Survival Factors and Metabolic Pathogenesis in Elderly Patients (≥ 65) with COVID-19 : A multi-center study of 223 Cases

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Abstract

Background

Elderly patients infected with COVID-19 are reported to be facing a substantially increased risk of mortality. Clinical characteristics, treatment options, and potential survival factors remain under investigation. This study aimed to fill this gap and provide clinically relevant factors associated with survival of elderly patients with COVID-19.

Methods

In this multi-center study, elderly patients (age ≥ 65 years old) with laboratory-confirmed COVID-19 from 4 Wuhan hospitals were included. The clinical end point was hospital discharge or deceased with last date of follow-up on Mar. 08, 2020. Clinical, demographic, and laboratory data were collected.

Univariate and multivariate analysis were performed to analyze survival and risk factors. A metabolic flux analysis using a large-scale molecular model was applied to investigate the pathogenesis of SARS-CoV-2 with regard to metabolism pathways.

Results

A total of 223 elderly patients infected with COVID-19 were included, 91 (40.8%) were discharged and 132 (59.2%) deceased. Acute respiratory distress syndrome (ARDS) developed in 140 (62.8%) patients, 23 (25.3%) of these patients survived. Multivariate analysis showed that potential risk factors were D-Dimer (odds ratio: 1.13 [95% CI 1.04 - 1.22], $p=0.005$), immune-related metabolic index (6.42 [95% CI 2.66 - 15.48], $p<0.001$), and neutrophil-to-lymphocyte ratio (1.08 [95% CI 1.03 - 1.13], $p<0.001$). Elderly patients receiving interferon therapy showed an increased probability of survival (0.29 [95% CI

0.17 - 0.51], $p<0.001$). Based on these factors, an algorithm (AlgSurv) was developed to predict survival for elderly patients. The metabolic flux analysis showed that 12 metabolic pathways including phenylalanine (odds ratio: 28.27 [95% CI 10.56 - 75.72], $p<0.001$), fatty acid (15.61 [95% CI 6.66 - 36.6], $p<0.001$), and pyruvate (12.86 [95% CI 5.85 - 28.28], $p<0.001$) showed a consistently lower flux in the surviving versus the deceased subgroup. This may reflect a key pathogenesis of COVID-19 infection.

Conclusion

Although a high mortality has been reported for elderly patients with COVID-19, in this analysis, several factors such as interferon therapy and activity of metabolic pathways were found to be associated with survival of elderly patients. Based on these findings, the survival algorithm (AlgSurv) was developed to assist the clinical stratification for elderly patients. Deregulation of metabolic pathways revealed in this study may aid in the drug development against COVID-19.

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a nonsegmented, single-stranded, and positive-sense RNA genome, recently discovered and categorized as the newest and seventh member of the Coronaviride family¹. As of Mar. 11, 2020, the world health organization (WHO) has officially declared the disease caused by SARS-CoV-2 a pandemic², following the initial outbreak started in Dec. 2019 in Wuhan, China. Currently, this epidemic is causing a substantial number of casualties worldwide³. The rapidly evolving situation and an increasing number of deaths has created a sense of urgency among scientists, leading to a large number of observational studies characterizing the clinical and epidemiological properties of SARS-CoV-2 pneumonia and its spread^{4 5 6}. Several of these studies investigated potential risk factors associated with the course of the coronavirus disease 2019 (COVID-19)^{7 8 9 10}. Based on these results, age, comorbidity, abnormal change-levels of cytokine storm, and immune cells may be potential risk factors. Especially, a recent report by Zhou et al provided compelling evidence to support these risk factors¹¹. However, the pathogenesis of SARS-CoV-2 and potential prognostic factors associated with SARS-CoV-2 pneumonia have not yet been determined.

This multi-center study investigated these potential factors associated with survival in an age-specific (≥ 65 years at diagnosis) cohort and attempted to analyze the pathogenesis of SARS-CoV-2. The developed algorithm was able to dichotomize elderly patients according to their likelihood of survival. Our finding may assist other medical units to improve the prognosis of elderly patients with COVID-19 and provide evidence for a more detailed understanding of pathogenesis in SARS-CoV-2 pneumonia.

Methods

Study design

This retrospective and multi-center cohort study was conducted in 4 different hospitals in Wuhan: TJH, RHWU, WPH, and WNH (Supplement Figure 1). These 4 hospitals are government designated hospitals assigned to treat patients with SARS-CoV-2 pneumonia. Clinical end point for this study was life status (discharged or deceased) at the end of the observation period.

