Malignancy History Affected the Prognosis of COVID-19 Patients via Release of Interleukin-6

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Abstract

Background: Coronavirus disease 2019 (COVID-19), a newly erupted respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the most of countries. The laboratory characteristics of COVID-patients accompanied with cancer and the risk factors for disease progression and survival of this particular population were few reported.

Methods: We enrolled 585 confirmed COVID-19 patients admitted to our hospitals with measured interleukin-6 level on admission. Laboratory tests and outcome were extracted from electronic medical records. Data was divided to cancer group and non-cancer group to explorer the risk factors of progression and survival.

Findings: A total of 44 patients with different cancer type (cancer group) and 541 patients without cancer (non-cancer group) were included. Cancer group had significant higher levels of NEUT, NLR, IL-6, and CRP than non-cancer group, but lymphocyte count and ALB were lower. Cancer group showed significantly higher progression rate (42·1% vs 22·5%) and mortality (27·27% vs 11·91%) than non-cancer group. Elevated IL-6 and CRP were the risk factors associated with progression among moderate patients and death in-hospital (all p<0·05) in non- cancer group. This correlation was not observed in caner group.

Interpretation: IL-6, CRP, NEUT, and NLR were elevated in COVID-19 patients with cancer, with lower level of LYMP and ALB. IL-6 and CRP were positively correlated with progression and poor outcome in patients without cancer. As one of combined diseases, despite malignancy history did not directly affect the prognosis of COVID-19, but it could play a role in the poorer outcome through release of IL-6 and CRP.

Introduction

Coronavirus disease 2019 (COVID-19), a newly erupted respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the most of countries on planet. The majority of patients infected COVID-19 exhibit mild to moderate symptoms, while approximately 15% could develop to severe stage and about 5% eventually develop acute respiratory distress syndrome (ARDS), even multiple organ dysfunction [1,2]. Accumulating evidence suggests that patients with severe COVID-19 might have a cytokine storm syndrome and immunosuppression, with hyperinflammation, mainly characterized by increased cytokines (interleukin-2, interleukin-7…), among which, interleukin-6 (IL-6) was regarded as a predictors of fatality[3]. Elevated IL-6 was a hallmark inflammatory signature seen in serum of patients with severe COVID-19 acute respiratory distress[4]. Elevated serum IL-6 correlates with respiratory failure, ARDS, and adverse clinical outcomes[5]. Malignancy, despite less frequently reported than COPD, hypertension, and diabetes, was notwithstanding controversial for the predictive value on COVID-19 severity. As Guan at al. reported, malignancy was one of the risk factors of disease severity[6]. While another Meta-analysis suggested that there was no correlation between malignant tumor and COVID-19 patients' aggravation[7]. It is worthy to mention that IL-6 has been proposed to play key role in pathogenesis and development of cancer. It has been reported

that tumor cells could release certain cytokine, of which one important role was to induce the production of proinflammatory cytokines, such as IL-6, from the stromal cells as well as tumor cells[8]. Hence, we aimed to compare the laboratory characteristics of patients with cancer and without cancer to determine explorer the risk factors for disease progression and survival, certainly the role of IL-6 included.

Methods

Study design and participants

In this retrospective cohort study, we enrolled all laboratory confirmed COVID-19 patient admitted to our hospitals who measured IL-6 levels on admission from January 1 to March 25, 2020. Patients were diagnosed as COVID-19 according to Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia recommended by the National Health Commission (NHC) of China (version 7·0)[9]. The study was approved by The Central Hospital of Wuhan Hospital Ethics Committee and written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Data Collection

Demographic, laboratory findings and outcome data were extracted from electronic medical records through a standardized data collection form. All data were collected and checked by 3 experienced clinicians independently.

Procedures

SARS-CoV-2 infection was confirmed by next-generation sequencing or real-time RT-PCR performed with pharyngeal swab or bronchoalveolar lavage fluid[10]. Routine laboratory examinations included blood examinations, coagulation and biochemical tests on admission. The clinical outcomes were evaluated by two experienced clinicians.

