





# Retrospective Evaluation of COVID-19 Therapeutics

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**Abstract.** The pandemic outbreak of COVID-19 created panic all over the world. As therapeutics that can effectively wipe out the virus and terminate transmission are not available, supportive therapeutics are the main clinical treatments for COVID-19. Repurposing available therapeutics from other viral infections is the primary surrogate in ameliorating and treating COVID-19. The therapeutics should be tailored individually by analyzing the severity of COVID-19, age, gender, comorbidities, and so on. We aim to investigate the effects of COVID-19 therapeutics and to search for laboratory parameters indicative of severity of illness. Multi-center collaboration and large cohort of patients will be required to evaluate therapeutics combinations in the future.

This study is a single-center retrospective observational study of COVID-19 clinical data in China. Information on patients' treatment modalities, previous medical records, individual disease history, and clinical outcomes were considered to evaluate treatment efficacy. After screening, 2,844 patients are selected for the study. The result shows that treatment with TCM (Hazard Ratio (HR) 0.191 [95% Confidence Interval (CI), 0.14–0.25];  $p < 0.0001$ ), antiviral therapy (HR 0.331 [95% CI 0.19–0.58];  $p = 0.000128$ ), or Arbidol (HR 0.454 [95% CI 0.34–0.60];  $p < 0.0001$ ) is associated with good prognostic of patients. Multivariate Cox regression analysis showed TCM treatment decreased the mortality hazard ratio by 69.4% ( $p < 0.0001$ ).

**Keywords:** COVID-19 · Therapeutics · Single-center retrospective observational study

## 1 Introduction

The quick spread and highly contagious nature of COVID-19 created a severe crisis worldwide. The absence of specific treatment for this disease further raises the public concerns. Therefore, governments the world over utilize all the possible measures to prevent the infection and decrease the disease's devastating outcomes. Although the current therapeutics and vaccines have made promising progress, supportive therapeutics are the main methods for COVID-19 clinically [1]. There is still a long way for therapeutic optimization and understanding of diverse therapeutic approaches under the high risk of the second COVID-19 wave.

As the diseases caused by the SARS-CoV-2 range from asymptomatic, mild pneumonia to acute severe respiratory distress syndromes (ARDS), septic shock, and multiple organ dysfunction syndromes (MODS) [2]. The clinicians widely use antiviral, antibacterial, and TCM therapies to treat patients. Antivirals generally act through two paths: first path directly attacks the virus and interrupts its replication machinery or its ability to attack host cells, and second path blocks the host-viral interactions on the host side. Lopinavir (LPV), a protease inhibitor of 3CLpro, showed an antiviral effect against the SARS-CoV-2 virus with the estimated EC<sub>50</sub> (half-maximal effective concentration) at 26.63  $\mu$ M. LPV is commonly administered in coformulation with the structurally related ritonavir (LPV/r), a mutagenic guanosine analog that inhibits cytochrome P450 metabolism of LPV and boosts lopinavir concentrations [3]. Arbidol blocks virus replication by inhibiting the fusion of the virus's lipid membrane with the host cells, which blocks viral entry and post-stages of entry by targeting viral proteins or virus-associated host factors [4]. Arbidol targets the SARS-CoV-2 spike glycoprotein and impedes its trimerization [5]. Arbidol may induce structural rigidity for binding at the RBD/ACE2 interface, which will inhibit the conformational dynamics required during virus entry [6]. Besides, it can also regulate the immune system by promoting interferon release from cells and continuing to play an antiviral role [7].

Fluoroquinolones are broad-spectrum antibiotics [8]; their mechanism of action is by inhibiting the activities of prokaryotic DNA gyrase-topoisomerase II and topoisomerase IV, which are involved in replication transcription and DNA synthesis [9]. Ciprofloxacin and moxifloxacin may interact with COVID-19 Main Protease [10]. Fluoroquinolones have limited ability to inhibit the replication of SARS-CoV-2 and MERS-CoV in cultured cells [11]. Azithromycin is an orally active synthetic macrolide antibiotic with a wide range of antibacterial, anti-inflammatory and antiviral properties. Azithromycin increased rhinovirus 1B- and rhinovirus 16-induced interferons and interferon-stimulated gene mRNA expression and protein production, and reduced rhinovirus replication and release [12]. Macrolides's antibacterial action is through inhibition of protein synthesis via binding to the 50S subunit of bacterial ribosomes [13]. Antibacterial therapy will be adopted to prevent bacterial co-infection and secondary bacterial infection are critical risk factors for the severity and mortality rates of COVID-19. It may increase drug resistance and raise the risks of allergic reactions.

TCM is an important weapon to contain the pandemic in Chinese history, which has been widely used to treat a variety of infectious diseases such as SARS, H1N1, and H5N1 [14, 15]. TCM can mitigate clinical symptoms, alleviate fever, shorten average hospitalization time, and slows down mild to severe transition [16]. Some plants have

been observed to be effective in laboratory or animal studies; however there is a need to be aware that plant products may interact with other drugs [17]. Heparin and vitamin C are effective natural products and TCM-based therapies for combating the COVID-19 and immune boosters [18]. The compound from Qingfei Paidu Decoction may directly interfere with Toll-like receptor 4 and regulate the downstream signaling pathways, leading to the inhibition of release of proinflammation factors [19]. Lianhuaqingwen exerted its anti-coronavirus activity by inhibiting virus replication, affects virus morphology and reducing the cytokine release from host cells [20]. The mortality rate of patients receiving TCM treatment was lower than those not receiving TCM treatment [21].

This study explores the factors that correlate with disease severity and hospitalization mortality, and reveals the impact of different therapies on patient clinical outcomes. It shows that treatment with TCM and antiviral therapy is associated with good prognostic of patients benefits from main therapeutic methods for moderate patients are antiviral and TCM therapy. Antibacterial therapy had reduced survival rate since antibiotics are ineffective at suppressing bacterial infections and antimicrobial resistance may be associated with harm to patients. The physiological parameters of patients such as MPV, PT-INR,  $K^+$ , EOS#, BASO#, BASO%, Ca, ALB/GLO, Lymph#, and EOS% are closely related to the severity of the disease.

## 2 Methods

### 2.1 Study Design and Participants

This study was a retrospective, observational study based on clinical data from Tongji Hospital in Wuhan. The severity of patients' illness is determined by WHO interim guidance with positive SARS-CoV-2 RNA detection in throat swab specimens. We categorize patients into three groups and analyze the data by statistical methods. Specifically, we analyzed the relationship of the treatment modalities, past medical history, individual disease history, and clinical outcomes among patients with different disease severity. We studied the correlation between the severity of illness and laboratory parameters as well as the relationship between laboratory parameters and patient survival rate.

Inclusion and exclusion criteria are as follows: we included (1) RCTs or (2) cohort or case-control studies reporting on the adjusted effect estimates of the association between CST using in COVID-19 patients and one of the following a-priori outcomes: (1) in-hospital mortality, (2) mechanical ventilation, (3) ICU admission, (4) viral shedding and (5) composite outcomes if reported.

### 2.2 Data Collection

We collect the clinical data for 3337 COVID-19 patients. Data were ascertained from hospital's electronic medical record and recorded in a standardized electronic case report form. The data include all the diagnostic, pathological, and therapeutic information. Baseline data (such as demographics, medical history, individual disease history, and physical examination), laboratory, treatment, and outcome data are extracted from electronic medical records. Laboratory tests include routine blood tests, biochemical tests,

coagulation tests, blood gas analysis, cytokine tests, ferritin, erythrocyte sedimentation rate, hypersensitive C-reactive protein, procalcitonin, etc. The treatment mainly includes TCM, immunotherapy, antiviral therapy, antibacterial therapy, and supportive therapy.

### 2.3 Statistical Analysis

Descriptive data contains normal and non-normal distributed types. The first type is expressed in terms of mean and standard deviation. Others are presented by median and interquartile range. Categorical variables were presented as percentages. We applied the Analysis of Variance or Kruskal-Wallis rank-sum for two kinds of data, respectively, comparing groups with varying disease severity. The chi-square test was performed to compare count data. We use Kaplan-Meier to plot to visualize survival curves, Log-rank test to compare the survival curves of two or more groups, and Cox proportional hazards regression for survival analysis to describe the effect of variables on survival.