Patients

Out of the total 223 recruited patients, 101 were from TJH, 63 were from WPH, 38 were from WNH, and 21 were from RHWU. The inclusion criteria for study participants are 1) age ≥ 65 and confirmed diagnosis of SARS-CoV-2 pneumonia in one of the four study sites, 2) Positive result of F137nCoV test for SARS-CoV-2 pneumonia, 3) CT-scan with a clear sign of viral pneumonia of the lungs, 4) available data on the clinical outcome. The exclusion criteria are 1) age < 65 , or deceased within a day after hospital admission, or no related health records, 2) no data on clinical outcome, 3) suspected cases without positive result of F137nCoV test, or confirmed cases using a different test, and 4) refusal to participate in this study. All data was recorded on the day of hospital admission following an informed consent procedure in an electronic medical system. Data was retrieved and sorted by professional medical staff. If missing values

were found, a direct patient interview or telephone communication took place to attempt to obtain the missing information. None of this data has been published previously.

Treatment Protocol and discharged Criteria for SARS-CoV-2 Pneumonia

The protocol for treating infected patients can be summarized according to two aspects: 1) symptomatic treatment as a basis, active prevention of complications, treatment of underlying diseases, prevention of secondary infections, and timely support of organ vital function, 2) oxygen-supply therapy including nasal catheter oxygen inhalation, oxygen-supply high nasal flow, invasive and non-invasive mechanical ventilation, or ECMO.

The criteria considered as discharged from SARS-CoV-2 pneumonia with subsequent hospital discharge includes: 1) stable and normal body temperature for > 3 days, 2) clear reduction of pneumonia inflammation examined via CT-scan, 3) double negative results of the F137nCoV test with at least 1 day interval, and 4) no comorbidity requiring transfer to another clinical department.

Detection of SARS-CoV-2 with F137nCoV Test

Upper respiratory tract samples from each patient were collected using nasopharyngeal and oropharyngeal swabs. Synthetic fiber swabs with plastic shafts were used to reduce any contamination risk. Subsequently RNA extraction (2–3ml) from each sample was performed with a viral nucleic acid Kit (Roche). The RNA samples were then purified using QIAquick Gel Extraction Kit (Qiagen). The products were used for a real-time reverse transcription PCR (RT-PCR) assay (F137nCoV), which detected and matched the COVID-19 RNA. A positive result of F137nCoV was defined with Ct (cycle- count threshold)-value < 37 while a Ct-value $\geq$ 40 was evaluated as a negative result. A Ct-value between 37 and 40 required repeated testing¹².

Estimation of Metabolic Flux and IM.Index

For the calculation of IM.Index (immune-related metabolic index) of each patient, a large-scale model was applied¹³. Laboratory values from each patient were applied as input to initialize the flux of corresponding metabolic reactions (Supplement Figure 2):

$$I_j(\text{reaction}, \text{role}) = \prod_{c(\text{object})} \text{objects} \in \text{reactant}(\text{reaction}, \text{role}).\text{objects} \quad (1)$$

role $\in \{e, g, i, s, \text{tr}(a), \text{tr}(r)\}$, (e: enzyme; g: gene; i: inhibitor; s: substrate; tr(a): transcriptional activator, tr(r): transcriptional repressor).

Subsequently, the flux of a metabolic pathway, flux(P), was calculated as the sum of intensities in reactions within this pathway deducted by the intensities of reactions going out into crosstalk pathways.

$$\text{flux}(P) = \left(\sum_{i \in P} I_i(\text{reaction}, \text{role}) / N(P) \right) - \text{flux}(\text{Crosstalk}(P)) \quad (3)$$

N(P): the number of reactions of the pathway P; Crosstalk(P): the crosstalks pathways related to the pathway P.

$$\text{IM.Index}[\text{patient}] = \sum \text{flux}(p) / N(P)$$

Statistical Considerations

The time interval for OS was calculated starting from the date of hospital admission until death from SARS-CoV-2 pneumonia or the date of the last follow-up. An event was considered death due to SARS-CoV-2 pneumonia. Mortality was determined via the vital status of each patient at the end of the study observation period. For data analysis continuous variables were reported as median (IQR) and categorical variables were shown as frequency or percentage. The least absolute shrinkage and selection operator (LASSO) was used for multivariable selection¹⁴. The area under curve (AUC) value was used to evaluate the accuracy of the vital status prediction. The Cox proportional hazards regression analysis was used to evaluate the prediction of the PM for OS. Proportional hazards assumption for the Cox proportional hazards regression model was assessed via the Schoenfeld residuals test. The 95% confidence intervals (CIs) were estimated via 5,000 bootstraps replicates. All statistical analyses were performed using R (version 3.6) and SAS (version 9.4). A $p < 0.05$ was considered as statistically significant.

