Lymphocyte May Be a Reference Index of the Outcome of Cancer Patients in COVID-19 Infection

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Abstract

Background: The novel coronavirus (COVID-19)−infected pneumonia is an international concern as it spreads through human populations and across national and international borders.

Methods: In this retrospective study, we consecutively included all cancer cases who had been identified as having a nucleic acid-confirmed COVID-19 infection from two designated hospitals in Wuhan, China. Non-cancer patients were also enrolled for comparison. The clinical data were gathered from the medical recordsfrom Jan 14 to March 12.

Results: Among the 117 cancer patients infected with COVID19, the median age was 63 years and 48.7% were male. Male, hematologic cancer, dyspnea on admission, and anti-cancer therapy significantly increased the risk of death. The amounts of cytokines and immune cells were correlated with the outcomeofcancer patients infected with COVIP-19. However, high level of TNF-a, IL-2R, IL-6, IL-8 did not increase the risk of death in non-cancer patients. Moreover, IL-2R and IL-6 markedly decreased in cancer patients recovered from COVID-19.

Conclusions: Cancer patients with COVID-19 were associated with high mortality (23.9%).The amounts of cytokines and lymphocytes could be utilized as the reference index in predicting the survival outcome of cancer patients with COVID-19.

Background

In December 2019, several pneumonia cases of unknown aetiology were identified in Wuhan, China [1]. The pathogen has been identified as a new enveloped RNA betacoronavirus known as 2019 novel coronavirus disease (COVID-19). Until June 28, 2020, more than 10 million laboratory-confirmed cases have been recorded globally.

Coronaviruses mainly cause respiratory tract infections, such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [2], which have resulted in more than 10000 cases in the past twenty years, with death rates of 37% for MERS-CoV and 10% for SARS-CoV [3, 4]. In contrast to MERS-CoV and SARS-CoV, COVID-19 have caused more deaths by multiple organ failure rather than respiratory failure, due to the widespread distribution of ACE2 (angiotensin converting enzyme 2)—the receptor for COVID-19—in various organs [5]. The main conditions predisposing to infection were malignancy and immune-suppressive therapy, such as chemotherapy or surgery [6]. Thus, cancer patients might be more susceptible to COVID-19 and have a poor prognosis.

Given the rapid spread of COVID-19, we aimed to describe the epidemiological, clinical, and laboratory parameters, treatment, and outcomes of cancer patients confirmed to have COVID-19 infection, and to find the factor predicting the outcome of cancer patients infected with COVID-19.

Methods

Patients

In this retrospective, two-center study, we reviewed the medical records for all patients with laboratory-confirmed COVID-19 infection and cancer history who were hospitalized in Tongji hospital of Tongji Medical College, Huazhong University of Science and Technology and Renmin Hospital of Wuhan University. The admission data of these patients was from Jan 14, 2020 to March 12, 2020. Following the WHO interim guidance, COVID-19 was diagnosed by real-time quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) assay or high-throughput sequencing of pharyngeal swab specimens. Nucleic acid confirmation of COVID-19 was conducted at the Chinese Center for Disease Prevention and Control until January 23, 2020, and subsequently in the two designated hospital in Wuhan, China. Only nucleic acid-confirmed patients were incorporated into the analysis.

We extracted the clinical symptom, comorbidity, and laboratory findings from electronic medical records. Patients were followed up to April 20, 2020. If additional information or clarification was required, data were obtained directly from attending doctors or other health care providers. For each patient, the symptoms during their hospitalization were documented in the present study, including fever, cough, expectoration, fatigue, diarrhea, etc. Fever was defined as axillary temperature more than 37.5 °C. All laboratory assessments were carried out depending on our institutional guidelines and clinical conditions of the patients. Laboratory testing included whole blood count, blood chemistry, coagulation test, lymphocyte subpopulation, and measures of procalcitonin, C-reactive protein (CRP), and serum cytokines. The primary composite end-point was death. The study was granted approval by the ethical committee of our institute with a waiver of written informed consent for emerging infectious diseases.