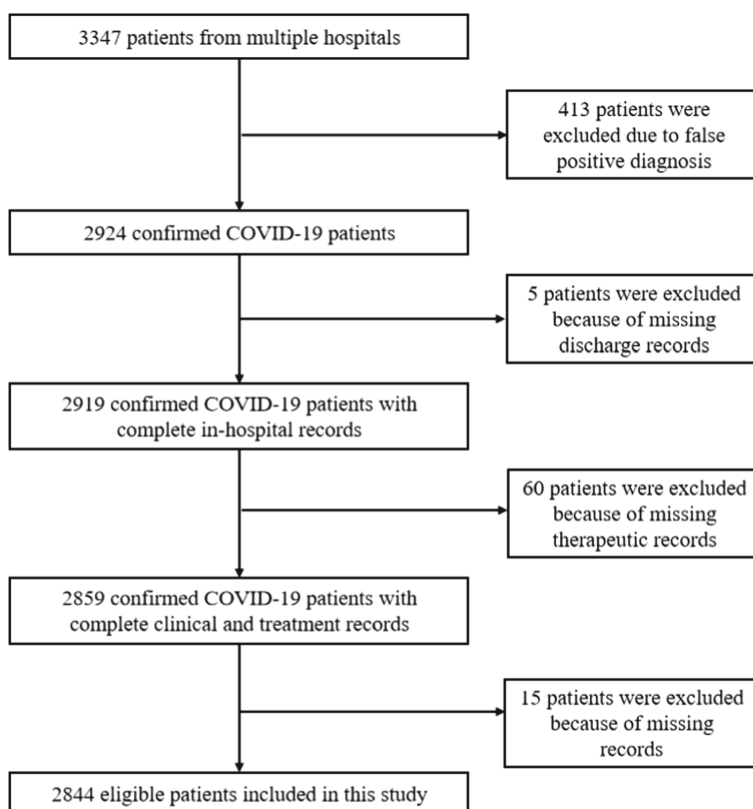
Kaplan-Meier curves and log-rank tests – are examples of univariate analysis. They describe the survival according to one factor under investigation, but ignore the impact of any others. Additionally, Kaplan-Meier curves and log rank tests are useful only when the predictor variable is categorical. They don't work quickly for quantitative predictors. An alternative method is the Cox proportional hazards regression analysis, which works for both quantitative predictor variables and categorical variables. Furthermore, the Cox regression model extends survival analysis methods to simultaneously assess several risk factors' effect on survival time.

Assess the association between different drugs and in-hospital mortality in patients admitted with COVID-19 using a Kaplan-Meier method. The Cox proportional hazards regression analysis was used to extend survival analysis methods to assess the effect of several risk factors for in-hospital mortality simultaneously. All statistical analyses were conducted using the R language.

## 3 Results

We collect the clinical data for 3337 COVID-19 patients from Tongji Hospital in Wuhan. The data include all the diagnostic, pathological, and therapeutic information, which is screened to finalize the patients' cohort for further statistical analysis. Patients were excluded because they have asymptomatic or mild clinical symptoms without pneumonia on CT imaging since they do not need therapeutic intervention for recovery. Patients who are not sick enough to be hospitalized or lack of clinical records are excluded in this study. 2,844 (85.23%) patients after screening were grouped into categories in this study: moderate, severe, and critical ill according to the severity of COVID-19 (Fig. 1). The definition of COVID-19 severity follows the WHO standards. The various therapeutics have been used to treat three groups of patients, including 242 moderate, 1995 severe, and 607 critically ill patients.

For our study, the most commonly used combination for critically ill patients is ventilator, oxygen-therapy, TCM, hormone therapy, antiviral therapy and antibacterial therapy. The combination of oxygen therapy, TCM, antiviral therapy and antibacterial



**Fig. 1.** Overview of participants selection included in this cohort. Some patients are excluded due to following factors such as missing important information and non-treatment cases for self-recovery.

therapy is most common for seriously ill patients. Moderate patients used a combination of TCM and antivirals at most.

The main therapeutic methods for moderate patients are antiviral (88.4%) and TCM (79.8%) therapy. Same patients receive a combination of different treatments, which causes the total percentage is greater than 100%. The therapeutics for severe patients are antiviral therapy (97.1%), oxygen therapy (89.3%), TCM (88.0%), and antibacterial therapy (72.8%). The treatment methods for critically ill patients are: oxygen therapy (98.7%), antiviral therapy (95.4%), antibacterial therapy (92.4%), hormone therapy (80.1%), and TCM (78.4%). Patients in less severity group have fewer therapeutics since some treatments are invasive, only applicable in severe conditions, and side effects. Oxygen therapy was used in a large proportion of patients (2508, 88.2%), while ventilator, intubate, hemodialysis, ECMO, and CRRT were mainly used in critically ill patients. 848 (29.8%) patients were treated with gamma globulin, 2,424 (85.2%) with TCM, 1,295 (45.5%) with hormone, 455 (16.0%) with immunotherapy, 2,119 (74.5%) with antibacterial therapy, and 2,731 (96.0%) with antiviral therapy for all three groups. The five

most widely used antiviral drugs are Arbidol (1800, 63.3%), Ganciclovir (191, 6.7%), Oseltamivir (201, 7.1%), Interferon (126, 4.4%), and Kaletra (269, 9.5%).

Descriptive data was presented as mean with standard deviation for normally distributed continuous variables, where the standard deviation is in the bracket following mean. For non-normally-distributed data, we list the variable median with interquartile range in the following bracket. Categorical or binary variables were presented as percentages. For a different group of patients, the number of patients is listed followed with the percentage of treatment or nontreatment (Table 1). The mean age was 58.74 years (SD 15.28), and the severe group has higher mean age. Aging is associated with endothelial dysfunction and weak immune protection, contributing to vascular pathologies and cardiovascular diseases [22]. 1393 cases (49.0%) were male, and the group of critically ill patients comprised more males (57.2%) patients. Sex differences in immune responses underlie COVID-19 disease outcomes [23]. There were no significant differences in height, weight, body mass index, and body surface area among patients with different disease severity within three groups.

We applied the Analysis of Variance or Kruskal-Wallis rank-sum (variables with non-normal distribution) for continuous variables between groups with different disease severity. The chi-square test was performed to compare count data. There were significant differences ( $p < 0.01$ ) in the proportion of patients with previous disease history in different disease severity. Patients in COVID-19 with comorbidities of hypertension, coronary, diabetes, chronic obstructive pulmonary diseases, malignancy, cerebrovascular disease, trauma history, or cardiovascular were more likely to be critically ill, associated with poorer outcomes in COVID-19 patients. Diabetes (13.7% overall) is associated with immunological dysregulation, which is potentially equivalent to accelerated aging, and could therefore potentially explain the poor prognosis in patients with diabetes mellitus and COVID-19. Preexisting cardiovascular diseases is an essential factor for myocardial injury as approximately 30% and 60% of patients with cardiac injury have coronary heart disease and hypertension previously [3, 4]. Patients with underlying cardiovascular disease, including hypertension, coronary heart disease, and cardiomyopathy are more likely to develop more severe adverse outcomes when myocardial injury occurs after COVID-19 infection and face a higher risk of death [24].

It is known that there is no effective therapeutics against COVID-19, and it will be informative to compare the available supportive treatment in the reduction of mortality and hospitalization time. We use Kaplan-Meier plots to visualize and Log-rank test to compare the impact on mortality by Arbidol, Ganciclovir, Oseltamivir, Interferon, Kaletra, antibacterial therapy, and TCM. There were significant differences ( $p < 0.0001$ ) in patients survival rate treated with or without Abidiol, antibacterial, or TCM. Patients who had been treated with either Arbidol or TCM had improved survival likelihood, whereas antibacterial therapy had reduced survival rate. The phenomenon about patients who receive antibacterial therapy shows bacterial infection symptoms reacts SARS-CoV-2 infection weaken the immune system that increases the risk of bacterial infection. However, the current antibacterial are not effective for the inhibition of bacterial infection (Fig. 2).

A separate univariate Cox regression evaluated each factor to show the statistical significance of each variable with overall survival. Univariate Cox regression yielded

**Table 1.** Statistics on baseline characteristics, treatment, and comorbidities among patients with different severities and overall.

