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Baseline characteristics and changes of biomarkers in disease course predict prognosis of patients with COVID-19

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Abstract

The outbreak of coronavirus disease (COVID-19) has brought great challenges to the world. The objectives of this study were to describe the baseline characteristics and changes of biomarkers of these COVID-19 patients and identify predictive value of the above markers for patient death. Using patient death as the observational endpoints, clinical data of inpatients in a special ward for COVID-19 in Wuhan, China were retrospectively collected. Univariate and multivariate Cox regression analyses were used to evaluate prognostic value of baseline characteristics and laboratory data changes. This study included clinical data of 75 patients. Age, c-reactive protein (CRP) and interleukin-6 levels were independent predictors of patient death. Survivors were characterized as having declining neutrophil counts, D-dimer, N-terminal pronatriuretic peptide, troponin I (TnI) and c-reactive protein levels, while counts of lymphocyte gradually came back. Non-survivors were characterized with increasing white blood cell counts (WBC) and neutrophil counts. Changes of WBC, TnI and interleukin-6 were also independently associated with patient death. Older age, baseline CRP and IL-6 levels may be used as meaningful predictors to identify patients with poor prognosis. Changes of biomarkers should be closely monitored in the management of patients with COVID-19, while constantly increasing levels of WBC, TnI and interleukin-6 in the disease course also predict patient death.

Keywords COVID-19 · C-reactive protein · Leukocyte count · Troponin I · Interleukin-6

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Introduction

The outbreak of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), has brought great challenges to the world [1–5]. The World Health Organization (WHO) has called for powerful containment and control measures to slow or reverse the virus spread [5] and described COVID-19 as a pandemic on Mar 11, 2020 [6].

Previous studies have reported the epidemiological and clinical characteristics of patients with COVID-19 [3, 7–10]. Identifying and prognosticing mortality and the most severely critical cases are extremely important in clinical practice. Previous studies suggested that severe patients tend to be older, more likely to have potential comorbidities, lower lymphocyte (Lym) counts, and higher levels of some cytokines [7, 9]. Indicators associated with inflammation, coagulation function, and cardiac injury were also predictors for poor prognosis [11–13]. Nevertheless, as a novel infectious disease, it is difficult to explore the early predictors of the prognosis of patients with COVID-19 because of the relatively short follow-up time; thus, further observation is urgently needed [9]. Except for baseline characteristics, the prognostic value of laboratory data changes should also be evaluated. Previous studies described the changes of major laboratory markers during disease course, however, the dynamical changes were not evaluated in multivariate analyses [9, 13] and the effects on patient prognosis need to be further clarified.

Our medical team has taken over a 50-bed special ward for COVID-19 patients in Wuhan, China since February 10, 2020. The purposes of the current study were to describe the baseline characteristics and changes of biomarkers of these COVID-19 patients and identify predictive value of the above markers for patient death.

Materials and methods

Study population

This retrospective, observational study was performed at ward E1-7, optics valley district, Tongji Hospital Affiliated with Tongji Medical College of HUST, Wuhan, China, which was taken over by the medical team from the Second Hospital of Shandong University for the treatment of COVID-19 patients. Patients requiring hospitalization in Optics Valley District were assigned according to the time of coming to the hospital and the bed situation of each ward. We cannot verify the influence of patient's allocation principle on data representativeness. A total of 80 patients admitted in our medical ward from Feb 11, 2020 to Mar 4, 2020 and all these patients were consecutively screened in the current study. Clinical data were collected from the hospital's medical record system. The inclusion criteria were as follows: (1) adult patients confirmed with COVID-19 (age ≥18 years); (2) documented baseline clinical characteristics and laboratory data within 24 h of admission could be obtained; (3) biomarkers at day 5–8 after admission for survivals, and day 2–4, day 5–8 after admission for non-survivals could also be obtained.

Patients with incomplete data were excluded. The protocol of the current study complied with the principles of the Declaration of Helsinki and has been approved by the Ethical Committee of Tongji Hospital Affiliated with Tongji Medical College of HUST and the Second Hospital of Shandong University.