Statistical Analysis

Continuous variables were shown as median and compared by the Mann-Whitney U test; categorical variables were summarized as number (%) and compared by χ2 test or Fisher's exact test between different groups. Scatter plots were drawn to describe lymphocyte subpopulation and plasma cytokine concentrations. The Kaplan-Meier method was utilized to measure the correlation of cytokines and lymphocytes with survival, and the Cox proportion hazard analysis was utilized to clarify potential significant differences in outcome. A two-sided p value of less than 0.05 was considered significant for all applied statistical test. All the analyses were calculated with the use of R language, version 3.6.3 (http://www.r-project.org/).

Results

Demographic and clinical characteristics

In the 117 cancer patients with laboratory-confirmed COVID-19 infection who had been hospitalized at the two designated hospital as of March 12, 2020, 56 had received anti-cancer treatment, including surgery

(16.2%), chemotherapy (19.7%), or radiotherapy (4.3%) as the most recent treatment in the last year and the other patients were cancer survivors in routine follow-up. The demographic and clinical parameters of the 117 patients are listed in Table 1. The median age was 63 years (interquartile range, 56 to 70). A total of 48.7% were male. Lung cancer was the most common type (25.6%); less common were digestive system cancer (23.9%), breast cancer (15.4%), thyroid cancer (8.5%), urinary system cancer (7.7%), gynecological tumor (6.8%), hematologic malignancies (6.8%), sarcoma (2.6%), head and neck cancer (0.9%) and cancer of unknown primary site (1.7%). Among the overall population, 48.7% had more than one coexisting illness, including diabetes (15.4%), hypertension (30.8%), cardiovascular disease (9.4%) and chronic obstructive pulmonary disease (COPD) (14.5%). Fever was present in 71.8% of the patients on admission. Less common symptom was cough (65.0%) and myalgia (50.4%); sputum production (39.3%), and diarrhea (14.5%) was uncommon.

Table 1
Clinicopathological characteristics of cancer patients infected with COVID-19.

Characteristics	All patients (n = 117)	Alive (n = 89)	Dead (n = 28)	P value
Age (years)				0.499
< 60	41 (35.0)	33 (37.1)	8 (28.6)	
≥ 60	76 (65.0)	56 (62.9)	20 (71.4)	
Gender				0.029
Female	60 (51.3)	51 (57.3)	9 (32.1)	
Male	57 (48.7)	38 (42.7)	19 (67.9)	
Diagnosis (n [%])				
Lung cancer	30 (25.6)	25 (28.1)	5 (17.9)	0.280
Breast cancer	18 (15.4)	16 (18.0)	2 (7.1)	0.166
Thyroid cancer	10 (8.5)	10 (11.2)	0 (0)	0.064
Digestive System Cancer[*]	28 (23.9)	20 (22.5)	8 (28.6)	0.509
Gynecological oncology[#]	8 (6.8)	8 (9.0)	0 (0)	0.100
Urinary system tumor[&]	9 (7.7)	4 (4.5)	5 (17.9)	0.021
Hematologic malignancies	8 (6.8)	2 (2.2)	6 (21.4)	< 0.001
Sarcoma	3 (2.6)	1 (1.1)	2 (7.1)	0.079
Head and neck cancer	1 (0.9)	1 (1.1)	0 (0)	0.573
Unknown primary site	2 (1.7)	2 (2.2)	0 (0)	0.424
Comorbidities				0.955
Diabetes	18 (15.4)	13 (14.6)	5 (17.9)	
Hypertension	36 (30.8)	26 (29.2)	10 (35.7)	
Coronary heart disease	11 (9.4)	7 (7.9)	4 (14.3)	
COPD	17 (14.5)	12 (13.5)	5 (17.9)	
Symptom				

Annotation: [*]indicating 11 intestine cancer, 4 esophageal cancer, 6 liver tumor, 7 stomach cancer; [#]indicating 2 ovary cancer, 4 cervical cancer, 2 endometrial cancer; [&]indicating 5 bladder cancer patient, 2 prostate cancer, 2 renal cancer.

