Oseltamivir, Lopinavir/ritonavir and Reduning May Improve Survival of COVID-19 Patients With High-risk

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Abstract

Background

No therapeutics have demonstrated specific efficacy for patients with COVID-19.

Methods

We retrospectively evaluated 351 patients with COVID-19 admitted to the Third People's Hospital of Yichang from 9 January to 25 March, 2020.Univariate logistic regression and least absolute shrinkage and selection operator (LASSO) regression were employed to identify risk factors associated with progression, which were then incorporated into the nomogram. Survival of patients between high-risk and low-risk groups was compared by kaplan-Meier analysis. Moreover, we assessed the effects of existing common drugs on survival of patients with high-risk.

Results

Based on the LASSO, four variables (white blood cell, C-reactive protein, whether lymphocyte $\geq 0.8 \times 10^9$/L, and whether lactate dehydrogenase $\geq$ 400 U/L) were selected for construction of the nomogram. Patients in the total cohort were stratified into low-risk group (total point < 160) and high-risk group (total point $\geq$ 160). Kaplan-Meier analysis demonstrated that there was significant difference in survival of patients between high-risk and low-risk groups (8-week survival rate: 71.41% vs 100%, P < 0.0001). Among the common drugs, we found that patients with high-risk received oseltamivir, lopinavir/ritonavir or Reduning injection exhibited better survival. The combination of these three drugs showed the effect of improving survival, although single drug may have no effect in different grouping analysis.

Conclusions

The combination of oseltamivir, lopinavir/ritonavir and Reduning injection may improve survival of COVID-19 patients with high-risk identified by our simple-to-use nomogram.

Background

Since December 2019, infection with the severe acute respiratory coronavirus 2 (SARS-CoV-2) has caused an international outbreak of respiratory illness termed coronavirus disease 2019 (COVID-19) [1, 2]. With the increase of cases and the accumulation of clinical experience, more and more detailed information about COVID-19 has been revealed. Many patients can be cured effectively at the early stage, but some COVID-19 patients may develop severe progressive pneumonia, acute respiratory distress syndrome (ARDS), or multiple organ failure, and even died abruptly [3–5]. The mortality rate in critically ill patients was as high as 49% [6]. However, there are no specific therapeutic agents for COVID-19 pneumonia [7–9].

There is an urgent need to early identify factors that can predict the exacerbation and survival of COVID-19 patients, and to screen potentially effective therapeutic drugs from existing drugs.

Hence, the present aims to provide a clue for the early identification and screening of high-risk COVID-19 patients who may rapid progress by constructing a nomogram, and to perform a comprehensive exploration of the efficacy of existing common drugs so as to provide ideas for clinical trial research.

Methods

Study participants

All confirmed patients with COVID-19 from January 9 to March 25, 2020 admitted into the Third People's Hospital of Yichang were collected. A confirmed case of COVID-19 was defined as a positive result on fluorescence reverse transcription polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens, or specific antibody assay of serum. According to the plan of diagnosis and treatment for COVID-19 (Trial version seventh) issued by the National Health Commission of China, patients with COVID-19 were divided into four types: Mild, Moderate, Severe and Critical [10]. As a supporting institution, the First Affiliated Hospital of Fujian Medical University participated in the treatment of COVID-19 patients in the Third People's Hospital of Yichang. Since no ethics committee has been set up in the Third People's Hospital of Yichang, this study was approved by the ethics committee of the First Affiliated Hospital of Fujian Medical University, and conducted according to Declaration of Helsinki guidelines. Requirement for written informed consent was waived by the ethics board of the First Affiliated Hospital of Fujian Medical University.

Data Collection

Clinical and laboratory data was obtained using standardized forms. Candidate variables were derived from electronic medical records which included demographic variables, including age, gender, and smoking history; clinical symptoms or signs; comorbid conditions, including diabetes mellitus (DM), hypertension, coronary heart disease (CHD), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cancer, immunodeficiency; and laboratory variables from blood. Laboratory assessments consisted of a complete blood count, blood coagulation function, tests of liver and renal function, C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH), and creatine kinase (CK).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) if they were normally distributed or median and interquartile (IQR) if not, and categorical variables were described as number and proportion (%). The complete dataset was randomly separated into training and validation datasets (the split ratio was 7:3). In the training set, candidate predictors with significant P values in univariate logistic

regression analysis were screened by the least absolute shrinkage and selection operator (LASSO) regression analysis to identify the best subset of features using glmnet package in R [11]. The lambda parameter that minimised expected model deviance was selected. The coefficients for each feature provided by LASSO regression model were used to generate the nomogram.

