

Cardiac Troponin T as the Underlying Risk Factor Associated With Disease Severity and Mortality in Patients With Coronavirus Disease 2019

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Abstract

Backgrounds: To describe the clinical characteristics of coronavirus disease 2019 hospitalized patients and further analyze the potential risk factors related to the severity of the disease and 28-day mortality of patients.

Methods: A total of 122 coronavirus disease 2019 patients hospitalized in Wuhan Third Hospital from 26 January 2020 to 16 March 2020 were included in this retrospective study. Clinical data of patients were retrospectively analyzed, and the risk factors associated with disease severity and 28-day mortality were screened by cox regression analysis.

Results: Of all 122 patients, the median age was 64 years old (interquartile range, 57- 71 years old). Compared with non-severe patients, severe patients had higher indices like cardiac troponin T and respiratory rate. In cox regression analysis, cardiac troponin T correlated with 28-day mortality most.

Conclusions: Abnormal cardiac troponin T value after admission were in strong correlation with 28-day survival status.

Introduction

By 11 September 2020, the global cumulatively confirmed cases were 27,486,960, the cumulative dead cases were 894,983 according to the statistics issued by Johns Hopkins University, USA. Over 100 countries and regions in world are suffering from the affliction of COVID-19[1, 2]. Cases of coronavirus disease 2019 (COVID-19) were isolated in Wuhan, China. And accompanied by a declaration of public health emergency of international concern from World Health Organization (WHO)[3], we all realized what a huge challenge the emerging disease is for globe public health governance[4] and it's exactly a protracted war for all of us.

In December 2019, a series of cases regarding unknown pneumonia appeared in Wuhan and subsequently identified as COVID-19. And the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses designated it as SARS-CoV-2. In the past two decades, SARS-CoV was the third documented coronavirus leading to major health emergency[5]. The etiological investigations related to SARS-CoV-2 are being carried out widely like the surface stability[6] and viral load in upper respiratory tract which could greatly enhance our ability to be confronted with future outbreaks.

Until now, it has been nine months since the first case of coronavirus disease 2019 was reported in Wuhan. The number of existing suspected and confirmed cases approached climax in February. Based on the current exported clinical cases, it was established that COVID-19 represented high transmission rate from human to human[7-9]. Of equal importance was the alarming morbidity and mortality of COVID-19[10, 11]. Herein, blocking transmission method, quarantine and protection of high-risk population were emergency strategies against COVID-19[12].

Above all, there's an urgent need to identify the clinical characteristics of patients infected with SARS-CoV-2 and determine risk factors for developing severe, which may contribute to assessment of severity, advance warning and active treatment, thus demeaning the morbidity and mortality. In the last few months, considerable studies have reported the clinical features and outcomes of COVID-19[13, 14]. However, few of them have further explored the risk factor of severity and death especially 28-day mortality among severe hospitalized patients, which is far from sufficient to comprehensively evaluate the role of COVID-19. Therefore, we retrospectively collected and analyzed the clinical characteristics and relevant risk factors for severity and death. We hope our study findings could provide scientific evidence for early warning and clinical therapy.

Method

Study Design and Patients: We performed a retrospective cohort study from 26 January 2020 to 16 March 2020. The criteria for patients who chosen to analyze. The process of patients who were included into the analysis were listed in Fig. 1. Inclusion criteria: (1) Over 18 years old; (2) All cases were confirmed with 2019 novel coronavirus pneumonia by positive results of nucleic acids detection. Exclusion criteria—the patients will be excluded if they lacked of corresponding information: (1) Demographic and baseline characteristics assessment. (2) Laboratory findings and radiological characteristic assessment. (3)

Clinical outcome and treatment assessment. According to the sixth edition diagnosis and treatment program of COVID-19 formulated by the National Health Commission of People's Republic of China, those who met at least one following criteria was assigned to the severe group: respiratory distress; respiratory rate \geq 30 breaths/min; $\text{SpO}_2 \leq 93\%$ at rest and $\text{PaO}_2/\text{FiO}_2 \leq 300$. Our study was approved by the Ethics Committee of Wuhan Third Hospital and written informed consent was obtained from patients before collecting data. The treatment of all the subjects enrolled in our study strictly complied with the sixth novel coronavirus infection diagnosis and treatment issued by National Commission and Health Committee of Republic of China.

Procedures: Information including demographic characteristics(gender, age, BMI), clinical features (temperature, respiratory rate, arterial oxygen saturation), comorbidities (hypertension, cardiovascular disease, malignancy, diabetes, renal failure, liver failure, chronic obstructive pulmonary disease), laboratory parameters (blood routine test, blood biochemical test, coagulation function test, inflammatory factors), radiological characteristics (chest tomography), treatment and prognosis were acquired via electronic medical records. Significantly, the definition of multiple lobe lesion refers to lesion involving in more than one lobe. Significantly, the outline of lesion range was drew and quantitatively measured by CT automatically. The result of lesion range was presented as percentage. The mortality was 28-day survival condition (survival/death).

Statistical Analysis: Continuous variables were expressed as medians and interquartile ranges (IQR), while categorical variables were expressed as numbers and percentages. In univariate analysis, continuous variables were analyzed by t test while categorical variables were analyzed by χ^2 test.

Binary cox regression model analysis was applied to determine hazard ratios (HRs) and 95% confidence intervals (95%CIs) of independent risk factors of 28-day mortality. Survival curves were developed by Kaplan-Meier Method and compared by log-rank test. Time to events(death) were defined as 28-day death. Two- sided p of < 0.05 was considered statistically significant in all tests. All of the analyses were conducted with SPSS software version 20.0.

Results

Epidemiological, demographic and baseline Characteristics

In our cohort the first patient was identified on 26 January. The process of enrollment was shown in Fig. 1. By 15 March 2020, 122 admitted hospitalized patients were diagnosed with COVID-19, among which 62 (50.82%) cases were allocated to severe group. From the beginning to the end, the number of severe cases accounted for a large proportion (Supplement 1).