Role of Funding

The funders were not involved in any activities of this study, aside from providing financing.

Results

Demographic and Clinical Features in the Elderly Cohort

The elderly cohort (age ≥ 65 years old) consisting of 223 patients, which were admitted between Jan. and Feb. 2020 to four different Wuhan hospitals: 101 from TJH, 63 from WPH, 38 from WNH, and 21 from RHWU. As shown in table 1, 132 (59.2%) patients died during hospitalization, 91 (40.8%) recovered and attained discharge criteria. The median age of this elderly cohort was 72.0 year (IQR 68.0 - 77.5). There was no significant age difference between both subgroups (survival vs. deceased). Gender was almost equally distributed (50.2% [M] vs. 49.8% [F]). Thirty-five (15.7%) patients were treated in an intensive care unit (ICU), and one of these patients was subsequently discharged. In 140 (62.8%) patients, symptoms of acute respiratory distress syndrome (ARDS) developed with 23 (25.3%) of these patients recovering. The majority of patients (74.4%) were affected by underlying diseases, hypertension (53.4%) being the most

common one (Table 1). The most common initial symptoms were fever (69.5%), cough (51.1%), and dyspnea (31.4%). The median body temperature on admission was 36.7°C (IQR 35.6 - 37.2), no difference of median temperature between both subgroups (survival vs. deceased) was seen. Similarly, both subgroups reported the same median interval (10 days) from symptom onset to hospital admission (Table 1). The hospitalization in the surviving subgroup was significantly longer than that of the deceased group (20.0 days [IQR 15.0 - 25.0] vs. 8.0 days [IQR 5.0 - 13.0]). The majority of patients received antiviral treatments (lopinavir/ritonavir; 96%), antibiotics (86.1%), and corticosteroids (71.3%). Additionally, almost half of patients received interferon (47.1%) and immunoglobulin (48.0%) treatment. In this cohort, the most frequently applied oxygen therapy were UOC (84.8%) and NIMV (43.9%). All key laboratory findings of this cohort are listed in table 1.

Potential Survival Factors Associated with Vital Status for Elderly Patients with COVID-19

The results of an univariate analysis showed that the odds of survival for elder patients with COVID-19 were higher in patients with an elevated lymphocyte count, albumin, creatinine, and blood platelet count (Table 2). Among the recorded comorbidities only hypertension was significantly associated with survival ($p = .042$), others such as diabetes, carcinoma, and coronary diseases did not have any influence on the survival in this cohort (Table 2). Drug treatments including antibiotics (OR: 10.16 [95% CI 3.73 - 27.69], $p < .001$), corticosteroids (OR: 2.03 [95% CI 1.13 - 3.65], $p = 0.018$) and immunoglobulin (OR: 2.43 [95% CI 1.4 - 4.21], $p = 0.002$) negatively influenced on the survival in this cohort, whereas interferon atmothrapy (OR: 0.29 [95% CI 0.17 - 0.51], $p < .001$) showed a positive association with survival. Other potential factors were listed in table 2. Using a multivariate analysis in this cohort (132 survivals vs. 91 deceased), the results showed that three significant survival factors were identified, including decreased D-Dimer, decreased IM.Index, decreased neutrophil-to-lymphocyte ratio (Table 2).

Pathological Alternation from the Admission to Clinical Endpoint

Laboratory markers regarding immunity, inflammation, metabolism, and other physiological functions were tracked from admission to the end point of clinical observation (Fig. 1). Baseline cellular counts of leukocyte and neutrophile increased continuously in deceased than in survival subgroups; whereas severe lymphopenia occurred in deceased subgroup. Levels of blood platelet count, calcium, and albumin were continuously reduced in the deceased subgroup (Fig. 1). From 10 days on, the level of total protein significantly decreased in deceased than in survival subgroup. The level of urea and lactate dehydrogenase were moderately higher in deceased than in survival subgroup (Fig. 1).