Definitions

The disease severity of COVID-19 was assessed according to the guideline of Chinese NHC[9]. Briefly, moderate cases were defined as patients with fever, dry cough, fatigue and other symptoms, pulmonary CT findings were exudation or consolidation, but oxygen saturation exceeded 93% without oxygen; severe grade signified respiratory frequency ≥ 30 times/minute, blood oxygen saturation ≤ 93%, oxygenation index ≤ 300 mmHg, and/or lung infiltration progression > 50% within 24 to 48 hours; and critical grade was defined as appearance of respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Poor progression included moderate grade progressed to severe or critical grades and even death.

Statistical Analysis

SPSS software (version 22·0) was used to analyze the data. Shapiro wilktest method was used to determine the distribution of continuous variables. Student-t test was used to test the score difference of each group in the normal distribution, and rank sum test was used to compare the difference in the normal distribution. The normal distribution measurement data is expressed by mean ± standard deviation (SD), and median (interquartile Range IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data. Chi-square test was used to compare the distribution differences among groups. When the number of predicted cases was less than 5, Fisher accurate probability method was applicated. The significant factors of univariable analysis were included into multivariable logistic regression model. A two-sided α of less than 0·05 was considered statistically significant.

Results

Demographic, laboratory findings, and outcomes of COVID-19 patients

A total of 585 laboratory confirmed COVID-19 patients whose IL6 levels had been measured at admission were included, 44 patients with different cancer type (cancer group) and 541 patients without cancer (non-cancer group). Cancer type included 6 gastrointestinal cancer, 5 urinary tumors, 4 lung cancer, 4 blood cancer, 4 head and neck cancer, 4 liver cancer, 3 cholangiocarcinoma, 3 prostate cancer, 3 glioma, 2 breast cancer, 2 thyroid cancer, 1 gynecological tumor, 1 esophagus cancer, 1 pancreas cancer, and 1 osteosarcoma.

The median age of cancer group was 67 years, older than non-cancer patients. Gender distribution of two groups did not show significant difference. As for laboratory findings, cancer group had significant higher levels of neutrophil count (NEUT), neutrophil-to-lymphocyte ratio (NLR), IL-6 and C-reactive protein (CRP) than non-cancer group, but lymphocyte count (LY) and serum albumin (ALB) were lower (all $p < 0·05$, Table 1). Among 44 patients with cancer, 38(86·4%) were moderate and 6(13·6%) were severe or critical on admission, the ratios were equal in non-cancer patients (Table 1, $p = 0·866$). But cancer group showed higher mortality and higher progression rate among moderate patients, as well as longer in-hospital time.

Risk factors associated with poor progression among moderate patients

To confirm which factors contributed to the different ratios of progression between cancer and non-cancer group, we enrolled all 510 moderate patients, whose data was studied in two groups: stabilization group (388 stabilized patients) and progression group (122 progressed patients). As shown in Table 2, the proportion of males and malignancy in poor progression group was higher than stabilization group.

The progression group also showed older age and higher levels of IL-6, CRP, NEUT, and NLR, as well as lower levels of ALB and LYMP compared to stabilized patients (all $p < 0{\cdot}05$). Based on the results of univariable logistic regression, factors with $p < 0{\cdot}05$ were included for the multivariable logistic regression. Interestingly, malignancy was not a risk factor associated with progression ($p = 0{\cdot}757$, Table 2), but age, levels of IL-6, CRP and ALB could play a role (Table 2).

To further confirm the roles of these risk factors, we then performed analyses in two groups separately. Unfortunately, in cancer group (n = 38), none of indicators included was significantly related to disease progression (all $p > 0{\cdot}05$, Table 3). Nevertheless, In non-cancer group, progressed patients showed older age, more males, higher levels of IL-6, CRP, NEUT and NLR, also lower levels of ALB and LYMP than stabilized patients (all $p < 0{\cdot}05$, Table 3), then multivariable logistic regression confirmed that IL-6, CRP, ARB and NLR were the risk factors associated with progression among moderate patients without cancer (Table 3).