Patients with COVID-19 were confirmed according to program of National Health Commission of the People's Republic of China [1, 2]. The confirmed patients should be positive for the throat swab samples, which were collected from all patients and performed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays for the identification of SARS-Cov-2 before admission. The detailed procedures see previous published literature [12]. Patients were judged to be moderate if they were present with imaging findings of pneumonia. Patients were judged to be severe if: (1) respiratory distress, respiratory rate ≥30 times/min; or SpO_2 ≤93% in a resting state; or oxygenation index ≤300 mmHg. Patients were judged to be critical if: (1) respiratory failure and mechanical ventilation were required; or (2) shock occurred; or (3) the condition was combined with other organ(s) failure and treatments in the intensive care unit (ICU) were needed [1, 2]. When the patient presented the above characteristics in anytime at admission or thereafter, they were identified as "critical".

Data collection

Observational endpoint of the current study was patient death. The following clinical data were collected: age, gender, comorbidities, white blood cell counts (WBC), Lym, platelet counts (PLT), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin (TB), international normalized ratio (INR), D-dimer, N-terminal pronatriuretic peptide (NT-proBNP), troponin I (TnI), creatine kinase (CK), lactate dehydrogenase (LDH), c-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6). All baseline data were always collected within the first 24 h after patient's admission because of COVID-19. During hospitalization, patients were reexamined to evaluate their situation and the reexamination time was decided according to their state of an illness. Biomarkers at day 5–8 after admission for survivals, and day 2–4, day 5–8 after admission for non-survivals

were also recorded. Data were collected in a designed table and were checked by other researchers.

Statistical analyses

Continuous variables were expressed as either means±standard deviations or medians (interquartile range [IQR]). Laboratory data in survivals (paired samples) were compared by paired *t* test or Wilcoxon rank sum test, while data in non-survivals (multiple samples) were compared by One-Way ANOVA, LSD test or Kruskal–Wallis test. Categorical variables were compared using χ^2 tests or Fisher's exact test. Changes of biomarkers were computed as laboratory data at day 5–8 divided by laboratory data at admission ($R_{\text{biomarkers}}$). Univariate Cox regression analysis was first used to evaluate prognostic value of baseline biomarkers or biomarkers changes. Variables significant at 0.10 (α) level were then included in the multivariate model. Multivariate model was simplified by a bidirectional stepwise elimination approach according to the Alaike Information Criterion (AIC). *p* values less than 0.05 were considered as statistically significant. All statistical analyses were performed using software IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and $R \times 64$ 4.0.2.

Results

Baseline characteristics of the study population

The clinical data of 80 COVID-19 cases were preliminary included, of which 75 cases were eventually included for further analysis. Cases were excluded due to incomplete data (5 cases). All included patients underwent chest computed tomography (CT) examination with imaging findings of pneumonia. The mean patient age was 59 ± 15 years (median 63 years, IQR 50–68 years). The proportions of male and female patients in this cohort were nearly the same (35/75 patients, 47% vs. 40/75 patients, 53%). Comorbidities were present in 34 patients (45%), including hypertension in 26 patients (35%), diabetes in 13 patients (17%), coronary heart disease in seven patients (9%), and respiratory diseases in three patients (4%).

All patients were treated with oxygen. Invasive mechanical ventilation was used in nine patients. Antiviral therapies were used in all patients, with lopinavir—ritonavir in 45 patients (60%), arbidol in 63 patients (84%). Glucocorticoids were used in 10 patients (13%), while intravenous immunoglobulin was used in 14 patients (19%). Two patients (3%) were given bedside hemofiltration.

Sixty-six patients were judged to have moderate and severe disease according to the program of the National Health Commission of the People's Republic of China at admission or during follow-up [1, 2]. All these patients recovered and successfully discharged from the hospital.

Nine critical patients died during treatment. The times of illness onset for seven of the non-surviving patients could be traced and were 14, 18, 19, 30, 33, 35, 37 days, respectively (the patients had been treated in other hospitals for several days). One patient succumbed to the disease 40 days after admission, however, the time of disease onset could not be traced.