Characteristics	All patients (n = 117)	Alive (n = 89)	Dead (n = 28)	P value
Dyspnea	54 (46.2)	32 (36.0)	22 (78.6)	< 0.001
Cough	76 (65.0)	59 (66.3)	17 (60.7)	0.590
Expectoration	46 (39.3)	33 (37.1)	13 (46.4)	0.377
Malaise	59 (50.4)	45 (50.6)	14 (50.0)	0.959
Headache	10 (8.5)	6 (6.7)	4 (14.3)	0.213
Muscle ache	10 (8.5)	9 (10.1)	1 (3.6)	0.280
Pharyngodynia	7 (6.0)	7 (7.9)	1 (3.6)	0.432
Diarrhea	17 (14.5)	13 (14.6)	4 (14.3)	0.967
Fever	84 (71.8)	65 (73)	19 (67.9)	0.596

Annotation: [*]indicating 11 intestine cancer, 4 esophageal cancer, 6 liver tumor, 7 stomach cancer; [#]indicating 2 ovary cancer, 4 cervical cancer, 2 endometrial cancer; [&]indicating 5 bladder cancer patient, 2 prostate cancer, 2 renal cancer.

28 (23.9%) cancer patients worsened and died of multiple organ failure, while 19 (16.2%) patients without a history of cancer died due to COVID-19 infection (Supplemental table 1). Male and the presence of dyspnea were more prevalent among patients died of COVID-19 than those alive (cancer patients p = 0.029, p < 0.001; non-cancer patients p = 0.006, p < 0.001). Moreover, patients with hematologic malignancy had the highest mortality than those with non-hematologic cancer (p < 0.001). However, age and comorbidities between the two groups were similar.

Laboratory findings

The laboratory findings on admission are shown in Table 2. Lymphocytopenia was present in 59.8% of cancer patients, thrombocytopenia in 17.9%, and leukocytosis in 13.7%. Most patients had increased levels of CRP; less frequent were increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer. The alteration of laboratory testing (leukocytes, neutrophils, lymphocytes, thrombocytes, prothrombin time, activated partial thromboplastin time, CRP, procalcitonin, bilirubin and troponin) was associated with outcome of cancer patients diagnosed with COVID-19 (p = 0.023, p = 0.002, p = 0.027, p = 0.045, p < 0.001, p < 0.001, p < 0.001, p = 0.003, p = 0.005, p < 0.001). Besides, cancer patients had more prominent laboratory abnormalities than non-cancer patients (Supplemental table 2).

Table 2
Laboratory findings of cancer patients infected with COVID-19 on admission to hospital.

Characteristics	All patients (n = 117)	Alive (n = 89)	Dead (n = 28)	P value
WBC, $\cdot 10^9$/L				
< 4	24/117 (20.5)	19/89 (21.3)	5/28 (17.9)	0.794
> 10	16/117 (13.7)	8/89 (9.0)	8/28 (28.6)	0.023
Neutrophil count, $\cdot 10^9$/L	3.9 (2.6, 5.6)	3.6 (2.5, 5.1)	6.3 (2.9, 8.9)	0.002
Lymphocytopenia	70/117 (59.8)	48/89 (53.9)	22/28 (78.6)	0.027
Thrombocytopenia	21/117 (17.9)	12/89 (13.5)	9/28 (32.1)	0.045
Prothrombin time, s	13 (12, 14)	13 (12, 14)	15 (13, 16)	< 0.001
APTT, s	36 (27, 42)	33 (27, 41)	41 (35, 49)	< 0.001
D-dimer, mg/L	1.1 (0.5, 2.9)	1.0 (0.5, 2.0)	2.5 (1.1, 7.3)	0.074
CRP	36 (7, 92)	26 (5, 56)	96 (54, 145)	< 0.001
Procalcitonin	0.09 (0.05, 0.26)	0.06 (0.04, 0.15)	0.39 (0.13, 1.07)	0.003
Total bilirubin	10.1 (6.7, 13.3)	9.9 (6.4, 13.0)	10.3 (8.3, 15.7)	0.005
ALT > 40U/liter	22/117 (18.8)	19/89 (21.3)	3/28 (10.7)	0.274
AST > 40U/liter	28/117 (23.9)	19/89 (21.3)	9/28 (32.1)	0.310
Troponin, pg/mL	1.9 (0, 4.4)	1.9 (0, 2.5)	15 (1.9, 61.8)	< 0.001
Annotation: Lymphocytopenia was defined as a lymphocyte count of less than 1000 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 100,000 per cubic millimeter. APTT indicates activated partial thromboplastin time. AST indicates aspartate aminotransferase				