	Level	Moderate	Severe	Critical	Overall	p
n		242	1,995	607	2,844	
Age (mean (SD))		48.88 (14.42)	57.70 (14.64)	66.10 (14.51)	58.74 (15.28)	<0.001
Inhospital length (mean (SD))		10.43 (6.94)	22.10 (12.06)	29.03 (16.64)	22.59 (13.66)	<0.001
Sex (%)	Female	126 (52.1)	1065 (53.4)	260 (42.8)	1451 (51.0)	<0.001
	Male	116 (47.9)	930 (46.6)	347 (57.2)	1393 (49.0)	
Height (median [IQR])		168.00 [160.00, 170.00]	165.00 [160.00, 170.00]	167.00 [160.00, 170.00]	165.00 [160.00, 170.00]	0.067
Weight (median [IQR])		65.00 [59.00, 72.88]	65.00 [57.00, 70.00]	64.00 [55.00, 70.00]	65.00 [57.00, 70.00]	0.322
BMI (median [IQR])		23.66 [21.92, 25.26]	23.44 [21.48, 25.50]	23.03 [20.92, 25.10]	23.44 [21.47, 25.39]	0.163
BSA (mean (SD))		1.81 (0.17)	1.80 (0.34)	1.79 (0.18)	1.80 (0.30)	0.798
Ventilator (%)	No	239 (98.8)	1902 (95.3)	263 (43.3)	2404 (84.5)	<0.001
	Yes	3 (1.2)	93 (4.7)	344 (56.7)	440 (15.5)	
Intubate (%)	No	241 (99.6)	1978 (99.1)	415 (68.4)	2634 (92.6)	<0.001
	Yes	1 (0.4)	17 (0.9)	192 (31.6)	210 (7.4)	
Oxygen therapy (%)	No	115 (47.5)	213 (10.7)	8 (1.3)	336 (11.8)	<0.001
	Yes	127 (52.5)	1782 (89.3)	599 (98.7)	2508 (88.2)	
Hemodialysis (%)	No	242 (100.0)	1992 (99.8)	524 (86.3)	2758 (97.0)	<0.001
	Yes	0 (0.0)	3 (0.2)	83 (13.7)	86 (3.0)	
ECMO (%)	No	242 (100.0)	1994 (99.9)	592 (97.5)	2828 (99.4)	<0.001
	Yes	0 (0.0)	1 (0.1)	15 (2.5)	16 (0.6)	

*(continued)*

**Table 1.** (continued)

	Level	Moderate	Severe	Critical	Overall	p
CRRT (%)	No	242 (100.0)	1994 (99.9)	530 (87.3)	2766 (97.3)	<0.001
	Yes	0 (0.0)	1 (0.1)	77 (12.7)	78 (2.7)	
Gamma globulin therapy (%)	No	220 (90.9)	1521 (76.2)	255 (42.0)	1996 (70.2)	< 0.001
	Yes	22 (9.1)	474 (23.8)	352 (58.0)	848 (29.8)	
TCM (%)	No	49 (20.2)	240 (12.0)	131 (21.6)	420 (14.8)	<0.001
	Yes	193 (79.8)	1755 (88.0)	476 (78.4)	2424 (85.2)	
Hormone therapy (%)	No	202 (83.5)	1226 (61.5)	121 (19.9)	1549 (54.5)	< 0.001
	Yes	40 (16.5)	769 (38.5)	486 (80.1)	1295 (45.5)	
Immunotherapy (%)	No	209 (86.4)	1740 (87.2)	440 (72.5)	2389 (84.0)	<0.001
	Yes	33 (13.6)	255 (12.8)	167 (27.5)	455 (16.0)	
Antiviral therapy (%)	No	28 (11.6)	57 (2.9)	28 (4.6)	113 (4.0)	<0.001
	Yes	214 (88.4)	1938 (97.1)	579 (95.4)	2731 (96.0)	
Arbidol (%)	No	150 (62.0)	631 (31.6)	263 (43.3)	1044 (36.7)	<0.001
	Yes	92 (38.0)	1364 (68.4)	344 (56.7)	1800 (63.3)	
Ganciclovir (%)	No	237 (97.9)	1874 (93.9)	542 (89.3)	2653 (93.3)	<0.001
	Yes	5 (2.1)	121 (6.1)	65 (10.7)	191 (6.7)	
Oseltamivir (%)	No	227 (93.8)	1848 (92.6)	568 (93.6)	2643 (92.9)	0.627
	Yes	15 (6.2)	147 (7.4)	39 (6.4)	201 (7.1)	
Interferon (%)	No	229 (94.6)	1914 (95.9)	575 (94.7)	2718 (95.6)	0.338
	Yes	13 (5.4)	81 (4.1)	32 (5.3)	126 (4.4)	
Kaletra (%)	No	228 (94.2)	1819 (91.2)	528 (87.0)	2575 (90.5)	0.001

(continued)

**Table 1.** (continued)

	Level	Moderate	Severe	Critical	Overall	p
Antibacterial therapy (%)	Yes	14 (5.8)	176 (8.8)	79 (13.0)	269 (9.5)	
	No	137 (56.6)	542 (27.2)	46 (7.6)	725 (25.5)	<0.001
	Yes	105 (43.4)	1453 (72.8)	561 (92.4)	2119 (74.5)	
Smoking (%)	No	242 (100.0)	1976 (99.0)	603 (99.3)	2821 (99.2)	0.265
	Yes	0 (0.0)	19 (1.0)	4 (0.7)	23 (0.8)	
Past disease (%)	No	136 (56.2)	956 (47.9)	181 (29.8)	1273 (44.8)	<0.001
	Yes	106 (43.8)	1039 (52.1)	426 (70.2)	1571 (55.2)	
Infectious disease (%)	No	231 (95.5)	1934 (96.9)	582 (95.9)	2747 (96.6)	0.269
	Yes	11 (4.5)	61 (3.1)	25 (4.1)	97 (3.4)	
Allergic history (%)	No	226 (93.4)	1818 (91.1)	571 (94.1)	2615 (91.9)	0.046
	Yes	16 (6.6)	177 (8.9)	36 (5.9)	229 (8.1)	
Blood transfusion history (%)	No	242 (100.0)	1980 (99.2)	601 (99.0)	2823 (99.3)	0.313
	Yes	0 (0.0)	15 (0.8)	6 (1.0)	21 (0.7)	
Past surgery (%)	No	201 (83.1)	1666 (83.5)	482 (79.4)	2349 (82.6)	0.064
	Yes	41 (16.9)	329 (16.5)	125 (20.6)	495 (17.4)	
Hypertension (%)	No	203 (83.9)	1448 (72.6)	344 (56.7)	1995 (70.1)	<0.001
	Yes	39 (16.1)	547 (27.4)	263 (43.3)	849 (29.9)	
Coronary (%)	No	237 (97.9)	1860 (93.2)	544 (89.6)	2641 (92.9)	<0.001
	Yes	5 (2.1)	135 (6.8)	63 (10.4)	203 (7.1)	
Diabetes (%)	No	222 (91.7)	1733 (86.9)	500 (82.4)	2455 (86.3)	0.001
	Yes	20 (8.3)	262 (13.1)	107 (17.6)	389 (13.7)	

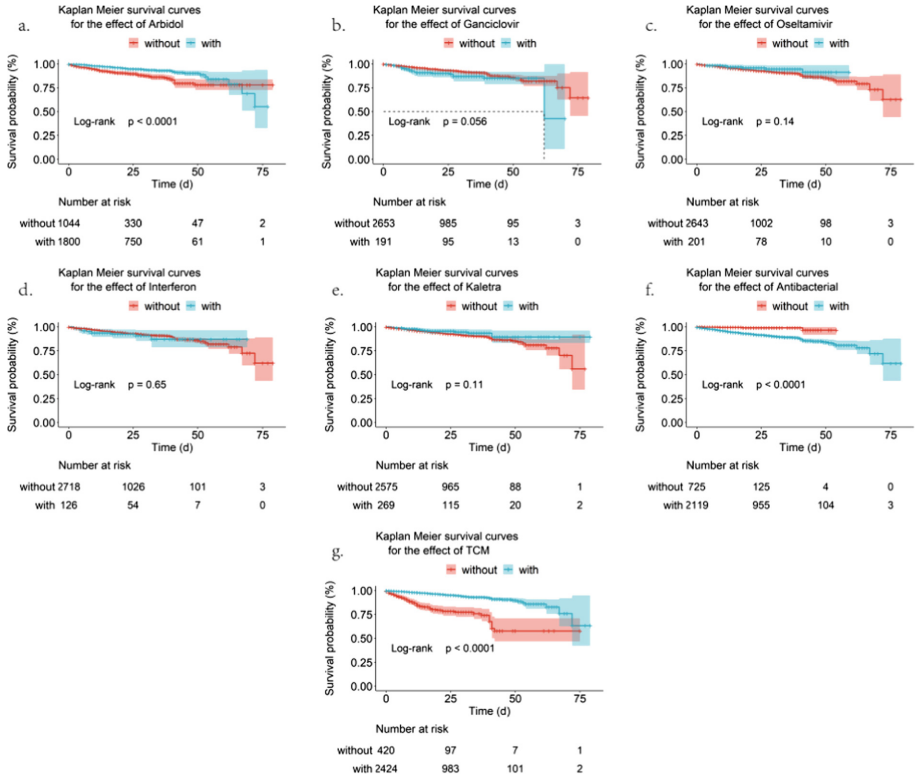
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**Table 1.** (continued)