As seen in Table 1, the median age was 64.0 years (IQR 57.0–71.0). Most of them were male (55.74%). The majority of patients denied the history of smoke. The kind and extent of clinical symptoms varied from person to person, while fever (83.61%) was the most common symptoms at the outset of illness. The respiratory rate of severe cases was significantly higher than non-severe ones ($P < 0.0001$) (Table 1). Comorbidities were universally existed in patients with COVID-19. In detail, 67.21% patients affected with COVID-19 suffered from comorbidity-54 patients had hypertension, 29 patients had diabetes, 19 patients had coronary heart disease, 8 had cerebrovascular disease and 7 patients had chronic obstruction pulmonary disease. In addition, the incidence of other underlying diseases was less than 5%, such as liver disease (3.28%), malignancy (1.64%) and kidney disease (1.64%). The proportion of patients with comorbidity was higher in severe group although there was no statistically significant difference. The comparison of demographic and baseline characteristics between survival and non-survival inpatients were also shown in Table 1. Single-factor analysis suggested that several factors were related to severity of disease while they were not associated with death among severe inpatients, which concluded BMI and respiratory rate. Surprisingly, the most common symptom—fever was found to be concerned with death($P = 0.027$).

Table 1
Demographics and baseline characteristics of patients with Coronavirus Disease 2019

Characteristic	All patients (N = 122)			Severe patients(N = 62)			P value*
	Non-severe (N = 60)	Severe (N = 62)	P value#	Survive (N = 44)	Death (N = 18)		
Age, median (IQR), yr	64 (57–71)	64.5 (58–70.5)	63.5(56–72)	0.9320	63.5(55–71)	63.5(57–73)	0.7147
Sex, no.(%)							
Female	54 (44.26)	28 (46.67)	26 (41.94)	0.5990	21(47.73)	5(27.78)	0.1480
Male	68 (55.74)	32 (53.33)	36 (58.06)		23(52.27)	13(72.22)	
Smoking history, no./total No.(%)							
Never smoked	80 (65.57)	41 (68.33)	39 (62.90)	0.0860	30(68.18)	9(50.00)	0.3930
Current smoker	31 (25.41)	11 (18.33)	20 (32.26)		12(27.27)	8(44.44)	
Ever smoker	11 (9.02)	8 (13.33)	3 (4.84)		2(4.55)	1(5.56)	
BMI, median (IQR)	23.77(22.22–25.71)	24.27(22.76–25.88)	23.11(21.22–25.39)	0.0094	23.08(21.50–24.59)	23.14(20.80–27.14)	0.2614
Comorbidity (Yes/No)	82(67.21)	39(65.00)	43(69.35)	0.6080	30(68.18)	13(72.22)	0.7540
Comorbidity (Number)							
=0	40(32.79)	21(35.00)	19(30.65)	0.8180	14(31.8)	5(27.78)	0.7010
=1	48(39.34)	22(36.67)	26(41.94)		17(38.64)	9(50.00)	
≥ 2	34(27.87)	17(28.33)	17(27.42)		13(29.55)	4(22.22)	
Comorbidity No. (%)							
Hypertension	54 (44.26)	28 (46.67)	26 (41.94)	0.5990	20(45.55)	6(33.33)	0.3800
Diabetes mellitus	29 (23.77)	12 (20.00)	17 (27.42)	0.3360	10(22.73)	7(38.89)	0.1950
COPD	7 (5.74)	3 (5)	4 (6.45)	0.7300	4(9.09)	0(0)	0.1860
Coronary heart disease	19 (15.57)	10 (16.67)	9 (14.52)	0.7430	7(15.91)	2(11.11)	0.6260
Cerebrovascular disease	8 (6.56)	4 (6.67)	4 (6.45)	0.9620	3(6.82)	1(5.56)	0.8540
Malignancy	2 (1.64)	0 (0)	2 (3.23)	0.1610	1(2.27)	1(5.56)	0.5070
Chronic liver disease	4 (3.28)	2 (3.33)	2 (3.23)	0.9730	1(2.27)	1(5.56)	0.5070

#P values indicate differences between Non-severe and Severe patients.

*P values indicate differences between survival and dead patients.

P< 0.05 was considered statistically significant.

Characteristic	All patients (N = 122)				Severe patients(N = 62)		
Chronic kidney disease	2 (1.64)	1 (1.67)	1 (1.61)	0.9810	1(2.27)	0(0)	0.5190
Fever	102 (83.61)	50 (83.33)	52 (83.87)	0.9360	34(77.27)	18(100)	0.0270
Respiratory rate, median (IQR)	22 (20–26)	20 (20–22)	26 (22–30)	0.0000	26(22.5–30)	27(22–30)	0.8936
Onset of symptom to hospital admission, median (IQR), d	10 (7–14)	10 (7–15)	9.5(7–12)	0.1517	10(7–12.5)	9(7–12)	0.3839
#P values indicate differences between Non-severe and Severe patients.							
*P values indicate differences between survival and dead patients.							
P< 0.05 was considered statistically significant.							

Laboratory findings and radiological characteristics

The laboratory findings and radiological characteristics were collected on admission and summarized in Table 2. In the severe group, leukocyte counts significantly increased compared with non-severe group($P= 0.0053$). The cell counts of neutrophil($P= 0.0002$) and lymphocyte($P< 0.0001$) were further analyzed. It was shown that both of them were elevated in severe group. However, the difference of lymphocyte count between survival and dead group was not significant. Then there was a significant difference between the two groups regarding coagulation function index such as D-dimer, fibrinogen and prothrombin time.