Compared to alive patients, dead patients had increased levels of TNF-α, IL-2R, IL-6, IL-8, and IL-10 tested on admission (Fig. 1 and Supplemental Fig. 1). However, high level of TNF-α, IL-2R, IL-6, IL-8 did not raise the risk of death in non-cancer patients. Importantly, the levels of TNF-α, IL-2R, IL-6, IL-8, and IL-10 were significantly correlated with survival time of cancer patients with COVIP-19. These odds were further proved by logistic regression model after adjusting for other risk factors, including age, gender, cancer type, comorbidities, symptom and anti-cancer treatment (Table 3). In addition, T lymphocytes, B lymphocytes, T helper (Th) cells, and T suppressor (Ts) cells were diminished in cancer patients with a primary composite end-point event of death (Fig. 2). Cancer patients with more B cells and Th cells had longer survival than those with less B cells and Th cells (p = 0.007, p = 0.035). We further examined if the levels of cytokines were changed when cancer patients recovered from COVID-19. Figure 3 showed that IL-2R and IL-6 significantly decreased in the patients with better illness. These results strongly suggesting

that the number of lymphocytes and cytokines could be used as independent prognostic factor predicting the outcome of cancer patients with COVID-19.

Table 3
Logistic regression analysis of survival of cancer patients tested for cytokines.

Characteristics	All patients	P value
Age at diagnosis	0.620 (0.179, 2.144)	0.401
Gender		0.016
Female	1 (Reference)	
Male	8.250 (1.044, 65.198)	
Cancer type		0.006
Non-hematologic cancer	1 (Reference)	
Hematologic cancer	5.380 (1.502, 19.269)	
Comorbidities		
Diabetes	1.343 (0.285, 6.328)	0.687
Hypertension	0.907 (0.234, 3.512)	0.756
Coronary heart disease	0.613 (0.150, 2.497)	0.331
COPD	1.254 (0.266, 5.907)	0.865
Symptom		
Dyspnea	11.556 (1.460, 91.474)	0.004
Cough	0.798 (0.169, 3.759)	0.865
Expectoration	4.855 (1.030, 22.898)	0.020
Malaise	1.365 (0.385, 4.840)	0.654
Headache	5.575 (0.455, 26.898)	0.060
Muscle ache	1.815 (0.230, 14.357)	0.650
Pharyngodynia	0.913 (0.116, 7.207)	0.877
Diarrhea	1.920 (0.542, 6.799)	0.153
Fever	2.179 (0.276, 17.202)	0.445
Treatment		
No	1 (Reference)	0.020
Yes	4.039 (1.043, 15.644)	
Cytokines		

Characteristics	All patients	P value
TNF-α	4.510 (1.257, 21.259)	0.031
IL-2R	4.775 (1.012, 22.532)	0.031
IL-6	6.566 (1.497, 15.062)	< 0.001
IL-8	4.811 (1.020, 22.687)	0.031
IL-10	8.201 (1.736, 38.748)	0.002

Treatments and outcomes

A majority of cancer patients (91.5%) received antivirus therapy, and 83.8% received intravenous antibiotic therapy; oxygen therapy was treated in 54.7% and mechanical ventilation in 28.1%; higher proportion of patients with critical disease received these therapies. Systemic glucocorticoids were given to 52 patients (44.4%).

Patients with non-hematologic cancer did not die rapidly compared to patients with hematologic cancer types (odds ratio [OR] 5.380, 95% CI 1.502–19.269; p = 0.006). Among patients with cancer, patients who underwent anti-cancer therapy in the past year had a markedly higher risk (33.3%) of death than did those not receiving therapy (15.0%) (OR 4.039, 95% CI 1.043–15.644; p = 0.020).

