table 3. Demographic, clinical, and immunological characteristics of the population after propensity-score matching.

	Propensity-score matching 1				Propensity-score matching 2			
	All (n = 1023)	Non-cancer (n = 930)	Cancer (n = 93)	***p*-Value**	All (n = 539)	Non-cancer (n = 490)	**Cancer (n = 49)**	***p*-Value**
Sex				1.000				0.967
Male	489/1023 (47.8)	445/930 (47.8)	44/93 (47.3)		326/539 (60.5)	297/490 (60.6)	29/49 (59.2)	
Female	534/1023 (52.2)	485/930 (52.2)	49/93 (52.7)		213/539 (39.5)	193/490 (39.4)	20/49 (40.8)	
Age, years	65 [56–71]; n = 1023	65 [56–71]; n = 930	65 [56–71]; n = 93	0.729	66 [57–74]; n = 539	66 [57–74]; n = 490	65 [58–73]; n = 49	0.789
hsCRP, mg/L	2.2 [0.9–23.4]; n = 1002	2.1 [0.9–21.05]; n = 911	10.2 [0.8–36.45]; n = 91	0.322	11.5 [1.1–100.7]; n = 539	11.2 [1.1–101.45]; n = 490	13.9 [1.0–53.4]; n = 49	0.779
>10	389/1023 (38.8)	342/911 (37.5)	47/91 (51.6)	0.012	300/539 (55.7)	271/490 (55.3)	29/49 (59.2)	0.711
Procalcitonin, ng/mL	0.06 [0.04–0.17]; n = 881	0.06 [0.04–0.15]; n = 802	0.12 [0.05–0.49]; n = 79	<0.001	0.09 [0.04–0.40]; n = 539	0.09 [0.04–0.38]; n = 490	0.13 [0.05–0.50]; n = 49	0.158
>0.5	130/881 (14.8)	110/802 (13.7)	20/79 (25.3)	0.009	124/539 (23.0)	111/490 (22.7)	13/49 (26.5)	0.662
Ferritin, ug/L	609.7 [349.15–964.25]; n = 595	604.1 [351.5–937.0]; n = 540	741.6 [341.95–1356.6]; n = 55	0.057	647.3 [350.25–1145.25]; n = 539	642.2 [354.25–1129.30]; n = 490	725.9 [318.7–1304.0]; n = 49	0.452
>400	421/595 (70.8)	382/540 (70.7)	39/55 (70.9)	1.000	378/539 (70.1)	345/490 (70.4)	33/49 (67.3)	0.777
IL-2 R, pg/mL	601 [406–849.5]; n = 831	594.5 [399.25–841.5]; n = 754	641 [472–940]; n = 77	0.048	729 [479.5–966.5]; n = 539	728.5 [480.25–966]; n = 490	744 [473–990]; n = 49	0.853
>710	310/831 (37.3)	275/754 (36.5)	35/77 (45.5)	0.153	279/539 (51.8)	253/490 (51.6)	26/49 (53.1)	0.967
IL-6, pg/mL	6.50 [2.84–26.46]; n = 841	6.03 [2.68–25.96]; n = 763	8.39 [4.31–36.06]; n = 78	0.034	19.06 [7.12–54.97]; n = 539	19.33 [7.12–54.37]; n = 490	18.65 [7.37–65.61]; n = 49	0.941
≥7	407/841 (48.4)	359/763 (47.1)	48/78 (61.5)	0.020	407/539 (75.5)	370/490 (75.5)	37/49 (75.5)	1.000
IL-8, pg/mL	9.0 [6.4–21.8]; n = 831	9.0 [6.3–20.8]; n = 754	9.4 [6.7–30.7]; n = 77	0.200	10.9 [6.8–37.85]; n = 539	11.0 [6.93–36.45]; n = 490	9.5 [6.5–39.3]; n = 49	0.816