The performance of nomogram was assessed by receiver operating characteristic (ROC) analysis and the area under the curve (AUC) with 95% confidence interval (CI), calibration plot combined with the Hosmer-Lemeshow (HL) test [12], and decision curve analysis (DCA) [13]. Then, the performance of nomogram was further validated in the validation dataset and total dataset using the same methods described above. Kaplan-Meier curves were employed to determine the differences in survival between different groups of COVID-19 patients. The Log-rank test was performed to compare the survival curves. Data analysis was conducted by SPSS Statistics software (v20.0, SPSS, USA) and R software (version 3.6.0). P values less than 0.05 were considered to be statistically significant.

Results

Characteristics Of The Patients

A total of 360 records were collected in the dataset. 9 records were excluded, of which 6 were duplicate and 3 were lack of laboratory data. Finally, 351 patients with COVID-19 were eligible for this retrospective study. Of these, we randomly selected 246 subjects (70%) into the training dataset, and the remaining 105 subjects (30%) were assigned to the validation dataset. The clinical characteristics of the training and validation datasets are summarized in Table 1.

Table 1
Clinical characteristics of patients infected with COVID-19

Characteristics	Total(n = 351)	Training dataset (n = 246)	Validation dataset (n = 105)	P value[a]
Demographics				
Age (years), median (IQR)	54(38–66)	54(38-66.25)	54(37-65.5)	0.581
Female sex, no. (%)	162(46.2)	117(47.6)	45(42.9)	0.418
Smoking history, n (%)	57(16.2)	41(16.7)	16(15.2)	0.74
Comorbid conditions, n (%)				
Hypertension	80(22.8)	53(21.5)	27(25.7)	0.407
Diabetes mellitus	41(11.7)	27(11.0)	14(13.3)	0.529
Coronary heart disease	20(5.7)	13(5.3)	7(6.7)	0.609
Cerebrovascular diseases	13(3.7)	9(3.7)	4(3.8)	0.922
COPD	9(2.6)	7(2.8)	2(1.9)	0.73
Cancer	9(2.6)	9(3.7)	0(0)	0.062
Immunodeficiency	1(0.3)	1(0.4)	0(0)	1
Laboratory data				
White blood cell ($\times 10^9$/L), median (IQR)	6.3(5.2–8.4)	6.35(5.2–8.5)	6.2(5.25–8.05)	0.725
Neutrophil ($\times 10^9$/L), median (IQR)	4.21(3.22–6.34)	4.215(3.2325–6.6425)	4.17(3.145–6.135)	0.696
Monocyte ($\times 10^9$/L), median (IQR)	0.21(0.15–0.28)	0.21(0.14–0.28)	0.21(0.15–0.27)	0.953
Lymphocyte ($\times 10^9$/L), median (IQR)	0.91(0.62–1.33)	0.91(0.5975–1.3325)	0.9(0.675–1.345)	0.412
Distribution, no. (%)				0.85
< 0.8 ($\times 10^9$/L)	133(37.9)	94(38.2)	39(37.1)	

Notes: IQR, interquartile; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; CRRT, continuous renal replacement therapy; NIVV, non-invasive ventilation; NA, not available; [a]For comparison between training dataset and validation dataset; [b]P<0.05.