Risk factors associated with death in-hospital

Table 1 showed the mortality between cancer group and non-cancer group were significantly different. We divided all 585 patients into survivor group (524 patients) and non-survivor group (61 patients) (Table 4). Not surprisingly, poorer survival was associated with higher proportion of males, more severe/critical presentation at admission, older age, high levels of IL-6, CRP, NEUT, NLR, and lower levels of ALB and LYMP, combination with malignancy was also concluded. Age, gender, IL-6 and CRP were proved meaningful in the subsequent multivariable logistic regression (all $p < 0{\cdot}05$, Table 4). However, malignancy was still not a risk factor associated with death in-hospital of COVID-19 ($p = 0{\cdot}223$, Table 4).

Subgroup analyses were then performed. As shown in Table 5, in cancer group, non-survivor demonstrated older age, lower ALB, and higher levels of IL-6, CRP and NLR. But all these factors s were meaningless in multivariable logistic regression (all $p > 0{\cdot}05$, Table 5). While in non-cancer group, age, IL-6 and CRP were proved as risk factors associated with death in-hospital (all $p < 0{\cdot}05$, Table 5).

Discussion

In this retrospective study, we analyzed the laboratory data of 585 COVID-19 infected cases in our hospital, including 44 cases accompanied with different cancers and 541 cases without cancer. The severity grading on admission was equal between these two groups.

In terms of laboratory tests, lymphopenia[11,12], as well as increased NLR were common feature and thought to be a critical factor associated with disease severity and mortality in COVID-19[13,14]. Our results confirmed lymphopenia and increased NLR in patients with poor outcome in-hospital in both tumor group and non-tumor group.

Studies demonstrated that most patients with severe COVID-19 exhibit substantially elevated serum levels of pro-inflammatory cytokines, including IL-6 and IL-1β, IL-17, G- CSF, GM-CSF…, characterized as cytokine storm[1,2,15,16] as well as C- reactive protein[17]. IL-6 is a call-to-arms for some components of the immune system, including macrophages. Macrophages fuel inflammation and can damage normal lung cells[18]. Elevated IL-6 could trigger cytokine release syndrome through cis signaling or trans signaling. After binding to IL-6 receptor, downstream JAKs (Janus kinases)-STAT3 (signal transducer and activator of transcription 3) signaling results in activation of either immune system cells (B and T cells, neutrophils, macrophages, and natural killer cells) which can contribute to cytokine release syndrome[19]; or endothelial cells, which then results in a systemic “cytokine storm” charactered by secretion of additional IL-6, vascular endothelial growth factor (VEGF) and reduced E-cadherin expression on endothelial cells[20]. The latter two enhance vascular permeability and leakage, which play an important role in pulmonary dysfunction in ARDS[5]. The severity of IL-6 elevation correlated with the need for mechanical ventilation and mortality[21]. Consistently with previous reports, our analysis showed increased IL-6 level in patients with progression and death in-hospital in both tumor group and non-tumor group. Univariable and multivariable logistic regression analysis confirmed that the increase of IL-6 was positively correlated with progression and poor outcome in non-cancer group. This relationship was not observed in cancer group, indicated that except for IL-6 or CRP, other factors

Interestingly, IL-6 has been proposed to play key role in pathogenesis and development of cancer. Tumor cells themselves and immune cells around tumor can release IL-6, and hence increase plasma levels of IL-6[22]. Besides, another analysis revealed an increase in circulating levels of IL-17A in cancer patients, of which the primary role is to induce the production of proinflammatory cytokines, such as IL-6, from the stromal cells as well as tumor cells[8].