	Level	Moderate	Severe	Critical	Overall	p
COPD (%)	No	241 (99.6)	1977 (99.1)	593 (97.7)	2811 (98.8)	0.01
	Yes	1 (0.4)	18 (0.9)	14 (2.3)	33 (1.2)	
Malignancy (%)	No	238 (98.3)	1950 (97.7)	579 (95.4)	2767 (97.3)	0.004
	Yes	4 (1.7)	45 (2.3)	28 (4.6)	77 (2.7)	
CKD (%)	No	239 (98.8)	1989 (99.7)	599 (98.7)	2827 (99.4)	0.007
	Yes	3 (1.2)	6 (0.3)	8 (1.3)	17 (0.6)	
Cerebrovascular disease (%)	No	237 (97.9)	1954 (97.9)	555 (91.4)	2746 (96.6)	<0.001
	Yes	5 (2.1)	41 (2.1)	52 (8.6)	98 (3.4)	
Immunodeficiency disease (%)	No	242 (100.0)	1,995 (100.0)	607 (100.0)	2,844 (100.0)	NA
Hepatitis (%)	No	234 (96.7)	1963 (98.4)	592 (97.5)	2789 (98.1)	0.107
	Yes	8 (3.3)	32 (1.6)	15 (2.5)	55 (1.9)	
Tuberculosis (%)	No	238 (98.3)	1961 (98.3)	592 (97.5)	2791 (98.1)	0.458
	Yes	4 (1.7)	34 (1.7)	15 (2.5)	53 (1.9)	
Trauma history (%)	No	241 (99.6)	1953 (97.9)	583 (96.0)	2777 (97.6)	0.004
	Yes	1 (0.4)	42 (2.1)	24 (4.0)	67 (2.4)	
Cardiovascular (%)	No	194 (80.2)	1363 (68.3)	305 (50.2)	1862 (65.5)	<0.001
	Yes	48 (19.8)	632 (31.7)	302 (49.8)	982 (34.5)	

Abbreviations: Body Mass Index, BMI; Body Surface Area, BSA; Extracorporeal Membrane Oxygenation, ECMO; Continuous Renal Replacement Therapy, CRRT; Chronic Obstructive Pulmonary Diseases, COPD; Chronic Kidney Disease, CKD.

similar results as survival analysis. Besides, we found differences in the characteristics of the patients' ventricle, intubate, hemodynamics, ECMO, CRRT, gamma globulin therapy, hormone therapy, infectious disease, coronary, malignant, CKD, or cerebrovascular disease had a significant impact ( $p < 0.01$ ) on survival. Treatment with TCM (HR 0.191 [95% CI 0.14–0.25];  $p < 0.0001$ ), antiviral therapy (HR 0.331 [95% CI 0.19–0.58];  $p = 0.000128$ ), or Arbidol (HR 0.454 [95% CI 0.34–0.60];  $p < 0.0001$ ) is associated with good prognostic of patients, and others were associated with poor outcome or a higher risk of death (Table 2).



**Fig. 2.** Kaplan-Meier survival curves. Kaplan Meier survival curves and log rank tests for the effect of Arbidol (a), Ganciclovir (b), Oseltamivir (c), Interferon (d), Kaletra (e), Antibacterial therapy (f), and TCM (g) treatments on mortality.

**Table 2.** Univariate Cox regression of baseline characteristics, treatment, and comorbidities.

	Beta	HR (95% CI for HR)	wald.test	p. value
Ventilator	3.86	47.6 (29–77)	243	9.82E–55
Intubate	2.99	19.9 (15–27)	399	1.07E–88
Oxygen therapy	17.2	28100000 (0-Inf)	0	0.99
Hemodialysis	2.28	9.75 (7.1–13)	199	4.23E–45
ECMO	1.23	3.43 (1.6–7.4)	9.69	0.00186
CRRT	2.4	11 (8–15)	224	1.17E–50
Gamma globulin therapy	1.15	3.17 (2.4–4.2)	60.3	8.15E–15
TCM	–1.66	0.191 (0.14–0.25)	130	3.40E–30

(continued)

**Table 2.** (continued)

	Beta	HR (95% CI for HR)	wald.test	p. value
Hormone therapy	2.07	7.95 (5–13)	76.7	2.01E–18
Immunotherapy	–0.121	0.886 (0.62–1.3)	0.45	0.5
Antiviral therapy	–1.1	0.331 (0.19–0.58)	14.7	0.000128
Arbidol	–0.79	0.454 (0.34–0.6)	31.2	2.39E–08
Ganciclovir	0.42	1.52 (0.99–2.4)	3.58	0.0584
Oseltamivir	–0.502	0.605 (0.31–1.2)	2.16	0.141
Interferon	0.14	1.15 (0.63–2.1)	0.2	0.653
Kaletra	–0.421	0.656 (0.39–1.1)	2.45	0.117
Antibacterial therapy	2.18	8.81 (3.6–21)	23	1.62E–06
Smoking	–0.856	0.425 (0.059–3.1)	0.72	0.395
Past disease	0.361	1.43 (1.1–1.9)	5.78	0.0162
Infectious disease	0.833	2.3 (1.3–4)	8.41	0.00374
Allergic history	–0.518	0.596 (0.32–1.1)	2.55	0.11
Blood transfusion history	1.2	3.3 (1.2–8.9)	5.6	0.018
Past surgery	0.113	1.12 (0.79–1.6)	0.41	0.522
Hypertension	0.178	1.2 (0.9–1.6)	1.48	0.224
Coronary	0.609	1.84 (1.2–2.8)	8.38	0.00379
Diabetes	0.108	1.11 (0.77–1.6)	0.32	0.569
COPD	0.249	1.28 (0.47–3.5)	0.24	0.624
Malignancy	0.743	2.1 (1.2–3.7)	6.66	0.00988
CKD	1.38	3.97 (1.5–11)	7.42	0.00643
Cerebrovascular disease	0.754	2.13 (1.3–3.5)	8.77	0.00306
Hepatitis	0.551	1.73 (0.77–3.9)	1.76	0.184
Tuberculosis	0.562	1.75 (0.78–4)	1.84	0.175
Trauma history	–0.0835	0.92 (0.38–2.2)	0.03	0.854
Cardiovascular	0.335	1.4 (1.1–1.8)	5.57	0.0183

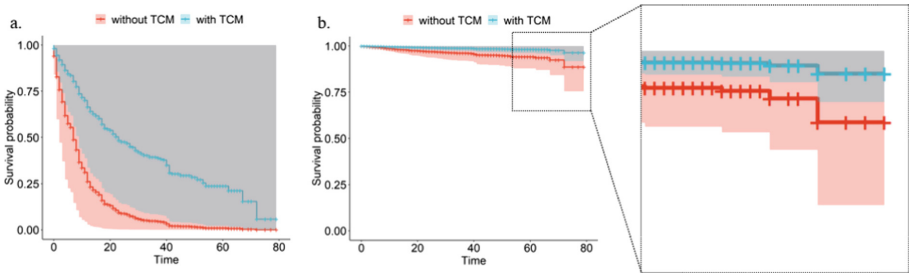
Besides, we used multivariate Cox regression analysis to describe how these factors work together to influence survival. Multivariate Cox regression analysis showed that treatment with TCM decreased the mortality hazard ratio by 69.4% ( $p < 0.0001$ ), while supportive treatment ventilator or intubate use was statistically associated with a higher risk of mortality due to COVID-19 (Table 3).

We constructed new data frames with two rows according to TCM treatment or not, and other covariates were fixed as used (not used). The resulting survival curve again indicates a strong relationship between TCM therapy and decreased risk of death (Fig. 3).

**Table 3.** Multivariate Cox regression analysis of baseline characteristics, treatment, and comorbidities.

	exp (coef) [confint]	coef	se (coef)	z	p.value
Ventilator	20.213 [11.273, 36.244]	3.006	0.298	10.091	6.08E−24
Intubate	3.267 [2.269, 4.705]	1.184	0.186	6.363	1.98E−10
Hemodialysis	1.511 [0.888, 2.569]	0.413	0.271	1.524	0.127617286
ECMO	0.660 [0.296, 1.471]	−0.415	0.409	−1.016	0.309832551
CRRT	0.791 [0.465, 1.346]	−0.234	0.271	−0.864	0.387582057
Gamma globulin therapy	0.725 [0.526, 1.000]	−0.322	0.164	−1.962	0.049745714
TCM	0.306 [0.225, 0.414]	−1.186	0.155	−7.633	2.30E−14
Hormone therapy	1.202 [0.702, 2.060]	0.184	0.275	0.670	0.502639462
Antiviral therapy	0.562 [0.302, 1.045]	−0.576	0.317	−1.821	0.068572796
Arbidol	0.794 [0.590, 1.068]	−0.231	0.151	−1.524	0.127407379
Antibacterial therapy	1.438 [0.557, 3.708]	0.363	0.483	0.751	0.452801778
Infectious disease	2.264 [1.260, 4.069]	0.817	0.299	2.732	0.006303463
Coronary	1.186 [0.773, 1.822]	0.171	0.219	0.782	0.434423283
Malignancy	1.305 [0.722, 2.357]	0.266	0.302	0.882	0.377638162
CKD	0.816 [0.293, 2.268]	−0.204	0.522	−0.390	0.696198216
Cerebrovascular disease	0.929 [0.534, 1.616]	−0.074	0.283	−0.262	0.793590892

Exp (coef): the exponentiated coefficients; coef: the regression coefficients; se (coef): standard error of the regression coefficient; z: coef/se (coef).