Non-survival patients were characterized as having older age ($p = 0.003$), lower lymphocyte ($p = 0.003$) and higher WBC ($p = 0.03$), BUN ($p = 0.002$), Cr ($p = 0.04$), INR ($p = 0.04$), D-dimer ($p < 0.001$), NT-proBNP ($p < 0.001$), TnI ($p < 0.001$), CK ($p = 0.001$), LDH ($p < 0.001$), CRP ($p < 0.001$), PCT($p < 0.001$), and IL-6 ($p < 0.001$) (Table 1).

Predictive value of baseline characteristics for patient death

Results of the univariate Cox analysis revealed that younger age, lower lymphocyte, and higher WBC, BUN, Cr, INR, D-dimer, NT-proBNP, CK, LDH, CRP, PCT and IL-6 levels were predictors of patient death. A multivariate Cox regression analysis, which was simplified by a bidirectional stepwise elimination approach according to AIC, were performed and age (Hazard ratio [HR] 1.11, 95% confidence interval [CI] 1.01–1.23, $p = 0.04$), CRP levels (HR 1.03, 95% CI 1.02–1.05, $p < 0.001$) and IL-6 levels (HR 1.02, 95% CI 1.01–1.04, $p = 0.004$) were independent predictors of patient death (Table 2).

Changes of laboratory data during treatment

For the 66 survivors, lower Neu ($p = 0.02$), higher Lym ($p = 0.04$), lower D-dimer ($p = 0.001$), lower NT-proBNP ($p = 0.01$), lower TnI ($p < 0.001$) and lower CRP ($p = 0.001$) levels were observed at day 5–8 compared with baseline (Table 3).

For the nine non-survivors, compared with baseline, WBC and Neu levels increased during the 1st week after admission ($p = 0.03$ and 0.02, respectively), meanwhile, levels of Lym tended to decrease ($p = 0.14$ for Kruskal–Wallis test, and $p = 0.05$ for baseline vs. day 5–8). It seemed that there was no obvious change for levels of BUN, Cr, D-dimer, NT-proBNP, TnI, CRP and IL-6 (Table 4).

Predictive value of laboratory data changes for patient death

Results of the univariate Cox analysis revealed that patient age ($p = 0.004$), R_{WBC} ($p < 0.001$), R_{Neu} ($p=0.007$), R_{Lym} ($p < 0.001$), R_{BUN} ($p = 0.001$), $R_{\text{D-dimer}}$ ($p = 0.002$), $R_{\text{NT-proBNP}}$ ($p = 0.002$), R_{TnI} ($p < 0.001$), and $R_{\text{IL-6}}$ ($p = 0.02$) were

Table 1 Baseline characteristics of COVID-19 patients at admission

	Total ($n=75$)	Non-survivals ($n=9$)	Survivals ($n=63$)	p value*
Age, years	58.8 ± 14.9	72.4 ± 10.1	57.0 ± 14.5	**0.003**
Gender, male (n, %)	35 (46.7%)	6 (66.7%)	29 (43.9%)	0.29
Comorbidities (n, %)	34 (45.3%)	6 (66.7%)	28 (42.4%)	0.29
WBC (10^9/L)	6.41 ± 2.06	7.81 ± 2.26	6.21 ± 1.97	**0.03**
Lym (10^9/L)	1.41 ± 0.62	0.85 ± 0.55	1.49 ± 0.59	**0.003**
PLT (10^9/L)[a]	255.5 (199.3, 322.5)	206.0 (160.5, 299.0)	259.0 (205.5, 323.0)	0.12
BUN (mmol/L)[a]	4.30 (3.40, 5.70)	7.70 (5.05, 21.20)	4.10 (3.18, 5.25)	**0.002**
Creatinine (μmol/L)[a]	70.0 (53.0, 82.0)	110.0 (59.5, 188.0)	65.0 (52.0, 79.3)	**0.04**
TB (μmol/L)[a]	7.9 (6.6, 11.5)	9.8 (7.3, 13.4)	7.7 (6.6, 11.4)	0.20
INR[a]	1.07 (1.03, 1.12)	1.17 (1.05, 1.28)	1.07 (1.01, 1.10)	**0.04**
D-dimer (μg/mL FEU)[a]	0.48 (0.22, 1.43)	2.16 (1.52, 9.69)	0.43 (0.22, 1.15)	**<0.001**
NT-proBNP (pg/mL)[a]	96.0 (36.0, 207.0)	943.0 (262.5, 2539.0)	67.0 (29.3, 163.8)	**<0.001**
TnI (pg/mL)[a]	2.60 (1.90, 7.60)	24.60 (13.90, 65.00)	2.25 (1.90, 4.90)	**<0.001**
CRP (mg/L)[a]	4.10 (0.80, 35.80)	119.70 (75.50, 144.50)	3.00 (0.70, 17.40)	**<0.001**
Procalcitonin (ng/mL)[a]	0.06 (0.05, 0.09)	0.21 (0.14, 0.47)	0.06 (0.05, 0.07)	**<0.001**
CK (μ/L)[a]	65.0 (43.5, 99.5)	188.0 (118.0, 296.0)	64.5 (42.0, 88.3)	**0.001**
LDH (μ/L)[a]	253.0 (183.0, 314.0)	465.0 (300.0, 576.0)	239.5 (174.8, 302.0)	**<0.001**
Interleukin-6 (pg/mL)[a]	3.62 (1.54, 14.27)	63.13 (28.16, 125.45)	3.13 (1.50, 8.01)	**<0.001**