In the other side, tumor patients are frequently combined with cachexia in various degrees according to tumor type and stage[23]. It has been shown elevated IL-6 levels correlated with weight loss and performance status as well as tumor burden[22,24]. A tumor-specific profile of cachexia-inducing factors analyze showed upregulated IL-6 level in pancreatic adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, stomach adenocarcinoma, colon adenocarcinoma, acute myeloid leukemia, breast carcinoma, hepatocellular carcinoma[25]. Logically, our data indicated IL-6 level in cancer group was nearly 3 times of that in non-cancer group. Meanwhile, the mortality in cancer group was identically 3 times of that in non-cancer group. Thus we lanced univariable and multivariable logistic regression analysis to determine whether this increased level of IL-6 could contribute to the higher mortality in patients with cancer. Tables 2 and 4 showed that cancer, as comorbidity, was not a significant factor that affected the progression and survival of COVID-19 patients, which was consistent with the previous meta-analysis[7]; nevertheless dramatically, IL-6, upregulated in cancer group, was confirmed as a marked indicator of poor survival in COVID-19 patients. In summary, despite that cancer itself could not directly play a role in the prognostic of COVID-19, it could conduce to a poorer outcome through release of IL-6.

Elevated serum C-reactive protein (CRP), a protein whose synthesis and release are regulated by IL-6, is also a biomarker of severe COVID-19 infection[5,26]. CRP ≥ 5 mg/dl was considered as an important evidence of severe inflammation. Elder patients with higher CRP had higher in-hospital mortality with a RR of 2 compared with lower CRP group[27]. Similarly in our results, CRP level was significantly higher in patients with progression and death in-hospital in both tumor group and non-tumor group. Univariable and multivariable logistic regression analysis confirmed that the IL-6 level was positively correlated with progression and poor outcome in non-cancer group. Furthermore, increased CRP concentrations have been reported in different cancer type[28]. As mentioned above, tumor cells have been shown to secrete IL-6, which in turn induced the production of CRP. Consequently, our data revealed the CRP level in cancer group was marked elevated related to non-cancer group, and this increase of CRP was positively correlated with progression and poor outcome in non-cancer group. Univariable and multivariable logistic regression analysis confirmed CRP, together with IL-6, was a significant factor that affected the mortality of COVID-19 patients.

It is worthy to mention that neither IL-6 nor CRP, or other indicator was proved to affect the progression and death within the cancer group, although some laboratory test showed significant difference between survivors and non-survivors in univariable logistic regression analysis. This signified the prognosis of COVID-19 patients with cancers might be affected by some other critical indicators that were not covered in our study. Guan et al. reported that in severe COVID-19 cases, IL-2R, TNF-α and IL-10 concentrations were significantly higher; while IFN-γ level, CD4 + T cells and CD8 + T cells were significantly lower[21]. Qin et al. observed lower level of helper T cells (CD3 + CD4+) and increased level of naïve helper T cells (CD3 + CD4 + CD45RA+) in severe group[15]. These infection-related biomarkers and inflammatory cytokines were closely associated development of cancer[29,30]. Further investigation on the effect of interaction between cancer and inflammation on the prognostic of COVID-19 patients should be performed.

Conclusion

This retrospective study revealed that IL-6, CRP, NEUT, and NLR were elevated in COVID-19 patients with cancer, with lower level of LYMP and ALB. IL-6 and CRP were positively correlated with progression and poor outcome in patients without cancer. As one of combined diseases, notwithstanding malignancy history did not directly affect the prognosis of COVID-19, but it could play a role in the poorer outcome through release of IL-6 and CRP.

Limitation

There were some limitations in this study. Firstly, due to the rapid pandemic outbreak and the heterogeneity of prescription of each medical worker, IL-6 concentration test was not performed in all the patients hospitalized. This could induce the possible selection bias and potentially lessened the representative value of our study. Secondly, due to the retrospective study design, not all laboratory tests were performed, especially some important immunological indicators as IL-10, IFN-γ and TNF-α, as well

as lymphocyte subsets quantification (CD3 + CD4+/CD8 + etc.). Therefore, profound immunological interaction could not be further explored. Moreover, our study was single-central and small-sized, which may make it difficult to generalize the result, larger sample research of multiple centers should be more representative.