**Fig. 3.** Visualized survival curves for the new data frames. The latest data framework only kept the values of TCM, modified the other parameters to the same value; the left panel was based on the different treatments all used or had comorbidity, the right panel is the opposite.

A total of 77 indicators derived from laboratory tests including routine blood tests, biochemistry, coagulation, blood gas, cytokines, ferritin, erythrocyte sedimentation rate,

hypersensitive C-reactive protein, and procalcitonin were included in this study. Except for Mean Corpuscular Hemoglobin (MCH), Monocyte count (Mono#), Actual bicarbonate (AB), Standard bicarbonate (SB), Base excess (BE), Standard base surplus (SBE), Blood carbon dioxide content, and Interleukin-1 $\beta$  (IL-1 $\beta$ ), the other 69 indices were significantly different ( $p < 0.001$ ) between patients with varying severities of disease (Table 4, Fig. 4).

**Table 4.** Statistics on laboratory indices among patients with different severities and overall.

	Moderate	Severe	Critical	Overall	p
N	242	1,995	607	2,844	
WBC#	5.69 [4.77, 6.72]	5.67 [4.82, 6.86]	8.04 [6.00, 10.97]	5.96 [4.95, 7.49]	< 0.001
RBC#	4.28 [3.98, 4.72]	4.08 [3.75, 4.45]	3.74 [3.33, 4.14]	4.04 [3.68, 4.42]	< 0.001
MCV	89.24 [86.59, 91.71]	90.00 [87.35, 92.66]	90.94 [87.90, 93.92]	90.13 [87.37, 92.84]	< 0.001
MCHC	342.00 [336.00, 348.00]	342.00 [335.33, 349.00]	339.73 [331.47, 346.62]	341.33 [334.84, 348.33]	< 0.001
MCH	30.60 [29.60, 31.50]	30.87 [29.80, 31.82]	30.85 [29.80, 31.92]	30.83 [29.78, 31.80]	0.021
RDW-CV	12.72 [12.13, 13.24]	12.63 [12.10, 13.22]	13.46 [12.70, 14.54]	12.78 [12.20, 13.50]	< 0.001
RDW-SD	41.30 [38.92, 43.51]	41.15 [38.98, 43.55]	44.05 [41.29, 48.02]	41.63 [39.30, 44.30]	< 0.001
Lymph%	31.30 [25.87, 36.21]	26.88 [21.28, 32.50]	15.46 [7.41, 21.17]	25.30 [18.71, 31.35]	< 0.001
Lymph#	1.74 [1.35, 2.11]	1.49 [1.18, 1.81]	0.99 [0.68, 1.33]	1.41 [1.08, 1.78]	< 0.001
Mono%	8.52 [7.44, 9.66]	8.90 [7.63, 10.37]	7.39 [5.14, 9.06]	8.64 [7.25, 10.10]	< 0.001
Mono#	0.48 [0.41, 0.58]	0.50 [0.41, 0.61]	0.52 [0.40, 0.68]	0.50 [0.41, 0.62]	0.004
Neut%	56.32 [51.56, 62.51]	61.21 [54.97, 67.30]	74.98 [67.39, 86.80]	63.03 [56.00, 70.50]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
Neut#	3.27 [2.59, 4.03]	3.46 [2.74, 4.47]	5.99 [4.20, 9.06]	3.73 [2.86, 5.12]	< 0.001
Hct	38.10 [35.88, 41.70]	36.75 [34.05, 39.42]	33.82 [30.33, 37.13]	36.40 [33.43, 39.22]	< 0.001
Eos%	2.30 [1.40, 3.21]	1.77 [1.10, 2.70]	1.06 [0.35, 2.18]	1.70 [0.95, 2.65]	< 0.001
Baso%	0.49 [0.30, 0.60]	0.40 [0.28, 0.58]	0.25 [0.16, 0.40]	0.40 [0.24, 0.55]	< 0.001
Eos#	0.13 [0.08, 0.19]	0.10 [0.06, 0.15]	0.08 [0.03, 0.14]	0.10 [0.05, 0.15]	< 0.001
Baso#	0.03 [0.02, 0.04]	0.02 [0.01, 0.03]	0.02 [0.01, 0.03]	0.02 [0.01, 0.03]	< 0.001
Hb	131.50 [122.00, 143.00]	125.50 [115.67, 135.50]	114.87 [102.16, 126.27]	124.00 [113.33, 134.75]	< 0.001
PLT#	227.00 [199.00, 264.17]	231.38 [192.00, 277.20]	196.47 [135.96, 254.97]	224.83 [183.50, 273.00]	< 0.001
MPV	10.40 [9.90, 11.00]	10.50 [9.97, 11.10]	11.06 [10.35, 11.80]	10.60 [10.00, 11.23]	< 0.001
PDW	12.00 [10.96, 13.30]	11.93 [10.81, 13.34]	13.03 [11.43, 15.00]	12.13 [10.95, 13.58]	< 0.001
Thrombocytocrit	0.24 [0.21, 0.27]	0.24 [0.20, 0.29]	0.22 [0.16, 0.27]	0.24 [0.20, 0.28]	< 0.001
P-LCR%	28.02 [23.89, 33.21]	28.52 [24.17, 33.60]	33.08 [27.27, 38.88]	29.38 [24.55, 34.64]	< 0.001
ALT	21.17 [13.88, 36.00]	23.63 [15.24, 37.00]	27.55 [18.22, 42.69]	24.00 [15.67, 38.00]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
AST	20.00 [16.00, 26.50]	22.00 [17.33, 28.85]	29.50 [22.14, 41.90]	23.00 [18.00, 31.20]	< 0.001
GGT	24.58 [16.00, 41.87]	28.33 [18.00, 47.75]	40.75 [25.50, 66.93]	30.00 [19.00, 51.00]	< 0.001
TBil	8.80 [6.93, 11.57]	8.50 [6.68, 11.00]	10.80 [8.02, 15.05]	8.84 [6.90, 11.77]	< 0.001
DBIL	3.30 [2.71, 4.10]	3.46 [2.80, 4.44]	5.07 [3.60, 7.29]	3.63 [2.90, 4.90]	< 0.001
IBIL	5.57 [4.24, 7.40]	4.97 [3.80, 6.60]	5.44 [4.22, 7.56]	5.13 [3.90, 6.82]	< 0.001
ALB	41.80 [40.00, 43.80]	37.64 [34.70, 40.65]	33.62 [30.84, 35.80]	37.10 [33.93, 40.50]	< 0.001
GLO	27.92 [26.15, 30.31]	30.00 [27.27, 32.92]	32.14 [28.40, 35.72]	30.13 [27.27, 33.40]	< 0.001
TP	69.78 [67.46, 72.93]	68.10 [65.15, 70.95]	65.67 [61.62, 69.26]	67.80 [64.63, 70.85]	< 0.001
ALB/GLO	1.49 [1.36, 1.66]	1.26 [1.09, 1.46]	1.07 [0.91, 1.24]	1.25 [1.05, 1.45]	< 0.001
Crea	67.67 [58.00, 77.00]	67.50 [57.00, 79.58]	72.88 [57.67, 93.89]	68.33 [57.00, 82.00]	< 0.001
Urea	4.50 [3.90, 5.60]	4.35 [3.60, 5.19]	6.20 [4.70, 9.83]	4.60 [3.78, 5.70]	< 0.001
UA	321.00 [256.00, 387.15]	271.33 [221.60, 330.42]	233.79 [173.73, 310.33]	268.17 [214.44, 333.35]	< 0.001
TC	4.44 [3.81, 5.07]	4.13 [3.60, 4.71]	3.57 [2.93, 4.31]	4.05 [3.47, 4.68]	< 0.001
K <sup>+</sup>	4.22 [4.07, 4.47]	4.25 [4.00, 4.48]	4.33 [4.06, 4.66]	4.26 [4.02, 4.50]	< 0.001
Na <sup>+</sup>	140.80 [139.70, 141.80]	140.17 [138.75, 141.50]	139.49 [137.40, 141.57]	140.13 [138.60, 141.53]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
Cl <sup>-</sup>	102.20 [100.90, 103.50]	101.72 [100.10, 103.22]	100.38 [98.04, 102.99]	101.60 [99.72, 103.22]	< 0.001
Ca	2.27 [2.20, 2.33]	2.19 [2.13, 2.24]	2.13 [2.06, 2.19]	2.18 [2.12, 2.25]	< 0.001
Glu	5.09 [4.75, 5.50]	5.54 [5.03, 6.54]	6.94 [5.87, 9.08]	5.69 [5.07, 6.99]	< 0.001
LDH	182.00 [162.00, 201.50]	206.00 [178.00, 241.25]	290.20 [234.50, 429.20]	213.85 [181.68, 260.83]	< 0.001
ALP	63.42 [53.50, 76.00]	65.75 [55.40, 78.50]	76.80 [61.36, 99.83]	67.00 [56.40, 81.94]	< 0.001
CKD-EPI formula	98.65 [90.65, 108.77]	93.79 [82.80, 103.90]	86.18 [67.35, 97.70]	93.30 [80.76, 103.50]	< 0.001
TT	16.10 [15.40, 16.60]	16.50 [15.90, 17.18]	16.51 [15.76, 17.80]	16.45 [15.80, 17.20]	< 0.001
PT	13.30 [13.00, 13.70]	13.53 [13.10, 14.00]	14.37 [13.67, 15.62]	13.63 [13.20, 14.20]	< 0.001
APTT	38.10 [35.90, 40.70]	38.20 [35.74, 41.30]	40.10 [36.79, 44.53]	38.50 [35.90, 41.80]	< 0.001
PT-INR	1.01 [0.98, 1.05]	1.03 [1.00, 1.08]	1.12 [1.04, 1.24]	1.04 [1.00, 1.10]	< 0.001
D-Dimer	0.26 [0.22, 0.39]	0.55 [0.30, 1.11]	2.27 [1.05, 4.27]	0.66 [0.32, 1.59]	< 0.001
Fbg	3.10 [2.74, 3.64]	4.06 [3.34, 4.89]	4.32 [3.58, 5.22]	4.03 [3.28, 4.90]	< 0.001
PTA	98.00 [92.75, 103.42]	95.00 [89.00, 101.00]	84.67 [73.00, 93.71]	93.67 [86.33, 100.00]	< 0.001
PaO <sub>2</sub>	110.00 [92.60, 137.00]	116.00 [96.07, 149.33]	102.33 [77.82, 139.07]	112.00 [90.40, 144.00]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
SaO <sub>2</sub>	98.20 [97.30, 99.00]	98.30 [97.10, 99.10]	96.58 [92.73, 98.60]	97.90 [95.96, 99.00]	< 0.001
PaCO <sub>2</sub>	42.50 [40.20, 44.80]	41.20 [37.85, 43.90]	38.45 [34.31, 43.61]	40.70 [36.60, 43.80]	< 0.001
AB	24.70 [23.20, 25.90]	24.50 [22.92, 25.81]	24.60 [21.90, 26.86]	24.50 [22.70, 26.02]	0.572
SB	24.30 [23.55, 25.10]	24.40 [23.20, 25.40]	24.82 [22.80, 26.75]	24.50 [23.20, 25.86]	0.107
BE	-0.10 [-1.05, 0.80]	-0.10 [-1.40, 1.10]	0.55 [-1.90, 2.60]	0.10 [-1.50, 1.70]	0.067
SBE	0.10 [-0.90, 1.20]	0.10 [-1.40, 1.38]	0.40 [-2.22, 2.60]	0.20 [-1.50, 1.80]	0.317
Blood carbon dioxide content	21.00 [19.90, 21.60]	21.50 [20.30, 23.00]	21.90 [19.40, 23.90]	21.60 [20.00, 23.35]	0.258
Calcium ion-PH correction	2.33 [2.19, 2.42]	2.30 [2.19, 2.41]	2.35 [2.23, 2.44]	2.32 [2.20, 2.42]	< 0.001
IL-6	2.79 [1.89, 5.26]	5.18 [2.79, 12.50]	24.90 [9.50, 76.53]	6.64 [3.10, 20.44]	< 0.001
IL-10	6.45 [6.12, 7.90]	7.20 [5.90, 9.78]	10.60 [7.66, 18.30]	8.30 [6.30, 12.96]	< 0.001
IL-8	9.00 [7.05, 13.12]	11.00 [7.90, 17.52]	19.60 [12.21, 40.29]	12.28 [8.30, 21.30]	< 0.001
TNF- $\alpha$	7.30 [6.07, 8.80]	7.80 [6.30, 9.90]	10.59 [8.00, 15.48]	8.25 [6.58, 10.60]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
IL-1 $\beta$	9.75 [7.20, 15.15]	8.70 [6.40, 12.10]	9.11 [6.80, 15.41]	8.80 [6.60, 13.20]	0.074
IL-2R	293.25 [234.25, 405.00]	441.50 [310.00, 623.50]	780.61 [519.26, 1179.76]	473.50 [317.00, 705.47]	< 0.001
Ferr	240.30 [121.80, 394.30]	428.80 [232.40, 682.65]	908.59 [496.69, 1620.17]	484.30 [266.97, 864.76]	< 0.001
ESR	9.00 [5.50, 17.25]	25.00 [12.00, 46.00]	37.00 [21.25, 60.00]	26.50 [13.00, 49.90]	< 0.001
HS-CRP	1.23 [0.60, 3.32]	5.87 [1.48, 20.08]	38.49 [16.14, 83.70]	7.91 [1.67, 28.37]	< 0.001
PCT	0.05 [0.04, 0.06]	0.06 [0.04, 0.08]	0.15 [0.07, 0.61]	0.06 [0.04, 0.10]	< 0.001
NT-ProBNP	37.50 [18.25, 69.00]	78.25 [34.00, 180.00]	552.12 [187.52, 1923.39]	101.50 [41.00, 312.25]	< 0.001
Mb	31.20 [26.45, 40.65]	32.30 [25.08, 44.75]	70.00 [38.17, 165.09]	35.03 [26.20, 56.80]	< 0.001
CK	66.25 [48.56, 90.88]	52.00 [37.00, 74.75]	59.92 [36.38, 126.54]	54.63 [37.60, 83.00]	< 0.001