Characteristics	Total(n = 351)	Training dataset (n = 246)	Validation dataset (n = 105)	P value[a]
≥0.8 (× 10^9/L)	218(62.1)	152(61.8)	66(62.9)	
Hemoglobin (g/L), median (IQR)	108(98–121)	107(97.75–120)	110(100–122)	0.365
Platelet (× 10^9/L), median (IQR)	130(98–170)	130(98-169.25)	130.5(96.25–171.5)	0.734
PT (s), median (IQR)	10.9(10.5–11.3)	10.9(10.5–11.3)	10.8(10.4–11.2)	0.157
APTT (s), median (IQR)	29.7(26.3–33.6)	29.85(26.8-33.575)	29.25(25.425–33.8)	0.284
Fibrinogen (g/L)	2.664(2.026–3.645)	2.664(2.026–3.542)	2.975(2.081–3.959)	0.192
D-Dimer (mg/L), median (IQR)	0.6(0.51–1.365)	0.62(0.52–1.518)	0.57(0.51–1.048)	0.052
TBIL (μmol/L), median (IQR)	9.19(6.63–13.77)	9.205(6.635–14.015)	8.99(6.745–13.385)	0.869
DBIL (μmol/L), median (IQR)	2.39(1.585–3.57)	2.41(1.6225–3.5375)	2.35(1.56–3.845)	0.866
Albumin (g/L), median (IQR)	37.4(34-40.9)	37.1(34-40.6)	38.1(34-41.3)	0.223
Globulin (g/L), median (IQR)	26.4(23.825–28.8)	26.4(23.725–28.875)	26.25(23.925–28.75)	0.907
ALT (U/L), median (IQR)	21(13.75-34)	20(14-34.5)	21(13–33)	0.69
AST (U/L), median (IQR)	21(16–28)	21(16–29)	22(17–28)	0.786
ALT peak (U/L), median (IQR)	35(24–61)	35(24–61)	34(22-61.5)	0.984
AST peak (U/L), median (IQR)	26(20–39)	26(20–42)	25(20–38)	0.432
Creatinine (μmol/L), median (IQR)	67.35(54.1-79.825)	67.25(54.65–80.35)	68.2(53.65–79.5)	0.57
Creatinine peak (μmol/L), median (IQR)	73.4(58.25-87.925)	73.1(58.2-87.75)	74(58.25–88.65)	0.993

Notes: IQR, interquartile; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; CRRT, continuous renal replacement therapy; NIVV, non-invasive ventilation; NA, not available; [a]For comparison between training dataset and validation dataset; [b]P<0.05.

Characteristics	Total(n = 351)	Training dataset (n = 246)	Validation dataset (n = 105)	P value[a]
LDH (U/L), median (IQR)	207(164.75–263)	203(164.25–269.5)	211.5(166-260.75)	0.882
LDH peak (U/L), median (IQR)	224.5(175-305.25)	225(175-311.5)	220(177.5–292)	0.762
Distribution, no. (%)				0.92
< 400 (U/L)	286(81.5)	200(81.3)	86(81.9)	
≥400 (U/L)	40(11.4)	29(11.8)	11(10.5)	
NA	25(7.1)	17(6.9)	8(7.6)	
CK (U/L), median (IQR)	63(41-111.5)	58.5(40-108.5)	69.5(43-126.75)	0.126
CK-MB (U/L), median (IQR)	12.1(9.4–17.7)	12.1(9.5–17.5)	12.2(9.33–18.48)	0.777
CRP (mg/L), median (IQR)	21.2(4.65-51.625)	20.7(4.35-52.475)	21.55(6.3-48.475)	0.764
PCT (ng/L), median (IQR)	0.08(0.05–0.135)	0.08(0.05-0.1375)	0.08(0.06–0.135)	0.665
Clinical classification, no. (%)				0.162
Mild	6(1.7)	2(0.8)	4(3.8)	
Moderate	279(79.5)	195(79.3)	84(80)	
Severe	33(9.4)	26(10.6)	7(6.7)	
Critical	33(9.4)	23(9.3)	10(9.5)	
Treatment, no. (%)				
Antiviral treatment	349(99.4)	244(99.2)	105(100)	1
Oseltamivir	262(74.6)	177(72.0)	85(81)	0.076
Lopinavir/ritonavir	238(67.8)	172(69.9)	66(62.9)	0.134
Ribavirin	44(12.5)	35(14.2)	9(8.6)	0.085
Arbidol	165(47.0)	116(47.2)	49(46.7)	0.412

Notes: IQR, interquartile; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; CRRT, continuous renal replacement therapy; NIVV, non-invasive ventilation; NA, not available; [a]For comparison between training dataset and validation dataset; [b]P<0.05.