Declarations

Ethics approval and consent to participate

The study was approved by The Central Hospital of Wuhan Hospital Ethics Committee and written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiahao Hu and Haixia Ding contributed equally as co-first authors.

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Tables

Table 1
Demographic, laboratory findings, and outcomes of COVID-19 patients.

	Cancer (n = 44)	**Non-cancer (n = 541)**	***P* value**
Age, years	67 (IQR: 54-80.5)	59 (IQR: 42–69)	0.005
Gender			
Female (%)	20 (45.5)	294 (54.3)	0.255
Male (%)	24 (54.5)	247 (45.7)	
Time in-hospital, days	31 (IQR: 19-48.5)	21 (IQR: 13–31)	< 0.001
Laboratory findings			
WBC, $\times 10^9$/L	6.15 (IQR: 4.55–7.51)	5.37 (IQR: 4.30–6.87)	0.065
NEUT, $\times 10^9$/L	4.18 (IQR: 2.89–6.32)	3.43 (IQR: 2.59–4.80)	0.015
LYMP, $\times 10^9$/L	0.85 (IQR: 0.58–1.40)	1.26 IQR: (0.84–1.71)	0.001
NLR	5.15 (IQR: 2.53–8.52)	2.61 (IQR: 1.68–4.92)	0.001
ALB, g/L	36.8 (IQR: 31.7–42.2)	39.5 (IQR: 35.15–43.2)	0.017
IL-6, pg/L	13.9 (IQR: 6.24–32.4)	4.19 (IQR: 2.15–12.23)	< 0.001
CRP, mg/dl	2.96 (IQR: 0.38–6.32)	0.59 (IQR: 0.11–3.37)	< 0.001
Severity			
Moderate (%)	38 (86.4)	472 (87.2)	0.866
Severe/Critical (%)	6 (13.6)	69 (12.8)	
Progression among moderate patients			
Stabilization (%)	22 (57.9)	366 (77.5)	0.006
Poor progression (%)	16 (42.1)	106 (22.5)	
Outcomes			

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender, severity, progression among moderate patients and outcomes) and Mann-Whitney U-test (for age, time in-hospital and laboratory findings).

Abbreviations: WBC, white blood cell count; NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

	Cancer (n = 44)	Non-cancer (n = 541)	*P* value
Survivor (%)	32 (72.73)	429 (88.09)	0.001
Non-survivor (%)	12 (27.27)	58 (11.91)	

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender, severity, progression among moderate patients and outcomes) and Mann-Whitney U-test (for age, time in-hospital and laboratory findings).

Abbreviations: WBC, white blood cell count; NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Table 2
Risk factors associated with poor progression among moderate patients.

	Stabilization (n = 388)	Poor progression (n = 122)	*P* value	Multivariable (95% CI for OR)	*P* value
Age, years	56 (IQR: 38–67)	67 (IQR: 53-80.5)	< 0.001	1.019 (1.001–1.037)	0.04
Gender					
Female (%)	223 (57.5)	54 (44.3)	0.011	1.006 (0.565–1.793)	0.983
Male (%)	165 (42.5)	68 (55.7)			
Comorbidities					
Cancer (%)	22 (5.7)	16 (13.1)	0.006	1.164 (0.446–3.036)	0.757
Hypertension (%)	114 (29.4)	62 (50.8)	< 0.001	0.919 (0.527–1.432)	0.352
Diabetes (%)	56 (14.4)	32 (26.2)	0.003	1.125 (0.642–2.135)	0.639
Coronary artery disease (%)	30 (7.7)	45 (36.9)	< 0.001	0.457 (0.134–1.122)	0.143
Chronic kidney disease (%)	11 (2.8)	21 (17.2)	< 0.001	0.789 (0.581–1.072)	0.129
Laboratory findings					
NEUT, $\times 10^9$/L	3.25 (IQR: 2.43–4.23)	4.18 (IQR: 2.8–6.74)	< 0.001	1.95 (0.425–8.952)	0.39
LYMP, $\times 10^9$/L	1.42 (IQR: 1.02–1.85)	0.75 (IQR: 0.53–1.21)	< 0.001	1.057 (0.179–6.436)	0.937
NLR	2.17 (IQR: 1.53–3.57)	5.15 (IQR: 2.96–10.72)	< 0.001	1.168 (0.994–1.374)	0.059
ALB, mean ± SD, g/L	40.66 ± 5.28	35.59 ± 5.53	< 0.001	0.943 (0.892–0.997)	0.039