≥62	78/831 (9.4)	64/754 (8.5)	14/77 (18.2)	0.010	89/539 (16.5)	80/490 (16.3)	9/49 (18.4)	0.869
IL-10, pg/mL	5.0 [5.0–6.2]; n = 830	5.0 [5.0–6.0]; n = 754	5.0 [5.0–8.33]; n = 76	0.001	5.0 [5.0–7.7]; n = 539	5.0 [5.0–7.6]; n = 490	5.4 [5.0–8.4]; n = 49	0.384
≥9.1	91/830 (11.0)	79/754 (10.5)	12/76 (15.8)	0.222	88/539 (16.3)	80/490 (16.3)	8/49 (16.3)	1.000
TNF-α, pg/mL	8.2 [6.5–9.8]; n = 831	8.15 [6.43–9.7]; n = 754	8.7 [6.7–9.9]; n = 77	0.386	8.4 [6.7–10.5]; n = 539	8.4 [6.7–11.2]; n = 490	8.2 [6.7–9.8]; n = 49	0.481
≥8.1	429/831 (51.6)	387/754 (51.3)	42/77 (54.5)	0.675	288/539 (53.4)	263/490 (53.7)	25/49 (51.0)	0.838
Lymphocytes, $*10^9$ per L	1.60 [1.19–2.05]; n = 1023	1.61 [1.22–2.05]; n = 930	1.45 [1.05–1.93]; n = 93	0.019	1.44 [1.02–1.90]; n = 539	1.46 [1.02–1.90]; n = 490	1.25 [0.83–1.83]; n = 49	0.248
<1.10	209/1023 (20.4)	181/930 (19.5)	28/93 (30.1)	0.022	162/539 (30.1)	145/490 (29.6)	17/49 (34.7)	0.562
CD	xx	xx	xx	xx	CD	xx	xx	xx
8 + T cells, per μL	335 [205.25–452.75]; n = 226	347 [222–460]; n = 189	234 [158–363]; n = 37	0.023	254 [98.25–391]; n = 142	265 [90–393]; n = 121	206 [114–327]; n = 21	0.652
<320	103/226 (45.6)	79/189 (41.8)	24/37 (64.9)	0.017	90/142 (63.4)	75/121 (62.0)	15/21 (71.4)	0.559
CD4 + T cells, per μL	xx	xx	xx	xx	CD	xx	xx	xx
	620 [385.25–805.5]; n = 226	634 [435–828]; n = 189	392 [149–633]; n = 37	<0.001	520 [255.5–741]; n = 142	555 [350–754]; n = 121	186 [66–466]; n = 21	0.001
<550	92/226 (40.7)	66/189 (34.9)	26/37 (70.3)	<0.001	77/142 (54.2)	59/121 (48.8)	18/21 (85.7)	0.004
Total T cells, per μL	962 [648.25–1320]; n = 226	1026 [737–1347]; n = 189	707 [494–904]; n = 37	<0.001	818 [457.75–1084.5]; n = 142	876 [491–1129]; n = 121	569 [306–726]; n = 21	0.014
<955	112/226 (49.6)	84/189 (44.4)	28/37 (75.7)	0.001	91/142 (64.1)	72/121 (59.5)	19/21 (90.5)	0.013
B cells, per μL	157 [98–248.5]; n = 226	165 [117–259]; n = 189	92 [56–174]; n = 37	<0.001	127 [76.25–199.5]; n = 142	141 [93–207]; n = 121	75 [52–114]; n = 21	0.002
<90	54/226 (23.9)	36/189 (19.0)	18/37 (48.6)	<0.001	42/142 (29.6)	29/121 (24.0)	13/21 (61.9)	0.001
NK cells, per μL	210 [110.25–296.75]; n = 226	212 [114–305]; n = 189	178 [74–261]; n = 37	0.075	160 [74.25–251.5]; n = 142	160 [75–255]; n = 121	156 [74–218]; n = 21	0.469