(continued)

**Table 4.** (continued)

	Moderate	Severe	Critical	Overall	p
CK-MB	0.60 [0.40, 0.82]	0.60 [0.40, 0.90]	1.15 [0.63, 2.53]	0.67 [0.40, 1.10]	< 0.001
HS-CTNI	3.15 [2.40, 4.65]	4.60 [2.90, 8.50]	15.56 [5.61, 71.00]	5.65 [3.20, 12.90]	< 0.001

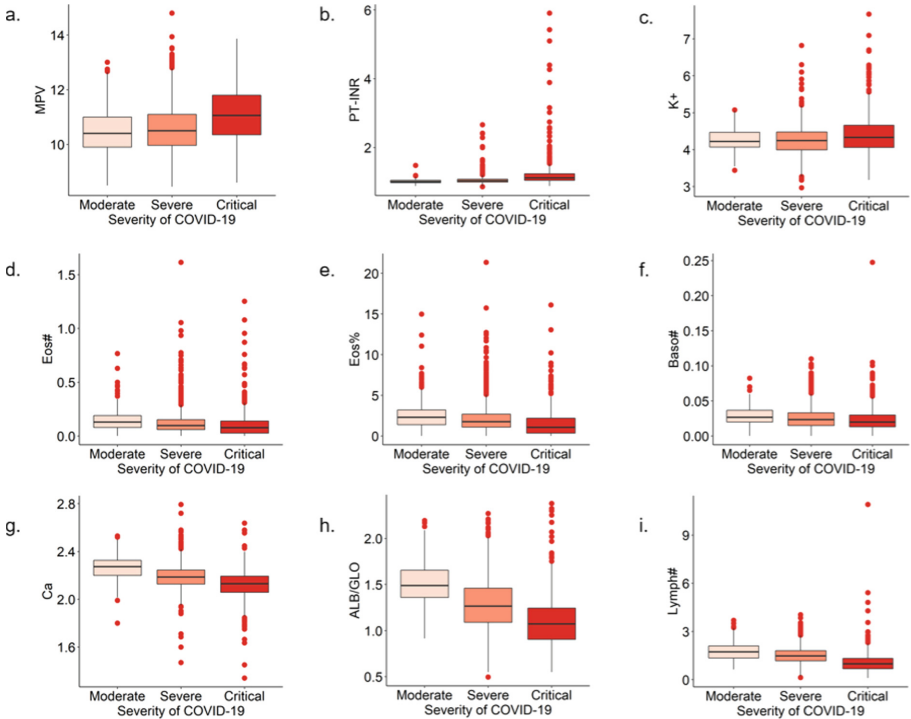
WBC#: White Blood Cell Count; RBC#: Red Blood Cell Count; MCV: Mean Corpuscular Volume; RDW-CV: Red Cell Volume Distribution Width-Coefficient of Variation; RDW-SD: Red Cell Volume Distribution Width-Standard Deviation; Lymph%: Lymphocyte Percentage; Mono%: Monocyte Percentage; Neut%: Neutrophil Percentage; Neut#: Neutrophil Count; Hct: Hematocrit; Hb: Hemoglobin; PLT#: Platelet Count; PDW: Platelet Distribution Width; P-LCR%: Platelet Large Cell Ratio; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-Glutamyltransferase; TBil: Total Bilirubin; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; ALB: Albumin; GLO: Globulin; TP: Total Protein; Crea: Creatinine; UA: Uric Acid; TC: Total Cholesterol; K<sup>+</sup>: Potassium Ions; Glu: Glucose; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; CKD-EPI formula: Estimation of Glomerular Filtration Rate; TT: Thrombin Time; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; Fbg: Fibrinogen; PTA: Prothrombin Time Activity; PaO<sub>2</sub>: Partial Pressure of Oxygen; SaO<sub>2</sub>: Oxygen Saturation; PaCO<sub>2</sub>: Partial Pressure of Carbon Dioxide; IL: Interleukin; TNF- $\alpha$ : Tumor Necrosis Factor- $\alpha$ ; Ferr: Ferritin; ESR: Erythrocyte Sedimentation Rate; HS-CRP: Hypersensitive C-reactive Protein; PCT: Procalcitonin; NT-ProBNP: N-Terminal Pro-Brain Natriuretic Peptide; Mb: Myoglobin; CK: Creatine Kinase; CK-MB: Creatine Kinase Isoenzyme MB; HS-CTNI: Hypersensitive Cardiac Troponin I.