Table 2
Laboratory findings and radiological characteristics of patients infected with Coronavirus Disease 2019 on admission to hospital

Normal Range	All patients (N = 122)			Severe Patients (N = 62)			
		Non-severe (N = 60)	Severe (N = 62)	P value [#]	Survive (N = 44)	Death (N = 18)	P value [*]
White blood cell count, $\times 10^9/L$	3.50–9.50	5.15 (4.10–7.90)	5.80 (4.15–5.55)	6.20 (4.10–9.00)	0.0053	5.45(3.95–7.75)	8.95(6-11.5) 0.0015
Neutrophil count, $\times 10^9/L$	1.80–6.30	3.55 (2.59–6.67)	3.14 (2.37–3.86)	4.57 (3.10–7.57)	0.0002	3.86(2.94–6.69)	7.70(4.35–9.89) 0.0011
Lymphocyte count, $\times 10^9/L$	1.10–3.20	0.89 (0.65–1.20)	1.09 (0.83–1.48)	0.78 (0.51–0.97)	0.0000	0.75(0.52–0.95)	0.81(0.35–0.97) 0.3495
Median Hemoglobin, g/L	115–150	124 (112–133)	124 (113–130)	124 (109–136)	0.7492	124(110–134)	130(109–145) 0.8004
D-dimer, mg/L	0-0.50	1.17 (0.49–4.10)	0.64 (0.39–2.65)	1.70 (0.74–5.29)	0.0027	1.12(0.5–4.8)	2.53(2.10–5.00) 0.8699
Fibrinogen, g/L	2.0–4.0	4.46 (3.60–5.14)	4.10 (3.20–4.78)	4.86 (3.90–5.31)	0.0187	4.84(3.72–5.29)	4.94(4.06–5.31) 0.4493
Prothrombin time, s	10.00–13.00	11.80(11.20–12.45)	11.50 (11.10–12.10)	12.00 (11.10–12.75)	0.0354	11.95(11.5–12.6)	12.3(11.2–13.4) 0.6934
Alanine aminotransferase, U/L	7–40	32 (19.5–50)	32 (19.5–53.5)	32.5 (19.5–46.5)	0.9482	30(19–48)	34(20–38) 0.7540
Aspartate aminotransferase, U/L	0–45.00	31.50 (23.00–49.00)	28.00 (22.00–38.00)	36.50 (25.00–58.00)	0.0018	24.00(35.50–56.50)	36.50(28.00–58.00) 0.9253
Albumin, g/L	40–55	34.50 (31–38)	37 (32–39.50)	33 (30–36)	0.0162	33.50(33.00–37.00)	32.95(29.00–34.00) 0.7829
Total bilirubin, $\mu\text{mol}/L$	2.00–21.00	9.10 (7.20–12.40)	9.55 (7.40–12.00)	9.05 (7.15–13.90)	0.6022	9.00(7.10–12.40)	9.90(8.00–16.00) 0.4138
Creatinine, $\mu\text{mol}/L$	40.00–105.00	69.20 (55.15–83.75)	63.70 (53.60–76.40)	72.30 (58.10–86.00)	0.0805	72.10(58.60–82.45)	72.30(58.10–100.00) 0.9977
Uric acid, $\mu\text{mol}/L$	150–430	253 (190–304)	252 (192–301)	256.5 (188–307)	0.3057	257(175–304)	256(192–380) 0.0535

[#]P values indicate differences between Nonsevere and Severe patients.

^{*}P values indicate differences between survival and dead patients.

P<0.05 was considered statistically significant.

	Normal Range	All patients (N = 122)			Severe Patients (N = 62)			
Alkaline phosphatase, U/L	53–128	64.5 (51–80)	65 (56.5–77)	62.5 (49–80)	0.8678	60.5(47.5–79)	67.5(53–82)	0.2685
Creatine kinase, U/L	30–180	80 (45–170)	58 (36.5–108)	124 (55–231)	0.0031	96.5(48.5–245.5)	163.5(102–231)	0.4597
Creatine Kinase Isoenzyme-MB, U/L	0–25	11 (8–15)	9 (8–13)	12.5 (9–16)	0.0215	12(8–15)	13(10–16)	0.5757
Cardiac troponin T, positive No.(%)	NA	20 (16.81)	1 (1.67)	19 (32.2)	0.0000	9(21.95)	10(55.56)	0.0110
Lactate dehydrogenase, U/L	114–240	250.5 (195–381)	215 (180–265.5)	368 (228–458)	0.0000	361.5(213–424)	401.5(294–644)	0.0648
Triglyceride, mmol/L	0.45–1.69	1.225 (0.90–1.74)	1.17 (0.88–2.00)	1.32 (1–1.71)	0.2762	1.26(1.00–1.62)	1.49(1.09–2.15)	0.1530
Total cholesterol, mmol/L	2.85–5.69	3.895 (3.30–4.60)	3.92 (3.40–4.51)	3.745 (3.23–4.67)	0.7177	3.80(3.28–4.70)	3.42(3.17–4.58)	0.7447
Arterial Oxygen Saturation	≥ 95%	95 (91–98)	98 (97–99)	91 (90–92)	0.0000	92(90–93)	89(86–91)	0.0013
Radiological characteristics								
Single lobe lesion of CT	NA	20 (16.67)	16 (27.59)	4 (6.45)	0.0020	3(6.82)	1(5.56)	0.8540
Multiple lobe lesion of CT	NA	100 (83.33)	42 (72.41)	58 (93.55)		41(93.18)	17(94.44)	
CT lesion range	NA	40 (20–60)	25 (10–40)	50 (30–70)	0.0000	50(30–70)	70(50–80)	0.0036

*P values indicate differences between Nonsevere and Severe patients.

*P values indicate differences between survival and dead patients.

P<0.05 was considered statistically significant.