WBC white blood cell counts, *Lym* lymphocyte counts, *PLT* platelet counts, *BUN* blood urea nitrogen, *Cr* creatinine, *TB* total bilirubin, *INR* international normalized ratio, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *TnI* troponin I, *CRP* c-reactive protein, *CK* creatine kinase, *LDH* lactate dehydrogenase

*p values for the comparison of baseline characteristics between non-survivals and survivals. Student's t test, Mann–Whitney U test or Fisher's exact test according to the characteristics of distribution

[a]Median (interquartile range)

predictors of patient death. A multivariate Cox regression analysis, which was simplified by a bidirectional stepwise elimination approach according to AIC, indicated that patient age ($p=0.007$, HR 1.17, 95% CI 1.04–1.31), R_{WBC} ($p=0.001$, HR 63.80, 95% CI 5.60–727.34), R_{TnI} ($p=0.002$, HR 1.34, 95% CI 1.12–1.62), and $R_{IL\text{-}6}$ ($p=0.02$, HR 1.32, 95% CI 1.05–1.66) were independent prognostic factors for patient death. A minimal AIC was achieved by the above model with the four variables (Table 5).

Discussion

This retrospective observational study described baseline characteristics and changes of biomarkers for survivors and non-survivors with COVID-19, and explored prognostic value of the above features for patient death. Only age, CRP and IL-6 levels were independent predictors of patient death. Levels of Neu, D-dimer, NT-proBNP, TnI and CRP decreased during disease course for survivors, while WBC and Neu levels increased during the first week for non-survivors. Lymphocyte, which is usually reduced in COVID-19, gradually came back in the disease course of survivors and tended to keep declining in non-survivors. Multivariate Cox regression analysis revealed that patient age, R_{WBC}, R_{TnI} and $R_{IL\text{-}6}$ were independent prognostic factors for patient death, in other words, patients with older age, increasing levels of WBC, TnI and IL-6 were more likely to be associated with poor prognosis.

CRP is widely used in clinical practice as a marker of infection and inflammation, although its prognostic value in patients with infection is controversial [14, 15]. Its relatively high sensitivity and low specificity make CRP suitable as a screening indicator. The predictive value of CRP in patients with severe acute respiratory syndrome (SARS), which is caused by the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), has also been reported [16]. SARS-Cov-2, the pathogen of COVID-19, has a similar receptor-binding domain structure to that of SARS-CoV [4]. Elevated CRP has been described in the recent outbreak of COVID-19 [1, 2]. Although a few studies have focused on prognosis prediction in COVID-19, the role of CRP has not been evaluated adequately. The current study emphasized the independent predictive value of CRP for critical status in patients with COVID-19, which should be paid attention in clinical practice. A HR of 1.04 indicated that the risk of death increased to 1.04^{N}-fold when CRP increased N mg/L.