By univariate Cox regression, several indexes including RBC#, MCH, Mono#, Neut#, UA, Fbg, PaCO<sub>2</sub>, Calcium ion -PH correction, and ESR showed lower statistical significance (p > 0.01). Larger MPV, PT-INR, and K + are associated with lower survival, whereas larger Eos#, Baso#, Baso%, Ca, ALB/GLO, Lymph#, and Eos% are associated with better survival (Table 5).

## 4 Discussion

Aging is associated with endothelial dysfunction, contributing to vascular disease and cardiovascular disease in the elderly [22]. Sex differences in immune response are the basis of COVID-19 disease outcomes [23]. High physiological concentrations of the steroid hormones 17 $\beta$ -estradiol and progesterone are powerful immunomodulators [25]. The combination of 17 $\beta$ -estradiol and progesterone is a potential therapeutic approach. Diabetes is associated with immune disorders, which may equate to accelerated aging. Patients with underlying cardiovascular disease, including hypertension, coronary heart disease, and cardiomyopathy are more likely to develop more severe adverse outcomes when myocardial injury occurs after COVID-19 infection and face a higher death risk [24]. Consider prioritizing and more aggressive treatment for COVID-19 patients based on the presence of underlying cardiovascular disease.

The P value of antiviral therapy was not less than 0.01 in multivariate COX analysis results, and reached significant level in univariate COX, which may be affected



**Fig. 4.** Boxplots of laboratory indices and severity of COVID-19. A-plot to i-plot are boxplots of indicator MPV (a), PT-INR (b),  $K^+$  (c), Eos# (d), Eos% (e), Baso# (f), Ca (g), ALB/GLO (h), and Lymph# (i) for different covid-19 severities, respectively.

by the difference of multiple antiviral drugs. Kaplan-Meier plots showed a significant improvement in the likelihood of survival of patients treated with Arbidol. Arbidol showed beneficial effects on fever recovery, viral clearance and shorter hospital stay in these patients, especially in males [26]. Arbidol monotherapy is more effective than lopinavir/ritonavir in treating COVID-19 [27]. Arbidol significantly contributed to clinical and laboratory improvement compared to Kaletra in a recent randomized controlled trial (IRCT 20180725040596N2) [28].

We used the Kaplan-Mayer method and Cox regression analysis to show the positive effect of TCM treatment on the patients' prognosis. This indication may increase the testing of the efficacy of TCM in clinical trials. Early combination of Lianhuaqingwen and Arbidol significantly accelerated recovery in patients with moderate COVID-19, but not in patients with severe COVID-19 [29]. SARS-CoV-2 infection weakens the immune system and increases the risk of bacterial infections. Patients treated with antibiotics showed a symbiosis of bacterial infections. However, current antibiotics are ineffective at suppressing bacterial infections, which may be influenced by the very high rate (74.5%) the use of antimicrobial therapy in critically ill patients [30]. For example, prescription drugs are significantly higher than the estimated prevalence of mixed bacterial infections; unnecessary antibiotic use may be high in patients with COVID-19; and antimicrobial

**Table 5.** Univariate Cox regression of laboratory indices.

	Beta	HR (95% CI for HR)	wald.test	p. value
WBC#	0.29	1.34 (1.3–1.4)	679	<0.001
RBC#	0.000851	1 (1–1)	3.43	0.0641
MCV	0.0679	1.07 (1–1.1)	19.6	<0.001
MCHC	–0.0152	0.985 (0.97–1)	6.85	0.00889
MCH	0.0592	1.06 (1–1.1)	3.34	0.0677
RDW-CV	0.198	1.22 (1.2–1.3)	99.2	<0.001
RDW-SD	0.0917	1.1 (1.1–1.1)	160	<0.001
Lymph%	–0.279	0.756 (0.74–0.78)	391	<0.001
Lymph#	–3.97	0.0188 (0.013–0.028)	384	<0.001
Mono%	–0.671	0.511 (0.48–0.54)	511	<0.001
Mono#	0.00404	1 (1–1)	3.65	0.056
Neut%	0.195	1.22 (1.2–1.2)	466	<0.001
Neut#	0.000191	1 (1–1)	4.5	0.0338
Hct	–0.0989	0.906 (0.88–0.93)	44.3	<0.001
Eos%	–2.89	0.0553 (0.039–0.079)	245	<0.001
Baso%	–9.33	8.91e–05 (2.6e–05–0.00031)	218	<0.001
Eos#	–28.5	4.2e–13 (5.8e–15–3.1e–11)	170	<0.001
Baso#	–26.5	3.01e–12 (1.8e–17–5e–07)	18.7	<0.001
Hb	–0.0284	0.972 (0.96–0.98)	48.6	<0.001
PLT#	–0.0205	0.98 (0.98–0.98)	370	<0.001
MPV	1.09	2.97 (2.6–3.4)	247	<0.001
PDW	0.378	1.46 (1.4–1.5)	283	<0.001
thrombocytocrit	–18.4	1.06e–08 (1.3e–09–8.7e–08)	294	<0.001
P-LCR%	0.137	1.15 (1.1–1.2)	229	<0.001
ALT	0.00245	1 (1–1)	36	<0.001
AST	0.00416	1 (1–1)	149	<0.001
GGT	0.00434	1 (1–1)	20.5	<0.001
TBil	0.0148	1.01 (1–1)	203	<0.001
DBIL	0.021	1.02 (1–1)	218	<0.001

*(continued)*

**Table 5.** (continued)

	Beta	HR (95% CI for HR)	wald.test	p. value
IBIL	0.0286	1.03 (1–1)	98.2	<0.001
ALB	−0.351	0.704 (0.68–0.73)	518	<0.001
GLO	0.0849	1.09 (1.1–1.1)	38.5	<0.001
TP	−0.163	0.849 (0.83–0.87)	171	<0.001
ALB/GLO	−4.75	0.00866 (0.0044–0.017)	186	<0.001
Crea	0.00239	1 (1–1)	110	<0.001
Urea	0.108	1.11 (1.1–1.1)	631	<0.001
UA	0.00146	1 (1–1)	3.65	0.0561
TC	−1.29	0.275 (0.23–0.32)	243	<0.001
K <sup>+</sup>	1.44	4.21 (3.2–5.5)	115	<0.001
Na <sup>+</sup>	0.15	1.16 (1.1–1.2)	129	<0.001
Cl <sup>−</sup>	0.119	1.13 (1.1–1.2)	57.8	<0.001
Ca	−7.05	0.000871 (0.00044–0.0017)	417	<0.001
Glu	0.182	1.2 (1.2–1.2)	319	<0.001
LDH	0.00494	1 (1–1)	856	<0.001
ALP	0.00486	1 (1–1)	99	<0.001
CKD-EPI formula	−0.0361	0.965 (0.96–0.97)	195	<0.001
TT	0.0452	1.05 (1–1.1)	56.6	<0.001
PT	0.17	1.19 (1.2–1.2)	505	<0.001
APTT	0.112	1.12 (1.1–1.1)	191	<0.001
PT-INR	1.31	3.69 (3.3–4.2)	433	<0.001
D-Dimer	0.21	1.23 (1.2–1.3)	422	<0.001
Fbg	0.0398	1.04 (0.92–1.2)	0.38	0.539
PTA	−0.0874	0.916 (0.91–0.92)	717	<0.001
PaO <sub>2</sub>	−0.0282	0.972 (0.97–0.98)	61.1	<0.001
SaO <sub>2</sub>	−0.108	0.897 (0.88–0.91)	147	<0.001
PaCO <sub>2</sub>	−0.0153	0.985 (0.96–1)	0.96	0.327
AB	−0.143	0.867 (0.82–0.92)	25	<0.001
SB	−0.189	0.828 (0.78–0.88)	35.3	<0.001
BE	−0.152	0.859 (0.82–0.9)	42.5	<0.001
SBE	−0.148	0.862 (0.82–0.91)	35.7	<0.001