Table 3
Treatments and clinical outcomes of patients with Coronavirus Disease 2019

	All patients (N = 122)		Severe patients(N = 62)			
	Non-severe (N = 60)	Severe (N = 62)	P value [#]	Survive (N = 44)	Death (N = 18)	P value [*]
Treatment						
Intravenous antibiotics, no.(%)	74 (60.66)	19 (31.67)	55 (88.71)	0.0000	37(84.09)	18(100) 0.0720
Antiviral therapy						
Arbidol	77 (63.11)	34 (56.67)	43 (69.35)	0.1460	30(68.18)	13(72.22) 0.7540
Lopinavir/Ritonavir	13 (10.66)	0 (0)	13 (20.97)	0.0000	5(11.36)	8(44.44) 0.0040
Lianhuaqingwen	83 (68.03)	45 (75)	38 (61.29)	0.1050	29(65.91)	9(50.00) 0.2430
Glucocorticoid therapy	41 (33.61)	5 (8.33)	36 (58.06)	0.0000	20(45.45)	16(88.89) 0.0020
Immunoglobulin	33 (27.05)	1 (1.67)	32 (51.61)	0.0000	20(45.45)	12(66.67) 0.129
Oxygen inhalation	80 (65.57)	33 (55.00)	47 (75.81)	0.0160	41(88.64)	8(44.44) 0.0010
Mechanical ventilation						
Noninvasive	34 (27.87)	0 (0)	34 (54.84)	0.0000	18(40.91)	16(88.89) 0.0010
Invasive	1 (0.82)	0 (0)	1 (1.61)	0.323	0(0)	1(5.56) 0.1150
Prognosis						
28_day_status of patients						
Discharge from hospital	74 (60.66)	45 (75.00)	29 (46.77)	0.0000	29(65.91)	0(0) 0.0000
Death	17 (13.93)	0 (0)	17 (27.42)		0(0)	17(94.44)
Inpatient treatment	31 (25.41)	15 (25.00)	16 (25.81)		15(34.09)	1(5.56)
ICU admission	46 (37.70)	1 (1.67)	45 (72.58)	0.0000	27(61.36)	18(100) 0.0020

[#]P values indicate differences between Nonsevere and Severe patients.

^{*}P values indicate differences between survival and dead patients.

P<0.05 was considered statistically significant.

In addition, patients with severe disease had more abnormal laboratory parameters than non-severe cases, including higher cardiac troponin T(cTnT),aspartate aminotransferase (AST), albumin, creatine kinase (CK) and lactate dehydrogenase (LDH) but lower arterial oxygen saturation (SaO₂). On the evidence of our result, the concentration of hemoglobin (Hb), alanine

aminotransferase (ALT), total bilirubin (TB), triglyceride (TG), total cholesterol (TC) and alkaline phosphatase (AP) weren't significantly correlated with severity. Concerning radiographic presentations, we found more (93.55%) patients in severe group on admission revealed multiple lobe lesion. Furthermore, lesion range in CT image also larger in severe group. The same laboratory index and radiological characteristic were repeatedly analyzed purely in patients developing severe. Of note, only four laboratory parameters indicated the association with death, including cTnT value($P= 0.011$), leukocyte count ($P= 0.0015$), neutrophil count($P= 0.0011$) and SaO₂($P= 0.0013$). Apart from it, the larger lesion ranges on CT scan also predicted the fatal outcome.

Treatment and Clinical Outcomes

Most cases received intravenous antibiotics therapy (60.66%), and many received antiviral therapy (Arbidol, 63.11%; Lopinavir/ritonavir, 10.66%). Glucocorticoid therapy was given to 41 patients, with a higher percentage among those patients in severe group. Glucocorticoid use also occupied a higher proportion among non-survivors than survivors. But whether the severe condition needs glucocorticoid therapy or the side effect of it contribute to the poor prognosis were unclear. The complex causal relationship has to be further studied. Mechanical ventilation was required in 34 patients, all of whom were coming from severe group. During our study, the primary end point event all occurred in 17 severe patients. Eventually, in survival group, 29(65.91%) patients were discharged from hospital on 28th day compared to none in non-survival group. Fifteen of 44 (34.09%) patients in survival group continued the inpatient therapy. There is no doubt that all of the subjects who died had transferred into ICU for continue therapy.

The dynamic change of lymphocyte after admission to hospital in severe group

The result in Table 1 inferred that lymphocyte could help recognize the patients with severe disease. To determine the role of white blood cell especially lymphocyte in COVID-19, we dynamically observed the change of lymphocyte value from the first day to the 27th day after the admission to hospital among patients suffered from severe disease (Fig. 2). On one hand, non-survivors developed severe lymphopenia compared to survivors during hospitalization. On the other hand, it was illustrated that lymphocyte gradually showed a wavelike decrease change until death occurred among non-survivors even with treatment. Over all it implicated that lymphopenia may be a good indicator of poor prognosis.

Analysis of 28-day mortality in all and severe subjects

Binary cox regression model was performed to figure out the factors in strong relation with 28-day mortality. The results of the model were summarized in S2 and S3. In accordance with the results before, certain factors (cTnT value, leukocyte count, neutrophil count and SaO₂) were statistically significantly related to 28-day mortality in severe subjects (S2). In addition to the parameters mentioned above, respiratory rate and lymphocyte were manifested to be associated with 28-day mortality in all subjects(S3). On the basis of cox regression analysis result in severe (Fig. 3B) and all (Fig. 3A) inpatients were respectively demonstrated in forest plot. No matter the target population was, we found that cTnT was the strongest risk factor($P< 0.05$), compared to leukocyte count, neutrophil count and CT performance. High SaO₂ was a protective factor. In the entire cohort, patients with lymphocytosis also showed a favorable survival status on 28th day. At last, survival curves were constructed based on the result of cox regression analysis to investigate promising parameter with predictive value (Fig. 4). The abnormal cTnT or neutrophil group appeared to have a lower survival curve than the normal group did.

Discussion

In our cohort, we comprehensively and systematically describe the clinical characteristics of patients with laboratory-confirmed COVID-19 infection. It was suggested that part of the baseline characteristics, radiological and laboratory abnormalities could be the predictor of severity and death. In our research, leukocytosis, neutrophilia, increased cTnT, hypoxemia and larger lesion range in CT scan represented relatively fatal outcome on the 28th day after admission to hospital.