The cytokine storm plays an important role in the deterioration of COVID-19 [17]. Critical patients were characterized with higher levels of IL-6, IL-10, TNFα [17], meanwhile, although the counts of CD4+ and CD8+ T lymphocytes decreased [17], they were overactive and

Table 2 Univariate and multivariate Cox analyses revealing predictors for patient death

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.10 (1.03, 1.08)	**0.003**	1.11 (1.01, 1.23)	**0.04**
Gender	0.42 (0.10, 1.67)	0.22		
Comorbidities	2.45 (0.61, 9.81)	0.21		
WBC	1.37 (1.05, 1.80)	**0.02**		
Lym	0.14 (0.03, 0.60)	**0.008**		
PLT	0.996 (0.988, 1.004)	0.33		
BUN	0.16 (1.09, 1.24)	**<0.001**		
Creatinine	1.003 (1.001, 1.005)	**0.005**		
TB	1.01 (0.96, 1.07)	0.68		
D-dimer	1.15 (1.06, 1.26)	**0.001**		
NT-proBNP	24.03 (4.94, 116.98)	**<0.001**		
TnI	1.000 (0.999, 1.001)	0.82		
CK	1.003 (1.000, 1.005)	**0.03**		
LDH	1.008 (1.004,1.013)	**<0.001**		
CRP	1.03 (1.02, 1.05)	**<0.001**	1.03 (1.02, 1.05)	**<0.001**
Procalcitonin	10.41 (2.68, 40.51)	**0.001**		
Interleukin-6	1.02 (1.01, 1.03)	**<0.001**	1.02 (1.01, 1.04)	**0.004**

WBC white blood cell counts, *Lym* lymphocyte counts, *PLT* platelet counts, *BUN* blood urea nitrogen, *Cr* creatinine, *TB* total bilirubin, *INR* international normalized ratio, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *TnI* troponin I, *CK* creatine kinase, *LDH* lactate dehydrogenas, *CRP* c-reactive protein

Table 3 Changes of laboratory data for the 66 survivors

	Baseline	Day 5–8	*p* value*
WBC (10^9/L)	6.21 ± 1.97	5.87 ± 1.66	0.10
Neu (10^9/L)	3.99 ± 1.86	3.50 ± 1.51	**0.02**
Lym (10^9/L)	1.49 ± 0.59	1.60 ± 0.47	**0.04**
BUN (mmol/L)[a]	4.10 (3.18, 5.25)	4.00 (3.30, 4.63)	0.36
Creatinine (μmol/L)[a]	65.0 (52.0, 79.3)	67.0 (54.0, 84.5)	0.06
D-dimer (μg/mL FEU)[a]	0.43 (0.22, 1.15)	0.27 (0.22, 0.69)	**0.001**
NT-proBNP (pg/mL)[a]	67.0 (29.3, 163.8)	51.5 (24.5, 149.5)	**0.01**
TnI (pg/mL)[a]	2.25 (1.90, 4.90)	1.90 (1.90, 3.18)	**<0.001**
CRP (mg/L)[a]	3.0 (0.7, 17.4)	1.3 (0.7, 5.3)	**0.001**
Interleukin-6 (pg/mL)[a]	2.8 (1.5, 6.9)	3.2 (1.5, 6.0)	0.56

WBC white blood cell counts, *Neu* neutrophil counts, *Lym* lymphocyte counts, *BUN* blood urea nitrogen, *Cr* creatinine, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *TnI* troponin I, *CRP* c-reactive protein

*p values for the comparison of biomarkers at baseline and day 5–8. Paired t test or Wilcoxon rank sum test according to the characteristics of distribution

[a]Median (interquartile range)

should partially account for the severe immune injury [18]. IL-6 is one of pro-inflammatory cytokines which elevated significantly in disease course of COVID-19, extremely in deteriorated patients [11, 13, 17, 19]. In the present study, higher IL-6 at admission was independently associated with patient death. Further, although levels of IL-6 did not change significantly in both survivors and non-survivors in the present study, increasing levels of IL-6 was identified as an independent predictor for patient death. Therefore, it is necessary to monitor levels of IL-6 during the disease course of COVID-19. Tocilizumab, a recombinant human IL-6 monoclonal antibody, has also been used for the treatment of severe or critical COVID-19 patients [19]. Treatment aiming at cytokine storm in COVID-19 may be given high hopes in future.