Metabolic Alteration between Deceased and Survival in COVID-19

We hypothesized a difference in metabolic pathways between deceased and surviving subgroups. A genome-scale metabolic flux analysis was conducted for both subgroups. The results showed that fluxes from 12 metabolic pathways in the deceased patients were consistently and significantly higher than that of the surviving patients (Fig. 2A). These changes were seen among others in the phenylalanine- (OR: 28.27 [95% CI 10.56 - 75.72], $p < 0.001$), tyrosine- (25.81 [95% CI 9.8 - 67.99], $p < 0.001$), glutathione- (17.23 [95% CI 7.16 - 41.46], $p < 0.001$), purine- (16.34 [95% CI 6.88 - 38.88], $p < 0.001$), fatty acid- (15.61 [95% CI 6.66 - 36.6], $p < 0.001$), pyruvate- (12.86 [95% CI 5.85 - 28.28], $p < 0.001$) -metabolic pathways (Table 3). A similar differences were observed between the patients surviving after ARDS and those who did not (Supplement Figure 3). However, the difference of metabolic flux was not observed between gender. The results of metabolic flux also showed that immune-related metabolic index (IM.Index) was significantly lower in the surviving subgroup than that of the deceased subgroup (9.14 [95% CI 8.86 - 9.34] vs. 9.64 [95% 9.3 - 10.0]; Table 1, Fig. 2C). Further, levels of three cytokines (IL6, IL8, and IL10) showed a similar differentiation between both subgroups (Fig. 2C).

Algorithm for Survival Prediction in Elderly Patients with COVID-19

Given the high mortality rate of elderly patients, an algorithm (AlgSurv) for the prediction of survival was developed based on the weight of the three significant predictors (Table 2). The AlgSurv yielded an AUC of 0.863 (95% CI 0.817 - 0.909) in successfully predicting survival in this cohort as well as a Harrell's c-index of 0.769 (95% CI 0.73 - 0.808) for OS. In this elderly cohort, the AlgSurv was able to define a high-risk subgroup with a significantly lower prognosis (hazard ratio: 5.85 [95% CI 3.76 - 9.08]) versus a low-risk subgroup with a high probability of survival (Fig. 3). The predicted 30-days OS rates of the high- and low-risk subgroups in this cohort is illustrated in Fig. 3 (cutoff ≥ 106 and < 106).

Discussions

In this multi-center study, potential survival factors were analyzed in an elderly cohort of 223 patients suffering from COVID-19, 59.2% of whom later died of the infection. Six survival factors significantly associated with survival were identified including decreased D-Dimer, decreased IM.Index, and decreased neutrophil-to-lymphocyte ratio. Based on these factors, an algorithm AlgSurv was developed, which yielded an AUC of 0.863 for predicting life status and C-index of 0.769 for OS, respectively.

The complicated interaction between the pathogenesis of SARS-CoV-2 and survival factors remains under investigation. It was hypothesized that like other coronavirus SARS-CoV-2 may evolve to alter metabolic pathways in its host to meet a drastically increasing demand of resource for replication and

expansion^{15 16}. In this study, a system-level metabolic flux analysis was performed to assess changes in metabolic pathways characteristic for older patients surviving the infection versus those that did not.

The fluxes of 12 metabolic pathways consistently showed lower flux in surviving versus the deceased subgroup. All of these metabolic pathways were involved with energy and nutrient metabolism such as glucose¹⁷, fatty acid¹⁸ and nucleic acid¹⁹. This finding provides important evidence that metabolism may play an important role in the general pathogenesis of COVID-19.

As the virus replicates itself, a large amount of energy and nutrients are needed and extracted from the metabolism of the host cells²⁰. In cellular metabolism, pyruvate metabolism connects the ATP production from the citric acid cycle with oxidative phosphorylation pathways and many biosynthetic pathways²¹. Moreover, this pathway was recently found to be a predictor of outcome following a H7N9 virus infection²². In our cohort, the flux of fatty acid metabolism was significantly increased in the deceased versus surviving subgroup. Its upregulation could indicate an enhanced virus replication in parallel to the deterioration of the host health condition. Of note, purine release and metabolism has a high impact on inflammatory responses relating to cytokine signaling²³. The enhanced activity of purine metabolism in the deceased subgroup may indicate a strong inflammatory response at system level, which in turn decreases the probability for survival. In addition, the consistently higher level of cytokines (IL6, IL8 and IL10) were found in the deceased than surviving subgroup further confirmed a stronger inflammatory response in this subgroup.

The phenylalanine metabolism was observed to be highly upregulated in the deceased subgroup. These findings indicate that SARS-CoV-2 may function in a similar way as the respiratory syncytial virus²⁴ in utilizing the phenylalanine residue for the production of internal viral protein and its subsequent assembly into viral particles to deteriorate the pneumonia in its host.

Relatively low expressed fluxes in these metabolic pathways in the surviving subgroup may therefore imply that virus replication and related inflammatory responses were not as extensive as that in the deceased subgroup. This may significantly contribute to survival in elderly patients with COVID-19. The immune-related metabolic index (IM.Index) was used to summarize the metabolic flux in a genome-scale model and shown to be significantly lower in the surviving patients. These results suggest that abnormally high metabolic activity during COVID-19 infection may be associated with a weakened immune function, which contributed to a lower probability of survival. The metabolic fluxes of 23 (25.3%) patients surviving ARDSs were also significantly lower than in those not surviving ARDSs. These results imply that patients suffering from ARDS and associated with relatively low metabolic activities have an increased probability for survival.