(*Continued*)

Table 3. (Continued).

		Propensity-score matching 1				Propensity-score matching 2		
<150	77/226 (34.1)	62/189 (32.8)	15/37 (40.5)	0.473	64/142 (45.1)	54/121 (44.6)	10/21 (47.6)	0.987
Death	149/1023 (14.6)	126/930 (13.5)	23/93 (24.7)	0.006	136/539 (25.2)	124/490 (25.3)	12/49 (24.5)	1.000
Time from illness onset to death or discharge, days	35 [26–43]; *n* = 1023	34 [26–43]; *n* = 930	36 [25–52]; *n* = 93	0.028	34 [25–42]; *n* = 539	33 [24.25–41]; *n* = 490	35 [29–49]; *n* = 49	0.055

Propensity-score matching 1: matching sex, age, symptoms, and comorbidities. Propensity-score matching 2: matching sex, age, symptoms, comorbidities, and immune indices (ferritin, lymphocytes, hsCRP, PCT, TNF-α, IL-1β, IL-2 R, IL-6, IL-8, IL-10). Data are median (IQR) or n/N (%). *p* values were calculated by Mann-Whitney U test, χ2 test, or Fisher's exact test, as appropriate. hsCRP = high-sensitivity C-reactive protein. IL-2 R = interleukin-2 R. IL-6 = interleukin-6. IL-8 = interleukin-8. IL-10 = interleukin-10. TNF-α = tumor necrosis factor alpha. NK cells = natural killer cells

Therefore, the elevated IL-6 might prompt immune damage in cancer patients with COVID-19. Other pro-inflammatory cytokines like IL-2 R and TNF-α also kept a higher level in cancer patients compared with non-cancer ones, joining in the cytokine storm damage.

T cells are essential to adaptive immune response.[4] CD8 + T cells played an important part in viral clearance by killing infected cells, and CD4 + T cells enhanced CD8+ and B cell responses. The number of CD8 + T cells and CD4 + T cells both sustained below the lower limit of normal range in the 6 weeks.[30] Moreover, a larger proportion of patients with elevated IL-10 was also observed in cancer cohort, which was an important anti-inflammatory cytokine that mediated T cell exhaustion.[31] The depletion and exhaustion of T cells of cancer patients both contributed to the COVID-19 viral persistence and mortality.

SARS-CoV-2 infects vascular epithelial cells and organs, expressing high levels of angiotensin-converting enzyme 2 (ACE2).[32] The subsequent host inflammatory response induces systemic microcirculatory dysfunction in the lung, heart, kidney, liver, and intestine.[33] With impaired T-cell-dependent immune response and inflammation due to cytokine storm, cancer patients face an uphill challenge with COVID-19. As our study suggests, monitoring of immunological indices is essential in cancer patients concerning the high proportion of immune dysregulation. For patients with dysregulated immune response, careful monitoring, and preemptive treatment may be helpful to improve clinical outcomes. Procalcitonin and lymphocyte count could be potentially used as biomarkers of high mortality risk, given that alteration of these indices had the shortest estimated median survival time. Appropriate immune targeted therapy could be an option of treatment for those with severe COVID-19 illness to release the immune toxicity.[34,35]

In conclusion, cancer patients with COVID-19 had a more dysregulated immune response during the 6 weeks since illness onset compared with non-cancer patients, and the more severe immune dysregulation might account for the poorer prognosis of cancer patients with COVID-19. Due to the limited number of patients included in this study, larger nationwide or worldwide data are needed to validate the universal applicability of our findings.

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Conflicts of interest

We declare no conflicts of interests for all authors.

Authors' contribution

G-Y C and Y G contributed equally to this work. G-Y C, C-R L, and Q-L G conceptualized and designed the study and supervised the project. Y G, S-Q Z, Y Y, X-Y L, Y W, and R-D Y collected and double-checked the clinical data. G-Y C, Y G, and S-Q Z loaded the data into the database and contributed to the literature search. G-Y C, D L, and Y Y analyzed and interpreted the data. C-R L, Q-L G, and A Desai advised on the design of the study and revised the manuscript. All authors vouch for the respective data and analysis, revised, approved the final version, and agreed to publish the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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