Characteristics	Total(n = 351)	Training dataset (n = 246)	Validation dataset (n = 105)	P value[a]
Ganciclovir	10(2.8)	7(2.8)	3(2.9)	0.421
Interferon-alpha for nasal spray	224(63.8)	155(63.0)	69(65.7)	0.289
Antibacterial treatment	328(93.4)	229(93.1)	99(94.3)	0.678
Antifungal treatment	20(5.7)	13(5.3)	7(6.7)	0.33
Chinese patent medicine injection				
Reduning injection	112(31.9)	79(32.1)	33(31.4)	0.9
Xuebijing injection	183(52.1)	126(51.2)	57(54.3)	0.641
Tanreqing injection	84(23.9)	67(27.2)	17(16.2)	0.026[b]
Glucocorticoids	119(33.9)	85(34.6)	34(32.4)	0.365
Intravenous immunoglobulin therapy	66(18.8)	46(18.7)	20(19.0)	0.39
CRRT	5(1.4)	3(1.2)	2(1.9)	0.024[b]
NIVV or high-flow nasal cannula	37(10.5)	28(11.4)	9(8.6)	0.432
Invasive mechanical ventilation	12(3.4)	7(2.8)	5(4.8)	0.354
Aggravation, no. (%)				0.905
Mild to Moderate/Severe/Critical	0(0)	0(0)	0(0)	
Moderate to Severe	19(5.4)	14(5.7)	5(4.8)	
Moderate/Severe to Critical	31(8.8)	21(8.5)	10(9.5)	
No	301(85.8)	211(85.8)	90(85.7)	
Death, no. (%)	14(4.0)	9(3.7)	5(4.8)	0.766

Notes: IQR, interquartile; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; CRRT, continuous renal replacement therapy; NIVV, non-invasive ventilation; NA, not available; [a]For comparison between training dataset and validation dataset; [b]P<0.05.

Development and validation of nomogram for predicting the probability of progression of patients with COVID-19

Based on univariate logistic analysis of the training cohort, we identified 24 variables significantly associated with risk of progression (Table 2). Of the relevant variables, 4 predictive factors (including WBC, CRP, whether lymphocyte $\geq 0.8 \times 10^9$/L, and whether LDH $\geq$ 400 U/L) identified by LASSO regression were shown as a nomogram (Fig. 1a). In the training cohort, the AUC of our nomogram was 0.945 (95%CI: 0.91–0.98) (Fig. 1b). The calibration curve of our nomogram for the probability of exacerbation in the training dataset demonstrated good agreement between the predicted and observed risks (Fig. 1c). The Hosmer-Lemeshow test yielded a nonsignificant statistic (Chi-square = 7.951, P value = 0.539). We performed DCA to assess the clinical value of the nomogram (Fig. 1d). The DCA curve showed that, if the threshold probability of 30–80%, using this nomogram to identify patients who might aggravate would be more benefit than either “treat-all” or “treat-no” schemes.

Table 2
Univariate logistic regression of progression factors in patients with COVID-19

Variables	OR	95CI%	Estimate	S. E	z value	P value
Age (years)	1.339	1.191–1.498	0.041	0.012	3.399	0.001[b]
Sex						
Male	1	-	-	-	-	-
Female	0.699	0.337–1.448	-0.358	0.372	-0.964	0.335
Smoking	1.598	0.668–3.823	0.469	0.445	1.054	0.292
Hypertension	3.96	1.864–8.415	1.376	0.385	3.579	3.452E-04[b]
Diabetes mellitus	5.586	2.324–13.426	1.720	0.447	3.845	1.207E-04[b]
Coronary heart disease	8.542	2.678–27.24	2.145	0.592	3.625	2.889E-04[b]
Cerebrovascular diseases	5.29	1.347–20.777	1.646	0.698	2.358	0.018[b]
COPD	2.497	0.465–13.404	0.915	0.857	1.067	0.286
Cancer	8.625	2.193–33.922	2.155	0.699	3.084	0.002[b]
Immunodeficiency	1.00E + 10	0	16.392	882.743	0.019	0.985
White blood cell	1.339	1.197–1.498	0.292	0.057	5.116	3.120E-07[b]
Neutrophil	1.225	1.12–1.34	0.203	0.046	4.423	9.740E-06[b]
Monocyte	0	0-0.027	-7.771	2.122	-3.662	2.507E-04[b]
Lymphocyte						
Lymphocyte < 0.8(× 10^9/L)	1	-	-	-	-	

Notes: OR, odds ratio; CI: confidence interval; S. E, standard error; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; NA, not available; [b]P<0.05.