Clinical features varied among patients, so did the most common symptom fever. We discovered those who eventually died tend to be asymptomatic at onset of disease compared with the cases were alive. Nanshan Zhong's article also proposed that patients without fever and typical prototypes should be paid more attention to[15]. There's no doubt that the appearance of silent infection brought more burdens on safety precaution. Based on the result in our study, the presence of lymphocytosis was related to severity in accordance with Jinjin Zhang's research[16]. By tracking the change of lymphocyte count after admission to hospital dynamically, we surprisingly found that non-survivors' numbers of lymphocyte were far from recovery all the time, which implied the role of lymphocyte in antiviral effect. The immune system is crucial to defense against pathogens, while the lymphocyte was the main force of adaptive immunity. The current research concerned immune response in COVID-19 patients were unclear. Based on the available literature, they have figured out the part of candidate targets for immune response to SARS-CoV-2 which carried conserved T cell and B cell epitope[17]. Beyond that, during the infection of SARS, there was a significant changes of T lymphocyte and its subtypes in peripheral blood[18–20]. Especially in acute stage, lymphocyte count dramatically dropped[21, 22] which exactly coincide with our result. With regard to innate immune response, we also explored neutrophil was in relationship with 28-day mortality. Through the dynamic observation of neutrophil in other research, they also noticed neutrophil count increased over the follow-up period in severe group[23]. While in our study, we only collected the neutrophil count of patients on admission, it could have implication for severe status and worse clinical outcome. Taking the variance of it into consideration, we should also dynamically track the change of neutrophil count in the future. Zhuo Zhou et al. especially heighten the innate immunity in COVID-19 patients[24]. Neutrophil released cytokines to recruit other immune cells serving as a bridge linking innate and adaptive immunity to a great extent. Neutrophil was involved in cytokine storm[25] and inflammatory cascade reaction which was regarded as potential mechanism in severe COCID-19.

In addition to the hemogram changes mentioned above, most of cases also showed typical radiological characteristics of viral pneumonia on chest imaging[26]. Besides, in our study lesion range in CT scan could be a significant predictor which was consistent with MuLBSTA score that was developed by Ruijin Hospital in 2019 to predict prognosis of viral pneumonia. MuLBSTA score covered six indices: multi-lobular infiltrates; lymphocyte counts; bacteria coinfection; smoke status; hypertension and age[27]. More than the parameters it involved in, we noticed that high BMI was a risk factor for poor prognosis($P=0.0094$). It might be ascribed to inflammatory cytokine storm in obese patients[28, 29]. Now there have been overwhelming evidences to prove that cytokine storm did play a role in the progression of COVID-19[30–32]. Jose RJ proposed that high cytokine concentration usually led to an increased risk of multiorgan failure and eventually death[33]. Nanshan Chen thought manifestations of patients who died agreed with MuLBSTA score in general[34]. But we think the applicability and effectiveness of MuLBSTA score may be further validated and explored.

From a variety of laboratory manifestations, we screened out those related to risk factor for severity and death. Furthermore, we investigate the risk factor of 28-day mortality in all subjects and subgroup (severe group) respectively. The results in our study supposed that the value of cTnT could be of important value as a conventional indicator of myocardial injury in predicting survival status on 28th day. which is consistent with others' study[35]. Riccardo M. Inciardi et al also discovered that inpatients with concomitant cardiac disease and COVID-19 have an extremely poor prognosis with those without a history of cardiac disease[36]. It was recognized that severe hypoxemia, inflammation activation and hypotension may all contribute to cardiac injury. Therefore, someone speculated that he troponin elevation may be dependent on the production of Nox2-related ROS in oxidative stress reaction[37]. Herein, a number of certain researches have determined the relationship between COVID-19 and cardiac injury or dysfunction[38–40]. On one hand, ACE2 was supposed to play an important role which is a functional receptor widely expressed in respiratory and cardiovascular system at the same time throughout the process. When it comes to ACE2, most people thought that the infection of SARS-CoV-2 induced the downregulation of ACE2 via acute lung injury with subsequent dyspnea and hypoxia[41]. While G. Y. Oudit et al proved the appearance of SARS-CoV-2 in the heart also directly led to the reduction in AEC2 protein expression[42]. On the other hand, the severity of SARS infection largely relied on the load of virus as well as immunopathological response of host according to the accumulative evidence[43]. The common imbalance of Th1 and Th2 response easily contributed to cytokine storm which may be linked with myocardial injury[44]. Cardiac troponin T may be a sensitive marker help us discern severe patients. Furthermore, corresponding targeted treatment and preventive should be emergently provided for these patients. The potential underlying mechanism of myocardial injury caused by SARS-CoV-2 maybe cytokine cascade and coagulation abnormality. D-dimer – an index reflecting coagulation function a

was risk factor of mortality which was in line with Cao's study. Systematic inflammation response also brought vascular damage and disturbance of coagulation system, as a result of higher D-dimer value[45]. The mixture condition of coagulation function abnormality and infection undoubtedly exacerbated the problem, such as microcirculation disturbance, oliguria and myocardial infarction[46–48]. In this way, they set up a vicious circle in vivo and eventually developed severe in patients suffering from COVID-19. All above precisely solve the mystery why this kind of coronavirus triggered such high mortality. But the specific pathway hasn't been figured out totally.

Recently the role of age in viral infection drew the controversial conclusion. It's generally considered that immunity dropped with the age when suffered from emerging infectious disease. So they supposed that the elders with COVID-19 had more severe clinical symptom and needed more medical interventions[49–51]. Yet, there's no significant difference between the two groups regarding age in our study. During 2009 pandemic influenza (H1N1), the mortality among young patients was the top compared with the elders[52]. They attributed these to the retained natural immunity by sifting through the infection decades ago among elders. Otherwise, whether the antibody to SARS in 2003 could resist the emerging virus (COVID-19) needs further investigation.

The results in our study implied that one or multiple diseases easily happened in most severe affected patients although the difference between severe and non-severe group was not significant. It was widely supposed that cardiac renin angiotensin system and the key factor angiotensin converting enzyme 2(ACE2) play an important role in cardiovascular diseases. Fittingly, SARS-CoV-2 targeted on cells expressing ACE2 receptor like alveolar epithelial cells, airway epithelial cells, vascular endothelial cells and macrophages in lung and attached to it. The underdevelopment of ACE2 ultimately influenced blood pressure, electrolyte balance, increasing airway inflammation and vascular permeability[41]. Thus it can be seen that part of patients progressed to severe disease might ascribed to interaction between infection of CoV-2 and intrinsic RAS disturbance. From the double shock, those who suffered from comorbidities tended to worse symptoms and clinical outcome. In our study, the collection of comorbidity information was mainly derived from self-report and the past medical history. The patients with severe disease were unable to complete the corresponding examination for diagnosing comorbidity. So the existence of bias was inevitable. The observational study with a large sample size is necessary in the future.