The majority of patients received antivirals (lopinavir/ritonavir), antibiotics, and corticosteroids. The univariate analysis results showed that application of antibiotics (OR: 10.16) and corticosteroids (OR: 2.03) did not improve survival in this cohort. Only a dose reduction in corticosteroids during the course of treatment had a positive influence on survival. In contrast, patients receiving the interferon α therapy (OR: 0.29) showed a better prognosis in this cohort. The majority of patients (74.4%) in this cohort were

associated with underlying comorbidities. Although hypertension ($p = 0.042$) was slightly related to mortality, diabetics, carcinoma, and coronary heart diseases were not. This contradicts many recent studies that reported a significant association of underlying diseases with the mortality of patients with COVID-19 [8, 11]. The reason for this discrepancy could be that age is a risk factor for the mortality of COVID-19, however, comorbidity itself could only be an independent factor associated with age. In our age-specific cohort study, the influence of age was drastically reduced and therefore the age related dependency of comorbidity was compromised, leading to its dissociation with observed mortality.

Of note, no difference in the time interval from symptom onset to hospital admission was observed between survival and deceased subgroups. Similarly, no difference in body temperature on admission between both subgroups was observed. These results indicated guidelines recommending hospital admission within 10 days and body temperature between 36.5 to 37.2 on admission may be unrelated to the survival of elderly patients with COVID-19.

This study has several limitations. First, we focused only on elderly patients (≥ 65) infected with COVID-19 in Wuhan, China. The case-fatality rate in this study was therefore the highest among all reported studies to the present, and therefore much higher than the true mortality of COVID-19. The developed AlgSurv needs to be further validated with a large international cohort. Further, the treatment benefit of interferon therapy in this cohort needs to be verified in a randomized control trial. The discovered metabolic mechanisms related to the pathogenesis of COVID-19 were derived from this age-specific cohort. Follow-up studies will need to verify this issue in other cohorts.

Conclusion

To our knowledge, our study was the first to investigate an age-specific elderly patient cohort suffering from COVID-19. Although a high mortality has been reported for these patients, several potential survival factors were identified in this study, such as interferon therapy and activity reduction of metabolic pathways. These survival factors may be relevant to improving survival among elderly patients with COVID-19. The developed AlgSurv can be applied upon hospital admission for clinical risk stratification. Deregulation of different metabolic pathways revealed in this study may illustrate potential target for drug development against COVID-19.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics board of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology (No. IRBID:TJ-C 20200107). All participants agreed to take part in this study.

Consent for Publication

All participants agreed to publication

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

All authors declare that there is no conflict of interest to report. All authors completed the unified competing interest form; no support from any organization for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Author Contribution

Q.M., A.W., J.L.: Wrote the manuscript; J.L., S.D., K.H., and U.M.: Statistical analysis; Y.Y., M.L., F.W., K.M.: Data collection; L.W., P.W., H.C., J.L., Y.L.: Data preparation and analysis; J.Z., K.H.: revised the manuscript; X.Y., J.Z.: Conceptualization.