Variables	OR	95CI%	Estimate	S. E	z value	P value
Lymphocyte ≥ 0.8(× 10^9/L)	0.012	0.002–0.087	-4.449	1.026	-4.337	1.440E-05[b]
Hemoglobin (g/L)	0.942	0.92–0.965	-0.060	0.012	-4.969	6.740E-07[b]
Platelet (× 10^9/L)	0.984	0.976–0.993	-0.016	0.004	-3.627	2.868E-04[b]
PT (s)	1.785	1.335–2.387	0.580	0.148	3.912	9.140E-05[b]
APTT (s)	1.05	0.994–1.108	0.049	0.028	1.747	0.081
Fibrinogen (g/L)	0.542	0.363–0.81	-0.612	0.205	-2.990	0.003[b]
D-Dimer (mg/L)	1.114	1.059–1.171	0.108	0.026	4.201	2.650E-05[b]
TBIL (μmol/L)	1.018	0.963–1.075	0.017	0.028	0.624	0.533
DBIL (μmol/L)	1.023	0.983–1.065	0.023	0.021	1.129	0.259
Albumin (g/L)	0.876	0.819–0.938	-0.132	0.035	-3.814	1.369E-04[b]
Globulin (g/L)	1.016	0.932–1.108	0.016	0.044	0.362	0.717
ALT (U/L)	1.011	0.997–1.025	0.011	0.007	1.553	0.120[b]
AST (U/L)	1.032	1.011–1.054	0.032	0.011	2.954	0.003[b]
ALT peak (U/L)	1.005	1.001–1.009	0.005	0.002	2.400	0.016[b]
AST peak (U/L)	1.007	1-1.013	0.007	0.003	1.968	0.049[b]
Creatinine (μmol/L)	1.007	1-1.013	0.007	0.003	2.057	0.040[b]
Creatinine peak (μmol/L)	1.01	1.003–1.016	0.010	0.003	2.953	0.003[b]
CK (U/L)	1.001	1-1.003	0.001	0.001	1.445	0.148
CKMB (U/L)	1.005	0.999–1.012	0.005	0.003	1.621	0.105

Notes: OR, odds ratio; CI: confidence interval; S. E, standard error; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; NA, not available; [b]P<0.05.

Variables	OR	95CI%	Estimate	S. E	z value	P value
LDH peak (U/L)	1.005	1.003–1.006	0.004	0.001	4.610	4.03E-06[b]
LDH < 400 U/L	1	-	-	-	-	-
LDH ≥ 400 U/L	17.472	7.053–43.284	2.861	0.463	6.180	6.390E-10[b]
CRP (mg/L)	1.029	1.02–1.039	0.029	0.004	6.468	9.960E-11[b]
PCT (ng/L)	1.107	1.031–1.189	0.102	0.036	2.793	0.005[b]

Notes: OR, odds ratio; CI: confidence interval; S. E, standard error; COPD, chronic obstructive pulmonary disease; PT, prothrombin time; APTT, activated partial thromboplastin time; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate Aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CKMB, Creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; NA, not available; [b]P<0.05.

The validation of nomogram for predicting the probability of the exacerbation of patients with COVID-19 was provided in the Supplementary material and Fig. S1.

Nomogram For Predicting The Survival Of Patients With Covid-19

According to the nomogram developed in the training cohort, the total point of each of the 322 patients in the total cohort was calculated, and another 29 cases were excluded due to lack of information. Based on a total pointof 160 on the nomogram, corresponding to a 50%probability of disease progression, it was defined as the cut-off value. Patients in the total cohort were stratified into low-risk group (total point < 160, n = 289) and high-risk group (total point ≥ 160, n = 33). Median follow-up was 56 days. Kaplan-Meier analysis demonstrated a significant difference in the overall survival (OS) rates between high-risk group and low-risk group. The 8-week survival rate was 71.41% in the high-risk group, while all patients in low-risk group survived (Log-rank P < 0.0001, Fig. 1e). Time-dependent ROC curve analysis using timeROC package in R software showed that the nomogram achieved an AUC value of 0.96 (95%CI: 0.931–0.989) at 8-week of OS (Fig. 1f), demonstrating excellent performance of this nomogram for predicting survival of patients with COVID-19.