Discussion

In this study, we exhibited clinical data of 117 cancer patients and paired non-cancer patients with nuclei acid-confirmed COVID-19 infections. Similar to previous studies, fever and cough were the main symptoms and digestive symptoms were infrequent, which indicates a difference in viral tropism as compared to MERS-CoV, SARS-CoV, and seasonal influenza [7, 8]

Our study demonstrated that cancer patients had more prominent laboratory abnormalities than non-cancer patients, accompanied with cancer patients seriously ill as compared to patients without history of cancer [1, 9, 10]. 28 of the 117 cases progressed to severe pneumonia as of March 30, 2020, and died during hospitalization. Additionally, we showed that male, hematologic malignancies and dyspnea had been related to increased risk of death; patients who underwent anti-cancer therapy in the past year, had worse survival outcomes from COVID-19, alerting as a timely reminder to doctors that more attention should be paid to cancer patients, especially in male patients or those with specific cancer type.

Lymphocytopenia was common and associated with death, a finding that was in agreement with previous observations [11]. Many cytokines also regulate the immune system and play a role in virus immunity. TNFα secretion promotes T lymphocyte proliferation and survival, whereas IL-2 levels reflect the T lymphocyte activation status toward a Th1 immune response [12]. IL-6 is involved in the differentiation of B lymphocytes into Ig-secreting cells and participates in lymphocyte and monocyte differentiation [13]. IL-8 is a chemotactic factor that attracts T lymphocytes, neutrophils, basophils [14].

Previous studies have proved that elevated concentration of serum proinflammatory cytokines was related to pulmonary inflammation and respiratory failure in SARS patients [15]. MERS-CoV infection was also found to induce increased levels of proinflammatory cytokines [16]. In this study, cancer patients with higher concentration of TNF-α, IL-2R, IL-6 and IL-10 had higher risk of death. In addition, we analyzed the alteration of major immune cell types (CD4+, CD8+ T cells, B cells and NK cells) in 117 cancer patients and showed that lymphocytes were diminished in cancer patients died from COVID-19. This result suggests that COVID-19 might mainly act on immune cells, especially lymphocytes. Virus spreads through the respiratory and digestive mucosa and infects target cells, leads to a cytokine storm in severity illness cancer patients, generates the immune responses, and causes alteration in leukocytes and lymphocytes. Patients with severe illness developed acute respiratory distress syndrome and required mechanical ventilation. The decrease in the counts of lymphocytes suggests that the virus consumes the immune cells and blocks the immune function [17]. Lymphocyte deficiency might accelerate to exacerbations of patients [11]. In our study, IL-2R and IL-6 significantly decreased in the patients recovered from COVID-19. These results strongly suggesting that the number of cytokines and lymphocytes could be used as the prognostic factor in predicting the outcome of cancer patients with COVID-19. Further studies that characterize the immune response in cancer patients with COVID-19 are required.

This study has a few notable limitations. First, our study was undertaken in two designated hospital in Wuhan. Large-scale multicenter clinical trials are needed to clarify our findings. Second, data collection was clinically driven and not systematic. Third, we might leave out a series of asymptomatic patients or patients who had mild symptoms and were treated at home. Thus, our cohort represented the more severe population of cancer patients with COVID-19.

Conclusions

COVID-19 has spread rapidly since December 2019, and has been demonstrated to have a severe impact on human health. Moreover, compared to non-cancer population, COVID-19 infection caused higher proportion of multiple organ dysfunction syndrome in cancer patients and was linked to higher mortality (23.9%). Special attention should be given to these patients.

Declarations

Ethics approval and consent to participate

The study isapproved by the ethical committee of Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology with a waiver of written informed consent for emerging infectious diseases.

Consent for publication

Not applicable.