Finally, there were residual limitations that should be addressed. Firstly, because of the exclusion of non-severe outpatients those who were classified as moderate according to the guidance in our study, which might ignore the clinical features of them. Secondly, we explored a limited variety of comorbidity. There could be underlying complication associated with severity which was in our ignorance. Thirdly, the results in our study need internal and external validation to avoid biases due to the restrictions of sample size.

Until now, there's no effective targeted antiviral therapy. Under the circumstance, Symptomatic treatment and oxygen therapy seem to be considerably important. Someone put forward that therapeutic schedule should target on improving the immunity and suppressing the cytokine storm. Through the result in our study, we also suggest that the detection of parameters in peripheral blood like cTnT, leukocyte, neutrophil and lymphocyte are necessary. If possible, the subtype of lymphocyte will help depict the immune status of patients, which can be applied to understand the mechanism of disease, guide treatment, acquire relatively favorable prognosis. Measures to prevent or reduce transmission should be implemented. We hope that our research could provide new insights to help add knowledges to the field of COVID-19.

Conclusion

Our study found that neutrophilia, leukocytosis, hypoxemia and lesion range in CT image were significantly related to the fatal outcome. Most important was that abnormal cTnT value in severe patients were closely associated with 28-day survival status which might be a promising marker for poor prognosis. But the pathology of progressing to severity and even death needs more investigation in the future.

List Of Abbreviations

Coronavirus disease 2019, COVID-19; Interquartile range, IQR; Hazard ratio, HR; confidence interval, CI; Body mass index, BMI; cardiac troponin T,cTnT; aspartate aminotransferase, AST; albumin creatine kinase, CK; lactate dehydrogenase, LDH; arterial oxygen saturation,SaO₂;hemoglobin, Hb; alanine aminotransferase, ALT; total bilirubin, TB; triglyceride, TG; total cholesterol, TC; alkaline phosphatase, AP.

Declarations

Statement of ethics:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Ethics Committee of Wuhan Third Hospital (No.KY2020-043). All patients enrolled completed the informed consent form.

Consent to publication:

Not applicable. There's no individual person's data in the form.

Availability of data and material:

We declared that data and material described in the manuscript will be freely available to any scientists wishing to use them for non-commercial purposes.

Conflicts of interest:

The authors have no conflicts of interest to declare.

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Figures

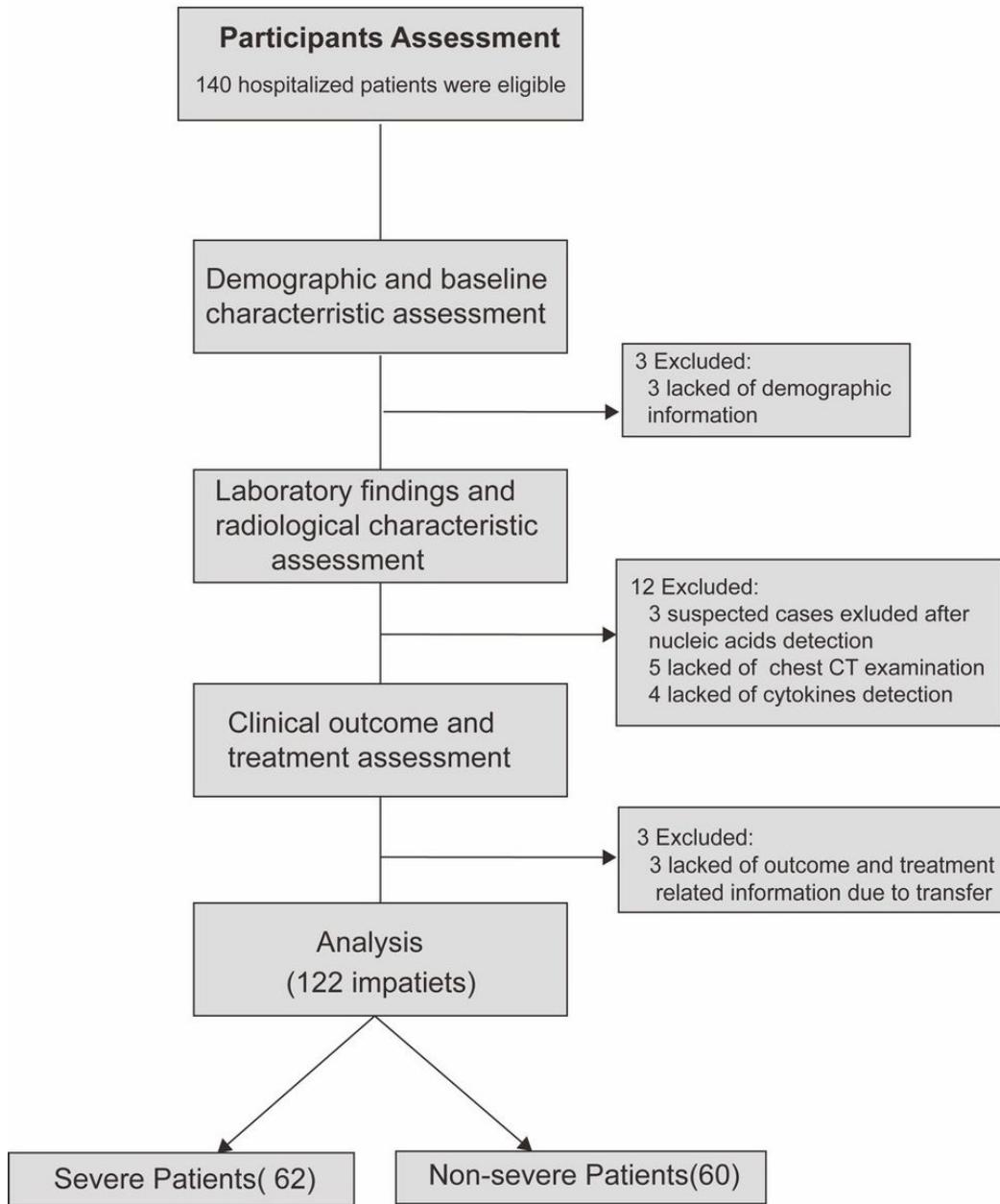


Figure 1

Flowchart of study population Process of participant assessment to analysis. Ultimately, a total of 122 hospitalized patients were used for analysis.