(continued)

**Table 5.** (continued)

	Beta	HR (95% CI for HR)	wald.test	p. value
Blood carbon dioxide content	-0.127	0.88 (0.83–0.94)	15.7	<0.001
Calcium ion–PH correction	0.959	2.61 (0.9–7.6)	3.13	0.0769
IL-6	0.00279	1 (1–1)	302	<0.001
IL-10	0.00571	1.01 (1–1)	48.8	<0.001
IL-8	0.00132	1 (1–1)	88.8	<0.001
TNF- $\alpha$	0.0454	1.05 (1–1.1)	232	<0.001
IL-1 $\beta$	0.0179	1.02 (1–1)	14.5	<0.001
IL-2R	0.000974	1 (1–1)	318	<0.001
Ferr	0.000183	1 (1–1)	148	<0.001
ESR	0.00563	1.01 (1–1)	3.27	0.0704
HS-CRP	0.0208	1.02 (1–1)	823	<0.001
PCT	0.147	1.16 (1.1–1.2)	207	<0.001
NT-ProBNP	9.06E–05	1 (1–1)	252	<0.001
Mb	0.00532	1.01 (1–1)	461	<0.001
CK	0.000887	1 (1–1)	116	<0.001
CK-MB	0.0348	1.04 (1–1)	147	<0.001
HS-CTNI	0.000605	1 (1–1)	179	<0.001

resistance may be associated with harm to patients [31]. All these results indicate a more rational use of antibacterial.

We found that larger MPV, PT-INR, and the higher K<sup>+</sup> concentration were associated with lower survival, while larger EOS#, BASO#, BASO%, Ca, ALB/GLO, Lymph#, and EOS% were associated with better survival, indicating greater attention to these physiological parameters during the patient's disease course.

To sum up, from this perspective studies, the doctors need to increase attention to elderly patients and patients with comorbidities, expand the use of TCM and rationalize the use of antibacterial in clinical practice, and pay attention to the changes of physiological parameters such as MPV, PT-INR, K<sup>+</sup>, EOS#, BASO#, BASO%, Ca, ALB/GLO, Lymph#, and EOS%.

## References

1. Naja, M., Wedderburn, L., Ciurtin, C.: COVID-19 infection in children and adolescents. *Br. J. Hosp. Med. (Lond)* **81**(8), 1–10 (2020)
2. Chen, N., et al.: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* **395**(10223), 507–513 (2020)

3. Chu, C.M., et al.: Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* **59**(3), 252–256 (2004)
4. Yang, C., et al.: Effectiveness of arbidol for COVID-19 prevention in health professionals. *Front Public Health* **8**, 249 (2020)
5. Vankadari, N.: Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. *Int. J. Antimicrob. Agents* **56**(2), 105998 (2020)
6. Padhi, A.K., Seal, A., Masood Khan, J., Ahamed, M., Tripathi, T.: Unraveling the mechanism of arbidol binding and inhibition of SARS-CoV-2: Insights from atomistic simulations. *Eur. J. Pharmacol.* **894**, 173836 (2021). <https://doi.org/10.1016/j.ejphar.2020.173836>
7. Blaising, J., Polyak, S.J., Pécheur, E.I.: Arbidol as a broad-spectrum antiviral: an update. *Antiviral Res.* **107**, 84–94 (2014)
8. Wolfson, J.S., Hooper, D.C.: The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. *Antimicrob. Agents Chemother.* **28**(4), 581–586 (1985)
9. Correia, S., et al.: Mechanisms of quinolone action and resistance: where do we stand? *J. Med. Microbiol.* **66**(5), 551–559 (2017)
10. Marciniec, K., Beberok, A., Pęczak, P., Boryczka, S., Wrześniok, D.: Ciprofloxacin and moxifloxacin could interact with SARS-CoV-2 protease: preliminary in silico analysis. *Pharmacol. Rep.* **72**(6), 1553–1561 (2020). <https://doi.org/10.1007/s43440-020-00169-0>
11. Scroggs, S.L.P., et al.: Fluoroquinolone antibiotics exhibit low antiviral activity against SARS-CoV-2 and MERS-CoV. *Viruses* **13**(1), 8 (2020). <https://doi.org/10.3390/v13010008>
12. Schögler, A., et al.: Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. *Eur. Respir. J.* **45**(2), 428–439 (2015)
13. Gielen, V., Johnston, S.L., Edwards, M.R.: Azithromycin induces anti-viral responses in bronchial epithelial cells. *Eur. Respir. J.* **36**(3), 646–654 (2010)
14. Wang, C., et al.: Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial. *Ann. Intern. Med.* **155**(4), 217–225 (2011)
15. Zhou, Z., et al.: Honeysuckle-encoded atypical microRNA2911 directly targets influenza a viruses. *Cell Res.* **25**(1), 39–49 (2015)
16. Zhang, D., et al.: The clinical benefits of Chinese patent medicines against COVID-19 based on current evidence. *Pharmacol. Res.* **157**, 104882 (2020)
17. Akalın, E., et al.: Traditional Chinese medicine practices used in COVID-19 (Sars-cov 2/Coronavirus-19) treatment in clinic and their effects on the cardiovascular system. *Arch. Turk. Soc. Cardiol.* **48**(4), 410–424 (2020)
18. Nile, S.H., Kai, G.: Recent clinical trials on natural products and traditional chinese medicine combating the COVID-19. *Indian J. Microbiol.* **61**(1), 10–15 (2020). <https://doi.org/10.1007/s12088-020-00919-x>
19. Yang, R., et al.: Chemical composition and pharmacological mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against Coronavirus Disease 2019 (COVID-19): in silico and experimental study. *Pharmacol. Res.* **157**, 104820 (2020)
20. Runfeng, L., et al.: Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacol. Res.* **156**, 104761 (2020)
21. Shu, Z., et al.: Clinical features and the traditional Chinese medicine therapeutic characteristics of 293 COVID-19 inpatient cases. *Front. Med.* **14**(6), 760–775 (2020). <https://doi.org/10.1007/s11684-020-0803-8>
22. Ungvari, Z., et al.: Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. *Nat. Rev. Cardiol.* **15**(9), 555–565 (2018)
23. Klein, S.L., Marriott, I., Fish, E.N.: Sex-based differences in immune function and responses to vaccination. *Trans. R Soc. Trop Med. Hyg.* **109**(1), 9–15 (2015)

24. Guo, T., et al.: Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* **5**(7), 811–818 (2020)
25. Mauvais-Jarvis, F., Klein, S.L., Levin, E.R.: Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinology* **161**(9), bqaa127 (2020). <https://doi.org/10.1210/endo/bqaa127>
26. Gao, W., et al.: Clinical features and efficacy of antiviral drug, Arbidol in 220 nonemergency COVID-19 patients from East-West-Lake Shelter Hospital in Wuhan: a retrospective case series. *Virolog. J.* **17**(1), 162 (2020)
27. Zhu, Z., et al.: Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J. Infect.* **81**(1), e21–e23 (2020)
28. Nojomi, M., et al.: Effect of Arbidol (Umifenovir) on COVID-19: a randomized controlled trial. *BMC Infect. Dis.* **20**(1), 954 (2020)
29. Fang, J., et al.: Efficacy of early combination therapy with Lianhuaqingwen and Arbidol in moderate and severe COVID-19 patients: a retrospective cohort study. *Front. Pharmacol.* **11**, 560209 (2020)
30. Langford, B.J., et al.: Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin. Microbiol. Infect.* **27**(4), 520–531 (2021). <https://doi.org/10.1016/j.cmi.2020.12.018>
31. Majumder, M.A.A., et al.: Antimicrobial stewardship: fighting antimicrobial resistance and protecting global public health. *Infect. Drug Resist.* **13**, 4713–4738 (2020)