Older age was an independent predictor for disease progression or death [9, 13]. Similar to previous studies, the present study revealed worse prognosis for patients with elder age. The declined T-cell and B-cell function and consequent defects in immune response with age may be reasons for the poor outcome for eldly patients [11, 13, 20]. The occurrence of more potential comorbidities may also contribute to the adverse outcome.

Higher levels of WBC and Neu have been identified as important features of non-survivors [11, 13], deteriorated patients [21] or ICU patients [9], however, they were not identified as predictors for adverse outcome in multivariate analysis [13, 21]. The present study found that WBC and Neu levels increased during the 1st week after admission in non-survivors, while decreased in survivors. Also, R_{WBC} was identified as an independent predictor for patient death, which was not reported by other studies as far as we know. Co-infection with bacteria may contribute to the higher WBC levels and poor outcome.

Lymphopenia, a feature of COVID-19, was observed in the present and previous studies [9, 13, 22]. Critical patients or non-survivors were also had lower lymphocyte levels [9, 13]. However, the result was negative in further regression analysis in the current and previous studies [13]. A recent flow cytometric analysis observed significantly reduced peripheral CD4+ and CD8+ T lymphocyte counts, as well as cell function over activation [18]. Therefore, the functional changes of lymphocytes should also be considered in future research.

Cardiac injury was also common in patients with COVID-19 [9, 13]. High TnI levels were observed in the current study and previous studies [9, 13]. However, the

Table 4 Changes of laboratory data for the nine non-survivors

	Baseline	Day 2–4	Day 5–8	*p* value*
WBC (10^9/L)[a]	7.81 ± 2.26	13.19 ± 5.54	13.63 ± 5.83	**0.03**
Neu (10^9/L)[b]	6.27 ± 1.89	11.86 ± 5.45	12.61 ± 5.93	**0.02**
Lym (10^9/L)[c]	0.85 ± 0.55	0.72 ± 0.28	0.49 ± 0.07	0.14
BUN (mmol/L)[d]	7.70 (5.05, 21.20)	10.30 (5.40, 20.95)	11.40 (6.50, 24.00)	0.71
Creatinine (μmol/L)[d]	110.0 (59.5, 188.0)	84.0 (58.0, 136.0)	78.0 (60.5, 129.5)	0.90
D-dimer (μg/mL FEU)[d]	2.16 (1.52, 9.69)	4.64 (2.82, 14.89)	5.17 (2.28, 10.33)	0.46
NT-proBNP (pg/mL)[d]	943.0 (262.5, 2539.0)	739.0(385.0, 1985.0)	1639.0 (546.5, 3098.0)	0.45
TnI (pg/mL)[d]	24.6 (13.9, 65.0)	17.4 (7.5, 67.4)	79.8 (19.7, 158.1)	0.36
CRP (mg/L)[d]	119.7(75.5, 144.5)	133.2 (54.1, 176.6)	66.9 (53.7, 144.9)	0.73
Interleukin-6 (pg/mL)[d]	60.0 (14.0, 79.2)	16.4 (11.6, 73.4)	53.9 (28.6, 84.1)	0.26[e]

WBC white blood cell counts, *Neu* neutrophil counts, *Lym* lymphocyte counts, *BUN* blood urea nitrogen, *Cr* creatinine, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *TnI* troponin I, *CRP* c-reactive protein

*p values for the comparison of biomarkers at baseline, day 2–4 and day 5–8. One-way ANOVA or Kruskal–Wallis test according to the characteristics of distribution

[a]p value (LSD test): baseline vs. day 2–4: 0.03, baseline vs. day 5–8: 0.02, day 2–4 vs. day 5–8: 0.85

[b]p value (LSD test): baseline vs. day 2–4: 0.02, baseline vs. day 5–8: 0.01, day 2–4 vs. day 5–8: 0.74

[c]p value (LSD test): baseline vs. day 2–4: 0.46, baseline vs. day 5–8: 0.05, day 2–4 vs. day 5–8: 0.21