Authors' contributions

XY participated in the design of the study, data collection, and paper writing. YG involved in the acquisition of data, and revising the manuscript. QCperformed the statistical analysis. QC participated in the revising of the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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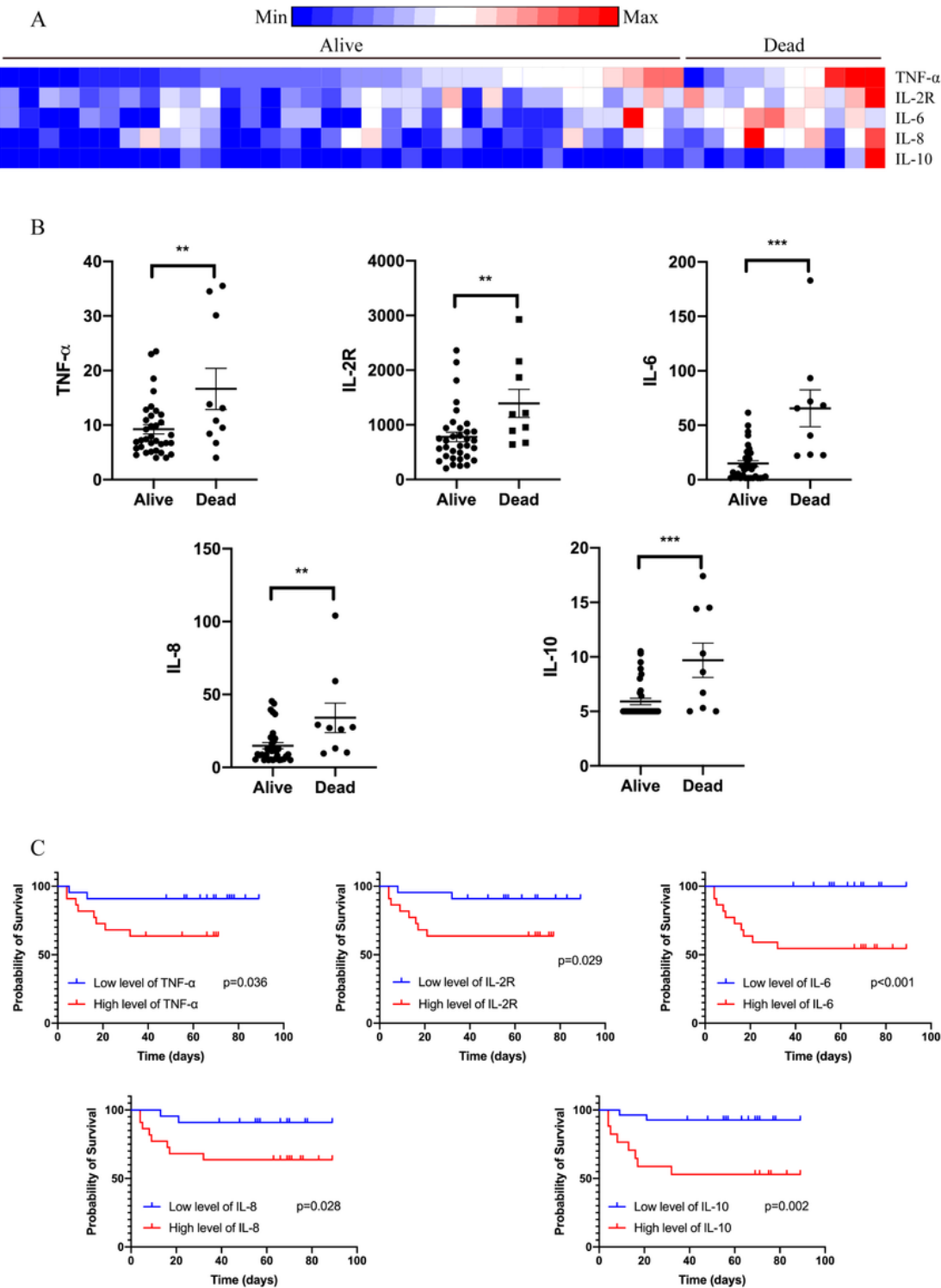
Figures