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Tables

Table 1. Clinical characteristics, treatments and laboratory findings

Characteristics	Overall	Survivor	Deceased	<i>P</i> -value
Number of patients	223	91 (40.8)	132 (59.2)	...
Median age, years	72.0 (68.0-77.5)	70.0 (67.0-74.5)	74 (69.0-80.0)	<.001
Sex	...	...	...	0.077
Male	112 (50.2)	39 (42.9)	73 (55.3)	...
Female	111 (49.8)	52 (57.1)	59 (44.7)	...
ICU care	...	...	...	<.001
Yes	35 (15.7)	1 (1.1)	34 (25.8)	...
No	188 (84.3)	90 (98.9)	98 (74.2)	...
Smoking	...	...	...	0.682
Yes	27 (12.1)	12 (13.2)	15 (11.4)	...
No	196 (87.9)	79 (86.8)	117 (88.6)	...
ARDS	140 (62.8)	23 (25.3)	117 (88.6)	
IM.Index	9.38 (9.06-9.78)	9.14 (8.86-9.34)	9.64 (9.30-10.00)	<.001
Comorbidities	166 (74.4)	67 (73.6)	99 (75.0)	0.876
Hypertension	119 (53.4)	41 (45.1)	78 (59.1)	0.042
CVDs	33 (14.8)	10 (11.0)	25 (17.4)	0.249
Diabetics	52 (23.3)	17 (18.7)	35 (26.5)	0.199
Carcinoma	9 (4.0)	3 (6.6)	3 (2.3)	0.164
Initial common symptome	213 (95.5)	86 (94.5)	127 (96.2)	0.744
Fever	155 (69.5)	59 (64.8)	96 (72.7)	0.237
Cough	114 (51.1)	44 (48.4)	70 (53.0)	0.499
Myalgia or Fatigue	43 (19.3)	15 (16.5)	28 (21.2)	0.395
Dyspnea	70 (31.4)	19 (20.9)	51 (38.6)	0.005
Admission body temperature, °C	36.7 (36.5-37.2)	36.7 (36.5-37.2)	36.7 (36.5-37.2)	0.883
Symptom onset to admission, days	10.0 (7.0-14.0)	10.0 (7.0-14.0)	10.0 (6.0-14.0)	0.647
Hospitalization, days	13.0 (7.0-20.0)	20.0 (15.0-25.0)	8.0 (5.0-13.0)	<.001
Systolic pressure, mm Hg	131.0 (120.0-146.0)	128.0 (120.5-141.0)	133 (120.0-148.5)	0.152
Respiratory rate, breaths per min	22.0 (20.0-26.0)	20.0 (20.0-25.0)	22 (20.0-29.3)	0.022
Pulse rate, beats per min	88.0 (80.0-100.5)	84.0 (78.0-96.0)	90 (80.0-103.0)	0.003
Treatments				
Therapy	...	...	...	...
Antibiotics	192 (86.1)	65 (71.4)	127 (96.2)	<.001
Antiviral treatment	214 (96.0)	65 (71.4)	124 (93.9)	0.086
Corticosteroids	159 (71.3)	57 (62.6)	102 (77.3)	0.024
Interferon atmothotherapy	105 (47.1)	59 (64.8)	46 (34.8)	<.001
Immunoglobulin	107 (48.0)	32 (35.2)	75 (56.8)	0.002
Oxygen therapy	213 (95.5)	82 (90.1)	131 (99.2)	0.002
UOC	189 (84.8)	82 (90.1)	107 (81.1)	0.087
HFNO	30 (13.5)	20 (22.0)	10 (7.6)	0.003
NIMV	98 (43.9)	7 (7.7)	91 (68.9)	<.001
IMV	39 (17.5)	1 (1.1)	38 (28.8)	<.001
ECMO	5 (2.2)	0	5 (3.8)	0.081
Laboratory findings				
WBC count, × 10 ⁹ /L	...	...	...	<.001
<3.5	19 (8.5)	9 (9.9)	10 (7.6)	...
3.5-9.5	128 (57.4)	70 (76.9)	58 (43.9)	...
>9.5	76 (34.1)	12 (13.2)	64 (48.5)	...
Neutrophil count, × 10 ⁹ /L	...	...	...	<.001
<1.8	9 (4.0)	5 (5.5)	4 (3.0)	...
1.8-6.3	107 (48.0)	64 (70.3)	43 (32.6)	...