[d]Median (interquartile range)

[e]Eight patients

Table 5 Univariate and multivariate Cox regression analyses revealing predictive value of laboratory data changes for patient death

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.10 (1.03, 1.18)	**0.004**	1.17 (1.04, 1.31)	**0.007**
Gender (female)	0.42 (0.10, 1.67)	0.22		
Comorbidities	2.45 (0.61, 9.81)	0.21		
R_{WBC}	12.63 (4.06, 39.24)	**< 0.001**	63.80 (5.60, 727.34)	**0.001**
R_{Neu}	1.44 (1.10, 1.87)	**0.007**		
R_{Lym}	0.003 (0.000, 0.046)	**< 0.001**		
R_{BUN}	2.45 (1.44, 4.17)	**0.001**		
R_{Cr}	1.61 (0.29, 8.88)	0.58		
$R_{D\text{-}dimer}$	1.15 (1.06, 1.26)	**0.002**		
$R_{NT\text{-}proBNP}$	1.18 (1.06, 1.31)	**0.002**		
R_{TnI}	1.17 (1.07, 1.27)	**< 0.001**	1.34 (1.12, 1.62)	**0.002**
R_{CRP}	0.96 (0.57, 1. 59)	0.86		
$R_{IL\text{-}6}$	1.24 (1.04, 1.48)	**0.02**	1.32 (1.05, 1.66)	**0.02**

WBC white blood cell counts, *Neu* neutrophil counts, *Lym* lymphocyte counts, *BUN* blood urea nitrogen, *Cr* creatinine, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *TnI* troponin I, *CRP* c-reactive protein, *IL-6* Interleukin-6

R = laboratory data at day 5–8/laboratory data at admission

role of TnI in multivariate regression analysis remained controversy [13, 23]. Previous study explored an obvious elevation of TnI in non-survivors and the stable in low levels for survivors [13]. Although the present study found that there was no obvious change for levels of TnI in non-survivors, there was a significant decline of this laboratory indicator in survivors. Different disease course may be a reason for this discrepancy. R_{TnI} was also identified as a significant predictor for patient death in the present study, indicating the importance of cardiac injury in patients with COVID-19. The mechanism of cardiac injury in COVID-19 is still not quite clear. Only a few interstitial mononuclear inflammatory infiltrates were found in the pathological tissues of one patient with COVID-19 [18],

whether the virus directly attacks the heart is still arguable because of the deficiency of substantial damage in histopathology. Inflammatory cytokines may also result in necrosis of myocardial cells [23]. Furthermore, increased metabolic demand during virus infection aggravated cardiac burden, especially in patients with potential cardiovascular diseases [23, 24].

Chest CT is important in the diagnosis and prognosis prediction of COVID-19 [25, 26]. Features of CT imaging include multiple macular shadows and interstitial changes, and then ground-glass opacities with a peripheral distribution [25, 26]. CT involvement score has been found to be helpful in evaluating the severity and extent of COVID-19 [26]. Although all patients in the current study underwent a lung CT scan, CT involvement scores were not calculated, which should be a limitation of our study.

This study also has several other limitations. First, it was retrospective in nature and several cases were excluded for incomplete data, which may be a source of bias. Some potential valuable variables, e.g. body mass index, ferritin, were also not evaluated. The five patients who were excluded during analyses were relatively mild and further evaluation of laboratory examinations were judged unnecessary by doctors, which may also affect the representativeness of the data. Second, our special ward was set for relatively severe COVID-19 patients; therefore, the mortality rate did not reflect the case fatality rate of the COVID-19 population. Third, the sample size and single-center nature were also limitations and multi-center data, including cabin hospital and ICU, should be analyzed to verify our conclusions.

In conclusion, older age, baseline CRP and IL-6 levels may be used as meaningful predictors to identify patients with poor prognosis. Changes of biomarkers should be closely monitored in the management of patients with COVID-19, while constantly increasing levels of WBC, TnI and IL-6 in the disease course also predict patient death.

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Compliance with ethical standard

Conflicts of interest None.