Figure 1

Figure 1

Serum cytokines on admission of cancer patients.Levels of TNF-α, IL-2R, IL-6, IL-8, and IL-10 were tested on admission of cancer patients with COVID-19 divided by outcome (A). Levels of TNF-α, IL-2R, IL-6, IL-8, and IL-10 were increased in patients died of COVID-19 (B). Levels of TNF-α, IL-2R, IL-6, IL-8, and IL-10 were correlated with survival time of patients with COVID-19 (C).
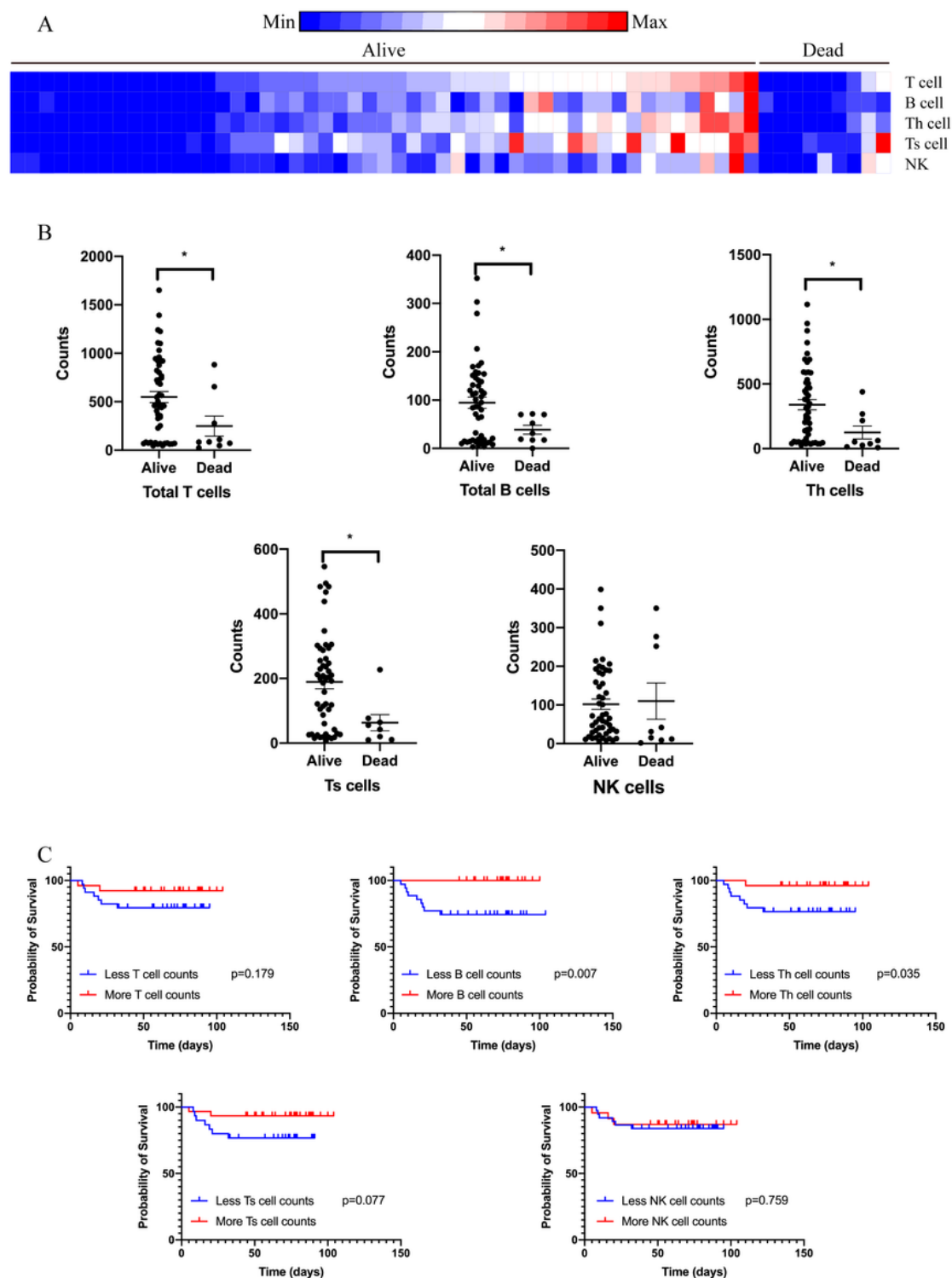
Figure 2