	>6.3	107 (48.0)	22 (24.2)	85 (64.4)	...	
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Lymphocyte count, × 10 ⁹ /L	...	...	...	0.000
<1.1	180 (80.7)	63 (69.2)	117 (88.6)	...
≥1.1	43 (19.3)	28 (30.8)	15 (11.4)	...
PLT count, × 10 ⁹ /L	...	...	...	<.001
<125	57 (25.6)	10 (11.0)	47 (35.6)	...
125-350	157 (70.4)	76 (83.5)	81 (61.4)	...
>350	9 (4.0)	5 (5.5)	4 (3.0)	...
APTT, s	...	...	...	0.017
<29	18 (8.1)	3 (3.3)	15 (11.4)	...
29-42	155 (69.5)	72 (79.1)	83 (62.9)	...
>42	50 (22.4)	16 (17.6)	34 (25.8)	...
PT, s	...	...	...	<.001
≤14.5	139 (62.3)	75 (82.4)	64 (48.5)	...
>14.5	84 (37.7)	16 (17.6)	68 (51.5)	...
D-D dimer, ug/ml FEU	...	...	...	<.001
<0.5	50 (22.4)	39 (42.9)	11 (8.3)	...
≥0.5	173 (77.6)	52 (57.1)	121 (91.7)	...
ALT, U/L	...	...	...	0.553
<33 (female) or 41 (male)	156 (70.0)	66 (72.5)	90 (68.2)	...
≥33 (female) or 41 (male)	67 (30.0)	25 (27.5)	42 (31.8)	...
AST, U/L	...	...	...	<.001
<32 (female) or 40 (male)	112 (50.2)	61 (67.0)	51 (38.6)	...
≥32 (female) or 40 (male)	111 (49.8)	30 (33.0)	81 (61.4)	...
LDH, U/L	...	...	...	<.001
≤214 (female) or 225 (male)	25 (11.2)	20 (22.0)	5 (3.8)	...
>214 (female) or 225 (male)	198 (88.8)	71 (78.0)	127 (96.2)	...
ALP, U/L	...	...	...	<.001
<35 (female) or 40 (male)	12 (5.4)	7 (7.7)	5 (3.8)	...
35-105 (female) or 40-130 (male)	185 (83.0)	83 (91.2)	102 (77.3)	...
>105 (female) or 130 (male)	26 (11.7)	1 (1.1)	25 (18.9)	...
γ-GT, U/L	...	...	...	0.224
<6 (female) or 10 (male)	2 (0.9)	2 (2.2)	0	...
6-42 (female) or 10-71 (male)	170 (76.2)	70 (76.9)	100 (75.8)	...
>42 (female) or 71 (male)	51 (22.9)	19 (20.9)	32 (24.2)	...
Urea, mmol/L	...	...	...	<.001
<2.6 (female) or 3.6 (male)	10 (4.5)	5 (5.5)	5 (3.8)	...
2.6-7.5 (female) or 3.6-9.5 (male)	130 (58.3)	72 (79.1)	58 (43.9)	...
>7.5 (female) or 9.5 (male)	83 (37.2)	14 (15.4)	69 (52.3)	...
Albumin, g/L	...	...	...	<.001
<35	152 (68.2)	48 (52.7)	104 (78.8)	...
≥35	71 (31.8)	43 (47.3)	24 (18.2)	...
Total cholesterol, mmol/L	...	...	...	1.000
<5.18	212 (95.1)	87 (95.6)	125 (94.7)	...
≥5.18	11 (4.9)	4 (4.4)	7 (5.3)	...
Total bilirubin, μmol/L	...	...	...	0.009
<21 (female) or 26 (male)	198 (88.8)	87 (95.6)	111 (84.1)	...
≥21 (female) or 26 (male)	25 (11.2)	4 (4.4)	21 (15.9)	...
hs-CRP, mg/L	...	...	...	<.001
<10.0	26 (11.7)	21 (23.1)	5 (3.8)	...
≥10.0	197 (88.3)	70 (76.9)	127 (96.2)	...

Data are median (IQR), or n (%). ICU = Intensive care unit; ARDS = Acute respiratory distress syndrome; UOC = Usual oxygen care, including standard nasal catheter and facemask inhalation; HFNO = High-flow nasal cannula oxygen; (N)IMV = (Non-) Invasive mechanical ventilation; ECMO = Extracorporeal membrane oxygenation; WBC = White blood cell; PLT = Blood platelet; APTT = Activated partial thromboplastin time; PT = Prothrombin time; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; LDH = Lactate

dehydrogenase; ALP = Alkaline phosphatase; γ -GT = gamma-Glutamyl transpeptidase; hs-CRP = high-sensitivity C-reactive protein.