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender and group), Independent t-test (for ALB) and Mann-Whitney U-test (for age, NEUT, LYMP, NLR, IL-6 and CRP). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

	Stabilization (n = 388)	Poor progression (n = 122)	*P* value	Multivariable (95% CI for OR)	*P* value
IL-6, pg/L	3.33 (IQR: 1.88–7.38))	13.9 (IQR: 4.48–52.45)	< 0.001	1.027 (1.013–1.042)	< 0.001
CRP, mg/dl	0.31 (IQR: 0.08–1.92)	3.59 (IQR: 1.04–6.56)	< 0.001	1.133 (1.049–1.224)	0.001

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender and group), Independent t-test (for ALB) and Mann-Whitney U-test (for age, NEUT, LYMP, NLR, IL-6 and CRP). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Table 3
Risk factors associated poor progression in different groups.

Cancer group	**Stabilization (n = 22)**	**Poor progression (n = 16)**	***P* value**	**Multivariable (95% CI for OR)**	***P* value**
Age, mean ± SD, years	62.82 ± 19.73	68 ± 18.11	0.414		
Gender					
Female (%)	11 (50.0)	8 (50.0)	1		
Male (%)	11 (50.0)	8 (50.0)			
NEUT, $\times 10^9$/L	3.66 (IQR: 2.42–4.66)	5.28 (IQR: 2.24–7.57)	0.061		
LYMP, mean ± SD, $\times 10^9$/L	1.15 ± 0.55	0.98 ± 0.49	0.315		
NLR	3.54 (IQR: 1.78–6.49)	5.15 (IQR: 2.98–11.61)	0.27		
ALB, mean ± SD, g/L	38.39 ± 5.53	35.03 ± 8.87	0.205		
IL-6, pg/L	9.18 (IQR: 4.33–29.86))	14.75 (IQR: 9.85–55.41)	0.055		
CRP, mg/dl	1.77 (0.24–3.56)	5.11 (0.95–13.56)	0.052		
Non-cancer group	**Stabilization (n = 366)**	**Poor progression (n = 106)**	**P value**	**Multivariable (95% CI for OR)**	**P value**
Age, years	56 (IQR: 38–66)	65.5 (IQR: 53–79)	< 0.001	1.019 (0.999–1.039)	0.06
Gender					
Female (%)	212 (57.9)	46 (44.3)	0.008	0.984 (0.521–1.856)	0.96
Male (%)	154 (42.1)	60 (56.6)			