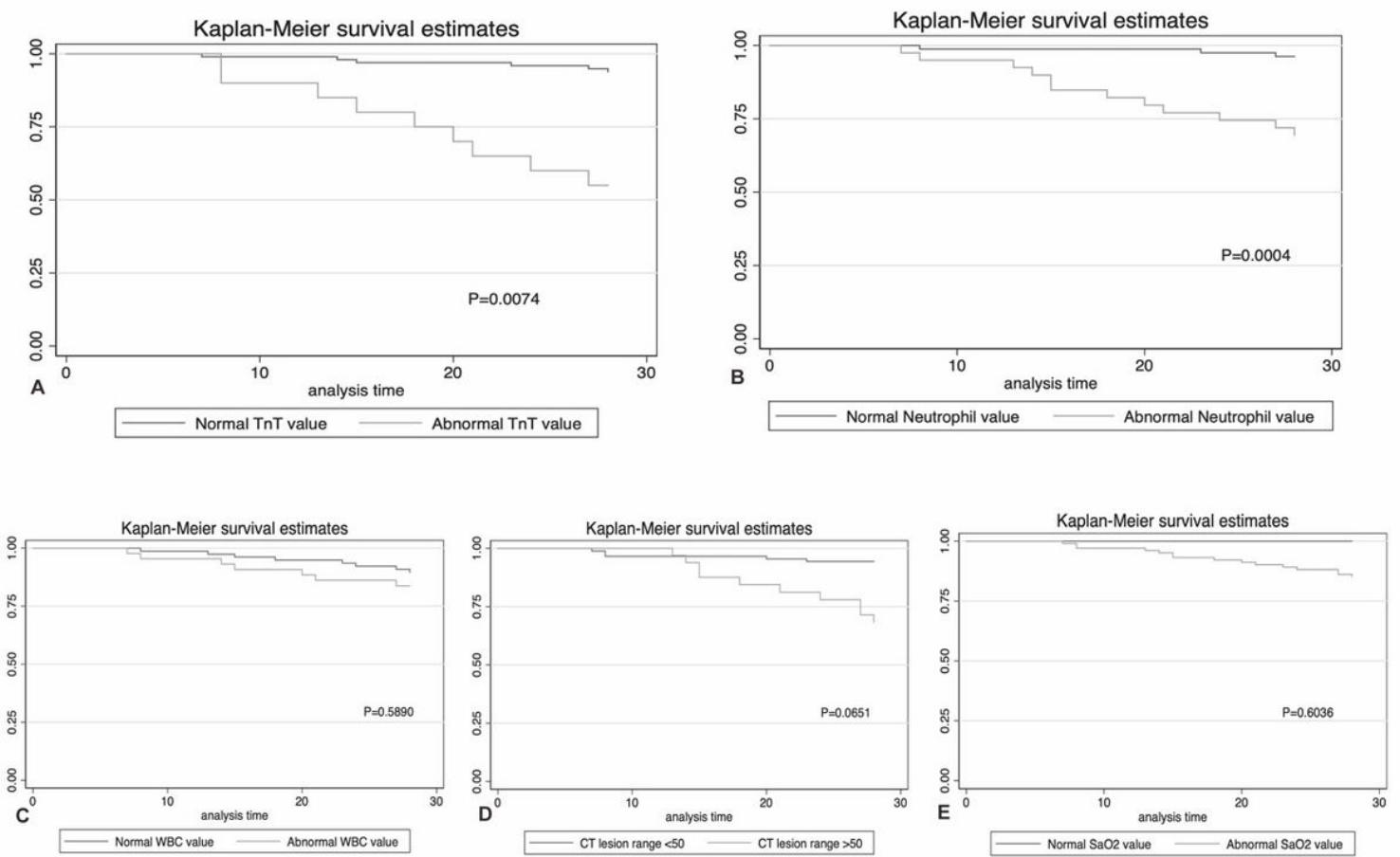
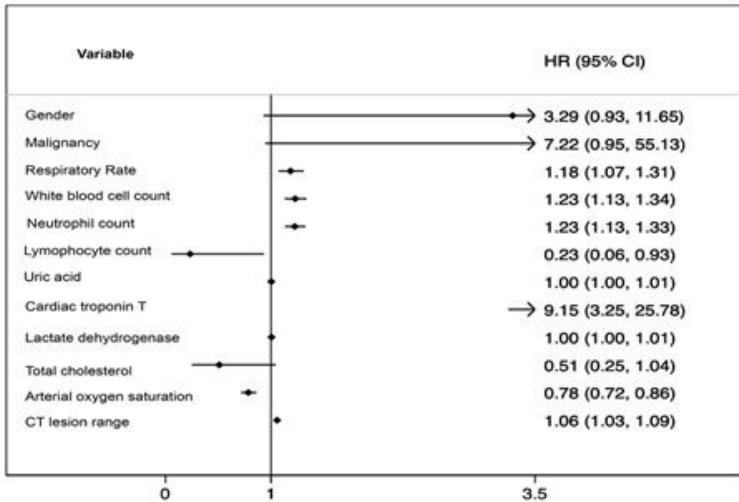
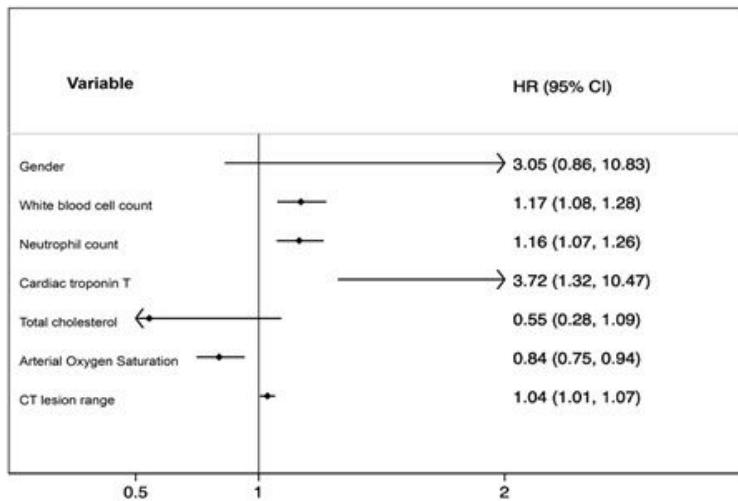