Ethical approval The protocol of the current study complies with the declaration of Helsinki and has been approved by the Ethical Committee of Tongji Hospital Affiliated to Tongji Medical College of HUST and the Second Hospital of Shandong University (No. KYLL-2020(LW)-022).

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References

1. National Health Commission of the People's Republic of China Diagnosis and treatment program for novel coronavirus infection pneumonia (5th ed, in Chinese). http://www.nhc.gov.cn/jkj/s3577/202002/a5d6f7b8c48c451c87dba14889b30147/files/3514cb996ae24e2faf65953b4ecd0df4.pdf Accessed 23 March 2020
2. National Health Commission of the People's Republic of China Diagnosis and treatment program for novel coronavirus infection pneumonia (6th ed, in Chinese). http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf Accessed 19 Nov 2020
3. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ (2020) Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 368:m606. https://doi.org/10.1136/bmj.m606
4. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395:565–574. https://doi.org/10.1016/s0140-6736(20)30251-8
5. WHO coronavirus disease (COVID-19) outbreak situation. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 1 May 2020
6. WHO characterizes COVID-19 as a pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed 23 March 2020
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506. https://doi.org/10.1016/s0140-6736(20)30183-5
8. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, Chen H, Wang D, Liu N, Liu D, Chen G, Zhang Y, Li D, Li J, Lian H, Niu S, Zhang L, Zhang J (2020) Characteristics of COVID-19 infection in Beijing. J Infect 80:401–406. https://doi.org/10.1016/j.jinf.2020.02.018
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323:1061–1069. https://doi.org/10.1001/jama.2020.1585

10. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 41(2):145–151. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003
11. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D (2020) Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180:1–11. https://doi.org/10.1001/jamainternmed.2020.0994
12. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhang J, Ning Q (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368:m1091. https://doi.org/10.1136/bmj.m1091
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Gu X, Guan L, Wei Y, Li H (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395:1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3
14. Biller K, Fae P, Germann R, Drexel H, Walli AK, Fraunberger P (2014) Cholesterol rather than procalcitonin or c-reactive protein predicts mortality in patients with infection. Shock 42:129–132. https://doi.org/10.1097/shk.0000000000000187
15. Koozi H, Lengquist M, Frigyesi A (2019) C-reactive protein as a prognostic factor in intensive care admissions for sepsis: a Swedish multicenter study. J Crit Care 56:73–79. https://doi.org/10.1016/j.jcrc.2019.12.009
16. Chang HL, Chen KT, Lai SK, Kuo HW, Su IJ, Lin RS, Sung FC (2006) Hematological and biochemical factors predicting SARS fatality in Taiwan. J Formos Med Assoc 105:439–450. https://doi.org/10.1016/s0929-6646(09)60183-2
17. Pedersen SF, Ho YC (2020) SARS-CoV-2: a storm is raging. J Clin Invest 130:2202–2205. https://doi.org/10.1172/jci137647
18. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8:420–422. https://doi.org/10.1016/s2213-2600(20)30076-x
19. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S (2020) The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin immunol 214:108393. https://doi.org/10.1016/j.clim.2020.108393
20. Goronzy JJ, Fang F, Cavanagh MM, Qi Q, Weyand CM (2015) Naive T cell maintenance and function in human aging. J Immunol 194:4073–4080. https://doi.org/10.4049/jimmunol.1500046
21. Liu W, Tao ZW, Lei W, Ming-Li Y, Kui L, Ling Z, Wei S, Deng Y, Liu J, Liu H, Yang M, Hu Y (2020) Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 133:1032–1038. https://doi.org/10.1097/cm9.0000000000000775
22. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513. https://doi.org/10.1016/s0140-6736(20)30211-7
23. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C (2020) Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 5:802–810. https://doi.org/10.1001/jamacardio.2020.0950
24. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, Chen L, Hou W, Feng Y, Zhu C (2020) Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 92:819–823. https://doi.org/10.1002/jmv.25809
25. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A (2020) Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. Am J Roentgenol 215:87–93. https://doi.org/10.2214/AJR.20.23034
26. Zhao W, Zhong Z, Xie X, Yu Q, Liu J (2020) Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. Am J Roentgenol 214:1072–1077. https://doi.org/10.2214/AJR.20.22976