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender), Independent t-test (for ALB) and Mann-Whitney U-test (for age, NEUT, LYMP, NLR, IL-6 and CRP). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Cancer group	Stabilization (n = 22)	Poor progression (n = 16)	*P* value	Multivariable (95% CI for OR)	*P* value
NEUT, $\times 10^9$/L	3.24 (IQR: 2.43–4.23)	4.09 (IQR: 2.8–6.55)	< 0.001	0.775 (0.59–1.018)	0.067
LYMP, $\times 10^9$/L	1.44 (IQR: 1.04–1.86)	0.74 (IQR: 0.51–1.21)	< 0.001	0.605 (0.236–1.55)	0.295
NLR	2.16 (IQR: 1.51–3.43)	5.23 (IQR: 2.94–10.45)	< 0.001	1.251 (1.037–1.509)	0.019
ALB, mean ± SD, g/L	40.8 ± 5.24	35.67 ± 4.92	< 0.001	0.932 (0.873–0.995)	0.034
IL-6, pg/L	3.22 IQR: (1.78–6.96)	13.3 (IQR: 4.07–51.54)	< 0.001	1.031 (1.016–1.047)	< 0.001
CRP, mg/dl	0.29 (IQR: 0.08–1.72)	3.49 (IQR: 1.08–6.28)	< 0.001	1.113 (1.02–1.215)	0.016

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender), Independent t-test (for ALB) and Mann-Whitney U-test (for age, NEUT, LYMP, NLR, IL-6 and CRP). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Table 4
Risk factors associated with death in-hospital.

	Survivor (n = 524)	Non-survivor (n = 61)	*P* value	Multivariable (95% CI for OR)	*P* value
Age, years	57 (IQR: 41–68)	78 (IQR: 64–86)	< 0.001	1.112 (1.073–1.152)	< 0.001
Gender					
Female (%)	294 (56.1)	20 (32.8)	0.001	0.266 (0.11–0.641)	0.003
Male (%)	230 (43.9)	41 (67.2)			
Comorbidities					
Cancer (%)	32 (6.1)	12 (19.7)	0.001	1.937 (0.662–5.883)	0.223
Hypertension (%)	174 (33.2)	31 (50.8)	0.006	1.244 (0.846–2.522)	0.554
Diabetes (%)	92 (17.6)	17 (27.9)	0.059		
Coronary artery disease (%)	53 (10.1)	30 (49.2)	< 0.001	0.865 (0.442–2.873)	0.064
Chronic kidney disease (%)	22 (4.2)	15 (24.6)	< 0.001	1.765 (1.045–3.643)_	0.319
Severity					
Moderate (%)	462 (88.2)	48 (78.7)	0.036	0.514 (0.162–1.628)	0.258
Severe/Critical (%)	62 (11.8)	13 (21.3)			
Laboratory findings					
NEUT, $\times 10^9$/L	3.42 (IQR: 2.54–4.6)	6.25 (IQR: 3.04–10.2)	< 0.001	1.755 (0.32–9.628)	0.517
LYMP, $\times 10^9$/L	1.29 IQR: (0.87–1.73)	0.73 (IQR: 0.52–1.22)	< 0.001	1.445 (0.168–12.434)	0.737
NLR	2.54 (IQR: 1.65–4.53)	6.07 (IQR: 3.35–17.98)	< 0.001	1.028 (0.949–1.113)	0.504

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender, severity and group), and Mann-Whitney U-test (for age and laboratory findings). The significant factors of univariate analysis were included into multivariable logistic regression model.
Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

	Survivor (n = 524)	Non-survivor (n = 61)	*P* value	Multivariable (95% CI for OR)	*P* value
ALB, g/L	40 (IQR: 35.6–43.4)	33.5 (IQR: 31-38.6)	< 0.001	0.986 (0.913–1.065)	0.723
IL-6, pg/L	3.86 (IQR: 2.1–9.74)	49.87 (IQR: 21.65–143.4)	< 0.001	1.008 (1.003–1.013)	0.003
CRP, mg/dl	0.49 (IQR: 0.11–2.99)	5.11 (IQR: 2.54–10.66)	< 0.001	1.114 (1.026–1.211)	0.01

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution data. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender, severity and group), and Mann-Whitney U-test (for age and laboratory findings). The significant factors of univariate analysis were included into multivariable logistic regression model.
Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Table 5
Risk factors associated with death in-hospital among different groups.