Effects of antiviral drugs on the survival of COVID-19 patients with high-risk

As all patients with low-risk were alive, we selected the high-risk patients (n = 33) to analyze the effects of drugs on the survival of patients with COVID-19. Of these patients, 9.1%, 24.2% and 66.7% were Mild type, Severe type and Critical type, respectively. Mean age was 66.8 years and median follow-up was 58 days.

As in shown Fig. 2a, kaplan-Meier analysis indicated that addition of antivirals may significantly improve the OS of COVID-19 patients with high-risk. In order to clarify which antiviral drugs can affect survival, we analyzed six commonly used antiviral drugs, including oseltamivir, lopinavir/ritonavir, ribavirin, arbidol, ganciclovir, and interferon-alpha (IFN-α) for nasal spray. Kaplan-Meier analysis showed that both oseltamivir and lopinavir/ritonavir significantly prolonged the OS of patients with COVID-19 (8-week survival rate: 79.58% vs. 38.1%, Log-rank $P < 0.05$; 85.56% vs. 41.56%, Log-rank $P < 0.01$; respectively; Fig. 2b-c), but ribavirin shorten that of patients (7-week survival rate: 50.0% vs. 89.66%, Log-rank $P < 0.05$; Fig. 2d). There were no effects of arbidol, ganciclovir and IFN-α on the survival of patients (Fig. S2a-c).

Effects of Chinese patent medicine injections on the survival of COVID-19 patients with high-risk

In China, three Chinese patent medicine injections (including Reduning injection, Xuebijing injection, and Tanreqing injection) have been used in the treatment of patients with COVID-19. The 8-week survival rate was higher in the Reduning group than the no Reduning group (100% vs. 59.14%, Log-rank $P < 0.01$, Fig. 3a), while lower in the Xuebijing group than the no Xuebijing group (59.7% vs. 100%, Log-rank $P < 0.01$; Fig. 3b). There was no difference in OS between patients treated with and without Tanreqing injection (Log-rank $P = 0.17$; Fig. 3c).

Effects of other drugs on the survival of COVID-19 patients with high-risk

As COVID-19 patients are seriously ill, various drugs may be always applied simultaneously. We found that OS at 8-week was shorter in the antifugal therapy group compared tothe no antifungal therapy group (48.61% vs. 84.71%, Log-rank $P < 0.01$; Fig. S3a). There were no significant differences in OS of COVID-19 patients whether they received with glucocorticoids, thymalfasin, intravenous immunoglobulin (IVIG), or ambroxol (Fig. S3b-e). Because all high-risk patients were treated with antibacterials, we cannot analyze the impact of antibacterials on survival.

Effects of the different combinations of oseltamivir, lopinavir/ritonavir and Reduning injection on the survival of COVID-19 patients with high-risk

Based on the above results, we further analyzed the effects of the different combinations of oseltamivir, lopinavir/ritonavir and Reduning injection on the survival of COVID-19 patients with high-risk.

As shown in Fig. 4a, patients treated with the combination of oseltamivir and lopinavir/ritonavir had longer OS than those who treated without oseltamivir and lopinavir/ritonavir (8-week survival rate: 84.38% vs. 20.0%, Log-rank $P < 0.01$), while those with oseltamivir alone or with lopinavir/ritonavir alone did not have longer OS (Log-rank $P = 0.15$ and $P = 0.23$, respectively). Patients treated with the combination of oseltamivir and Reduning or with oseltamivir alone exhibited better OS than those without oseltamivir and Reduning (8-week survival rate: 100% vs. 26.67%, Log-rank $P < 0.001$; 77.92% vs. 26.67%, Log-rank $P < 0.01$; respectively), while those with Reduning alone did not exhibit better OS (Log-rank $P = 0.073$) (Fig. 4b). The 8-week survival rates of patients treated with the combination of lopinavir/ritonavir and Reduning or with lopinavir/ritonavir alone were longer than those without lopinavir/ritonavir and