Figure 2

Circulating immune cell subpopulation on admission of cancer patients. Counts of T lymphocytes, B lymphocytes, Th cells, Ts cells, and NK cells were tested on admission of cancer patients with COVID-19 divided by outcome (A). Counts of T lymphocytes, B lymphocytes, Th cells, and Ts cells were diminished on admission of cancer patients with COVID-19 (B). Count of B lymphocytes and Th cells were correlated with survival time of patients with COVID-19 (C).
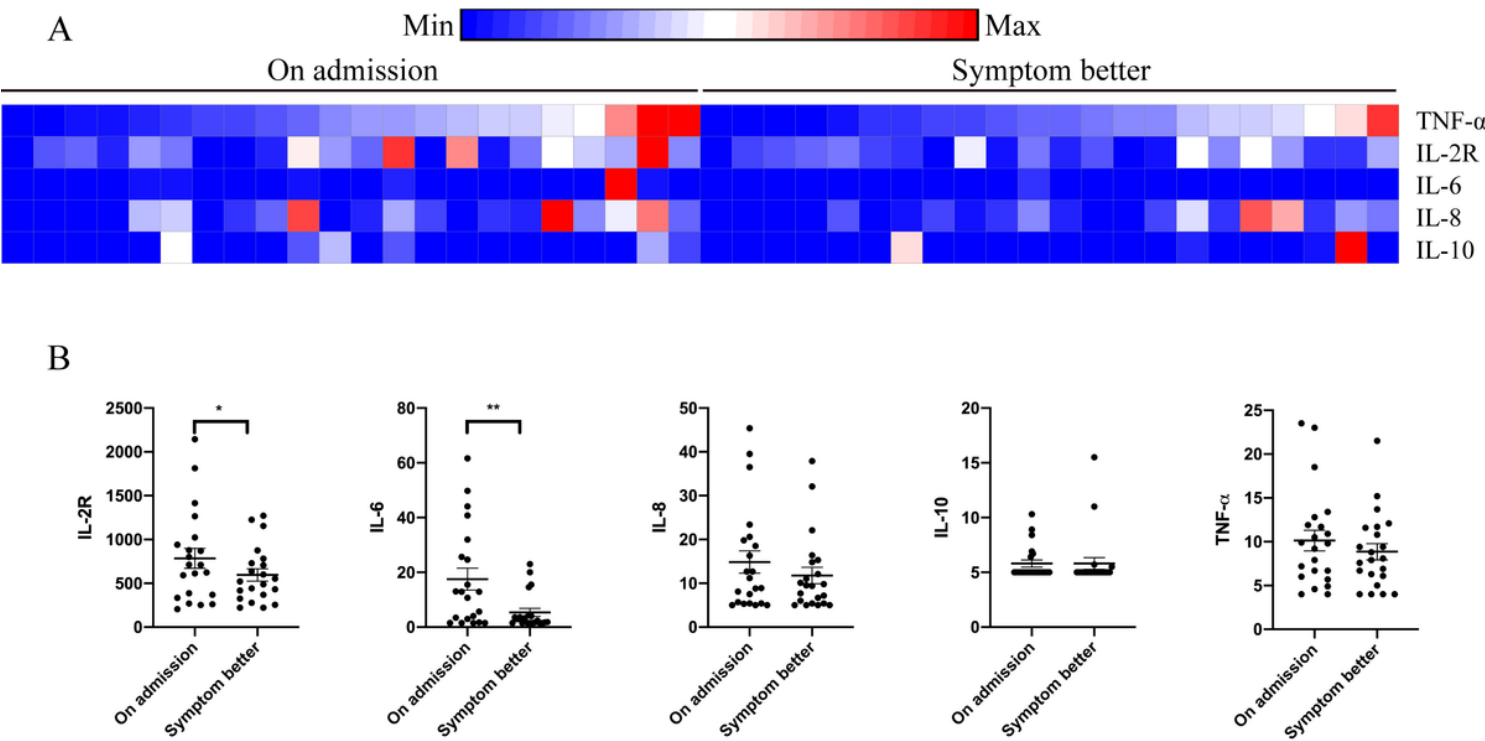
Figure 3

Figure 3

Serum cytokines alteration in cancer patients during therapy.Levels of TNF-⍺, IL-2R, IL-6, IL-8, and IL-10 were tested on admission and when symptom turning better (A). Levels of TNF-⍺, IL-2R, IL-6, IL-8, and IL-10 were changed when cancer patients recovered from COVID-19 (B).

Supplementary Files

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