Cancer group	**Survivor (n = 32)**	**Non-survivor (n = 12)**	***P* value**	**Multivariable (95% CI for OR)**	***P* value**
Age, mean ± SD, years	59.81 ± 18.76	76.83 ± 8.99	< 0.001	1.051 (0.927–1.191)	0.44
Gender					
Female (%)	16 (50)	4 (33.3)	0.323		
Male (%)	16 (50)	8 (66.7)			
Severity					
Moderate (%)	462 (88.2)	48 (78.7)	0.321		
Severe/Critical (%)	62 (11.8)	13 (21.3)			
NEUT, mean ± SD, $\times 10^9$/L	4.34 ± 2.21	8.17 ± 6.87	0.083		
LYMP, $\times 10^9$/L	1.01 (IQR: 0.66–1.45)	0.54 (IQR: 0.37–0.74)	0.05		
NLR, mean ± SD	4.93 ± 3.19	13.38 ± 12.24	0.037	1.197 (0.98–1.463)	0.078
ALB, mean ± SD, g/L	38.57 ± 6.42	30.15 ± 6.61	0.001	0.952 (0.718–1.264)	0.735
IL-6, pg/L	10.09 (IQR: 4.41–23.61)	39.5 (IQR: 21.18–127)	0.001	1.012 (0.965–1.062)	0.621
CRP, mg/dl	1.77 (IQR: 0.25–3.8)	10.8 (IQR: 5.11–15.58)	0.001	1.214 (0.959–1.536)	0.106
Non-cancer group	**Survivor (n = 492)**	**Non-survivor (n = 49)**	P **value**	**Multivariable (95% CI for OR)**	P **value**
Age, years	57 (41,68)	78 (62,87.5)	< 0.001	1.126 (1.08–1.173)	< 0.001

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution values. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender and severity), Independent t-test (for normal distribution values) and Mann-Whitney U-test (for non-normal distribution values). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.

Cancer group	Survivor (n = 32)	Non-survivor (n = 12)	*P* value	Multivariable (95% CI for OR)	*P* value
Gender					
Female (%)	278 (56.5)	16 (32.7)	0.001	4.305 (1.588–11.637)	0.004
Male (%)	214 (43.5)	33 (67.3)			
Severity					
Moderate (%)	433 (88)	39 (79.6)	0.092		
Severe/Critical (%)	59 (12)	10 (20.4)			
NEUT, mean ± SD, $\times 10^9$/L	3.4 (2.54–4.56)	6.22 (3,9.8)	< 0.001	1.494 (0.232–9.612)	0.673
LYMP, $\times 10^9$/L	1.3 (IQR: 0.88–1.73)	0.87 (IQR: 0.56–1.27)	< 0.001	0.992 (0.095–10.415)	0.995
NLR	2.5 (IQR: 1.64–4.39)	5.62 (IQR: 3.38–14.05)	< 0.001	1.021 (0.93–1.12)	0.665
ALB, g/L	40 (IQR: 35.6–43.4)	34.35 (IQR: 31.4-39.05)	< 0.001	0.99 (0.907–1.081)	0.826
IL-6, pg/L	3.7 (IQR: 2.03–8.95)	50.25 (IQR: 22.53-182.63)	< 0.001	1.008 (1.002–1.013)	0.007
CRP, mg/dl	0.47 (IQR: 0.1–2.93)	3.99 (IQR: 2.32–9.64)	< 0.001	1.11 (1.004–1.227)	0.041

Note: Quantitative *v*ales coincided with normal distribution are expressed by mean ± SD, and median (interquartile range, IQR) for the non-normal distribution values. Frequency (percentage) was used to express the counting data.

P-values: result from Chi-square test (for gender and severity), Independent t-test (for normal distribution values) and Mann-Whitney U-test (for non-normal distribution values). The significant factors of univariate analysis were included into multivariable logistic regression model.

Abbreviations: NEUT, neutrophil count; LYMP, lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; ALB, serum albumin; IL-6, interleukin-6; CRP, C-reactive protein.