Figure 1

(a b c d e) Survival curve in severe cases with COVID-19 K-M analysis demonstrated that abnormal cTnT or neutrophil was associated with 28th survival status among severe patients with COVID-19. P<0.05 displays statistically significance between two groups. cTnT, cardiac troponin T; Neu, neutrophil; WBC, white blood cell; SaO₂, arterial saturation oxygen.



a



b

Figure 1

a b Cox regression analysis for 28-day mortality Forest plots showed the result of cox regression analysis for risk of 28-day mortality (a)Analysis of 28-day mortality in all cases (b)Analysis of 28-day mortality in severe cases HR, Hazard Ratio; CI, Confidence Interval

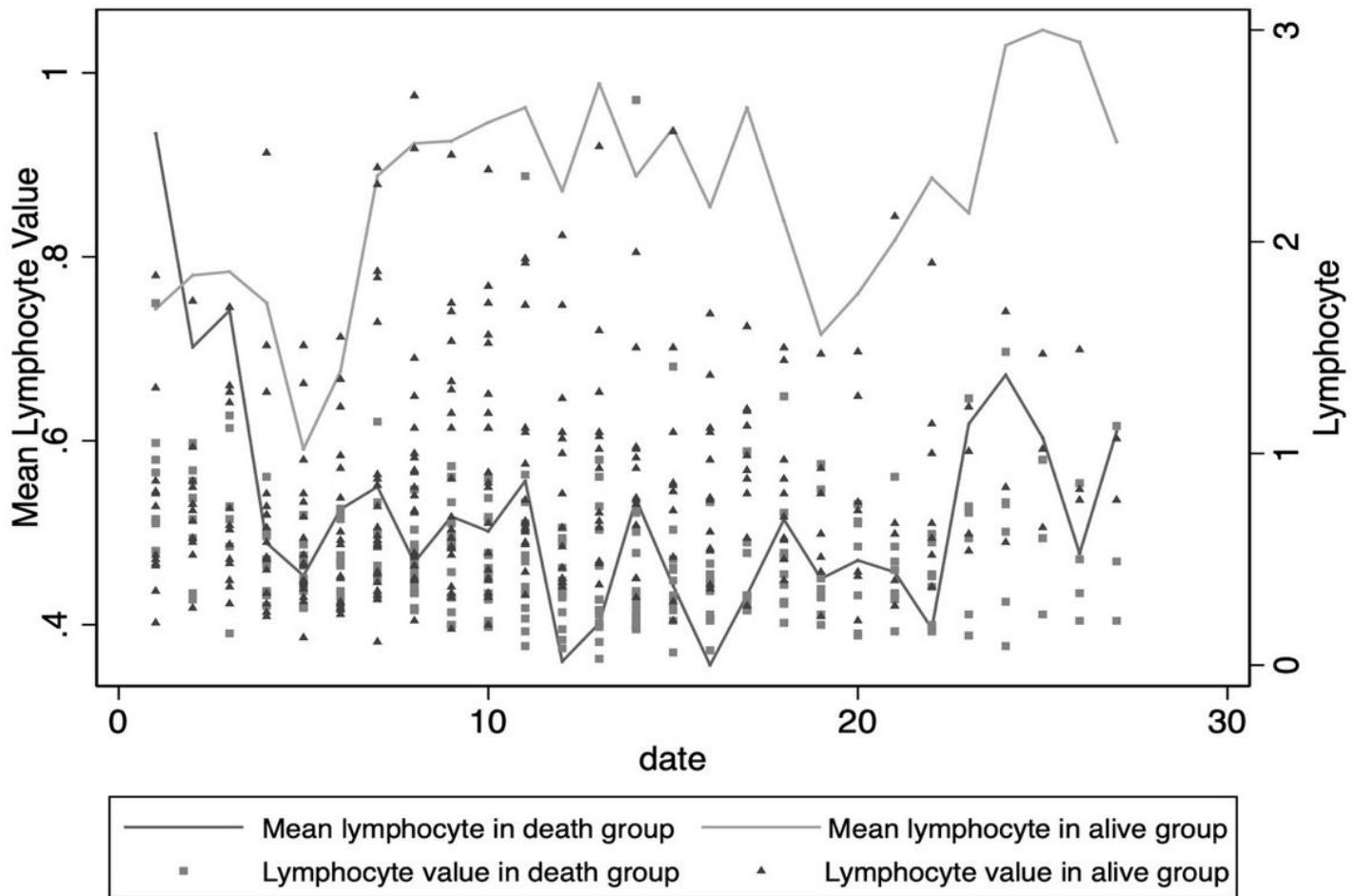


Figure 1

Dynamic Change of Lymphocyte count in severe cases with COVID-19 According to the days after admission to hospital, the double coordinates chart depicted the lymphocyte count in patients with severe disease. The timeline chart indicated the mean lymphocyte value every day, of which the solid line in dark represented non-survivor group while the solid line in light reflected survivors. The scatter plot illustrated the lymphocyte value of each one.

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