Table 2. Survival / Risk factors associated with mortality in age-specific patient with COVID-19			t cohort infected
Univariate analysis	AOR (95%CI)	Wald's <i>P</i> -value	
Demographic and clinical characteristics			
Hypertension: 1 vs. 0	1.76 (1.03,3.02)	0.040	
Respiratory rate, breaths per min	1.08 (1.02,1.13)	0.006	
Pulse rate, beats per min	1.03 (1.01,1.05)	0.001	
Treatments			
Antibiotics: 1 vs. 0	10.16 (3.73,27.69)	<.001	
Corticosteroids: 1 vs. 0	2.03 (1.13,3.65)	0.018	
Interferon atmotherapy: 1 vs. 0	0.29 (0.17,0.51)	<.001	
Immunoglobulin: 1 vs. 0	2.43 (1.4,4.21)	0.002	
Noninvasive mechanical ventilation (NIMV): 1 vs.0	27.3 (11.6,64.26)	<.001	
Invasive mechanical ventilation (IMV): 1 vs.0	36.77 (4.94,273.53)	<.001	
Immune components			
White blood cell (WBC) count, ×10 ⁹ /L	1.23 (1.14,1.34)	<.001	
Neutrophil count, ×10 ⁹ /L	1.28 (1.17,1.41)	<.001	
Lymphocyte count, ×10 ⁹ /L	0.2 (0.1,0.41)	<.001	
Neutrophil ratio	1.08 (1.03, 1.21)	<.001	
Lymphocyte ratio	0.12 (0.08, 0.23)	<.001	
Neutrophil / Lymphocyte ratio	1.12 (1.08,1.17)	<.001	
IM.Index	13.82 (6.19,30.83)	<.001	
Other laboratory findings			
Alanine transaminase (ALT), U/L	1.01 (1,1.03)	0.049	
Aspartate aminotransferase (AST), U/L	1.04 (1.02,1.06)	<.001	
Alkaline phosphatase (ALP), U/L	1.02 (1.01,1.04)	<.001	
Lactate dehydrogenase (LDH), U/L	1.0063 (1.0042,1.0085)	<.001	
gamma-Glutamyl transpeptidase (γ-GT), U/L	1.007 (1.0002,1.0139)	0.044	
Total bilirubin, μmol/L	1.11 (1.06,1.17)	<.001	
Albumin, g/L	0.83 (0.77,0.89)	<.001	
Creatine kinase (CK), U/L	1.0078 (1.0009,1.0147)	0.026	
Urea, mmol/L	1.11 (1.05,1.17)	<.001	
Uric acid, μmol/L	1.0025 (1.0005,1.0045)	0.013	
K+, mmol/L	1.63 (1.08,2.46)	0.020	
Na+, mmol/L	1.06 (1.01,1.11)	0.025	
Cl -, mmol/L	1.05 (1,1.09)	0.039	
P, mmol/L	9.36 (2.26,38.82)	0.002	
Mg ²⁺ , mmol/L	17.12 (3.1,94.6)	0.001	
high-sensitivity C-reactive protein (hs-CRP), mg/L	1.02 (1.01,1.03)	<.001	
Creatinine, umol/L	0.98 (0.97,0.99)	<.001	
Blood platelet (PLT) count, ×10 ⁹ /L	0.9928 (0.9893,0.9963)	<.001	
Prothrombin time (PT), s	1.24 (1.08,1.42)	0.003	
D-D dimer, μg/mL FEU	1.21 (1.12,1.32)	<.001	
Multivariate analysis	AOR (95%CI)	Wald's <i>P</i> -value	
Number of events / patients (%)	132 / 223 (59.2%)	...	
D-D dimer, μg/mL FEU	1.13 (1.04 - 1.22)	0.005	
IM.Index	6.42 (2.66 - 15.48)	< .001	
Neutrophil-to-lymphocyte ratio	1.08 (1.03 - 1.13)	< .001	
Covariate	Coefficient	Score	
D-D dimer, μg/mL FEU	2	2 × D-D dimer	

Neutrophil-to-lymphocyte ratio	1	1 × ratio
Total computed score and risk stratification		
Low risk		≤ 106
High risk		> 106
AOR = Adjusted odds ratio; CI = Confidence interval.		

Table 3. Odds ratio of metabolic pathway in age-specific patient cohort infected with COVID-19

Pathway Survival Analysis	AOR (95%CI)	Wald's <i>P</i> -value
Metabolic Pathway		
Phenylalanine.metabolism 28.27 (10.56,75.72)	)	<.001
Arginine.and.proline 27.68 (10.38,73.84)	)	<.001
Tyrosine.metabolism 25.81 (9.8,67.99)		<.001
Alanine.aspartate.and.glutamate.metabolism	25.72 (9.77,67.69)	<.001
Glutathione.metabolism	17.23 (7.16,41.46)	<.001
Cysteine.and.methionine.metabolism	16.78 (7.14,39.41)	<.001
Folate.biosynthesis	16.38 (6.9,38.88)	<.001
Purine.metabolism	16.34 (6.88,38.81)	<.001
Steroid.biosynthesis	15.62 (6.66,36.62)	<.001
Retinol.metabolism	15.62 (6.66,36.61)	<.001
Fatty.acid.metabolism	15.61 (6.66,36.6)	<.001
Pyruvate.metabolism	12.86 (5.85,28.28)	<.001
Propanoate.metabolism	12.82 (5.84,28.15)	<.001
AOR = Adjusted odds ratio; CI = Confidence interval.		

Supplementary Figure Captions

Supplement Figure 1: **A multi-cent study design**

Supplement Figure 2: **Estimation of metabolic flux in a large-scale molecular model**

Supplement Figure 3: **Difference of metabolic flux between surviving and deceased subgroups in ARDS**

Figures

Figure 1

Pathological Alteration from the Admission to Clinical Endpoint.

Figure 3

Clinical stratification and prediction of overall survival (OS) on the basis of developed survival algorithm AlgSurv. A: OS in the low- and high-risk subgroups defined by a cutoff of < 106 and ≥ 106 . B: Predicted OS rates in the elderly cohort. Smooth lines represent mean predicted OS probabilities for each risk group.

Supplementary Files

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