Reduning (100% vs. 26.67%, Log-rank P < 0.01; 70.1% vs. 26.67%, Log-rank P < 0.01; respectively), while that of patients treated with Reduning alone was not longer than that of those without lopinavir/ritonavir and Reduning (Log-rank P = 0.073)(Fig. 4c). As shown in the Fig. 4d, patients treated with the combination of these three drugs exhibited better OS than those without these three drugs or with single drug (7-week survival rate: 100% vs. 25.0%, Log-rank P < 0.001; 8-week survival rate: 100% vs. 66.67%, Log-rank P = 0.048; respectively), but not better than that of two drugs (8-week survival rate: 100% vs. 78.79%, Log-rank P = 0.13).

Discussion

In our study, we constructed a novel nomogram incorporated 4 simple and common predictors, including WBC, CRP, whether lymphocyte $\geq 0.8 \times 10^9$/L, and whether LDH $\geq$ 400 U/L. Because there were 24 variables associated with the progression of COVID-19 in univariate logistic regression analysis, we used LASSO regression for construction of prediction nomogram. LASSO regression is suitable for the regression of high-dimensional data and used to screen the optimal combination of predictors from the primary dataset [11], markedly raised the accuracy of the exacerbation risks in patients with COVID-19. The ROC analysis showed that the AUC of our nomogram was 0.945, indicating outstanding performance for prediction. Thus, our model may have a strong clinical transformation value. To evaluate the prognostic value of nomogram, we stratified patients with COVID-19 into high-risk group and low-risk group with significantly different survival rate. It was noteworthy that all patients in the low-risk group were alive. The AUC at 8-week of ROC was 0.959, indicating excellent performance of predicting survival.

We further explored effects of drugs on the survival of patients with high-risk. This is the first comprehensive report on effects of existing common drugs on the survival of patients with COVID-19. Among them, we found oseltamivir, lopinavir/ritonavir and Reduning injection improved the survival of patients. Oseltamivir is indicated for the treatment and prophylaxis of seasonal influenza, and it is not recommended by the plan of diagnosis and treatment for COVID-19 (Trial version seventh) [10]. However, a recent research reported that 3 of 4 patients with COVID-19 received oseltamivir, and all clinical symptoms and CT imaging abnormalities had resolved. All these 4 patients had 2 consecutive negative RT-PCR test results, indicating oseltamivir appeared to inhibit the ability of the virus to multiply in a patient's body.

Lopinavir/ritonavir is used for the treatment of human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome coronavirus (MERS-CoV) [7, 14–16]. Whether lopinavir/ritonavir can be used in the treatment of COVID-19 has attracted much attention. A recent trial of lopinavir/ritonavir showed that it did not significantly accelerate clinical improvement, and reduce mortality in adults hospitalized with severe COVID-19 [7]. However, when using our nomogram to distinguish high-risk patients, we found that lopinavir/ritonavir may improve their survival. The possible explanation for the inconsistency is thatlopinavir/ritonavir has no benefits for low-risk patients, which may cover up its benefits for high-risk patients.

In this study, we also found that a Chinese patent drug Reduning may be effective in the treatment of COVID-19. Previous animal study reported that Reduning administration significantly decreased both IL-6 and IL-10 production in severe pneumonia induced by influenza A virus (H1N1) [17]. Reduning is a traditional Chinese medicine (TCM) injection refined from three Chinese herbal medicines, namely, artemisiae annuae, honeysuckle, and gardenia, formulated for injection. Among them, artemisia annua is a kind of herb that was first introduced in traditional Chinese medicine 1000 years ago. Artemisia annua has been reported to play an important role in immunomodulation [18, 19], which may be the reason for the effective treatment of severe COVID-19 due to cytokine storm. The detail mechanism of the drug is worth of further study.

We additionally analyzed the effects of different combinations of these three drugs on the survival of COIVD-19 patients with high-risk. We found all the different combinations of drugs showed the effects of improving survival, although single drug may not show the effect in different grouping analysis. Another reason may be that the drugs may exert a therapeutic effect through synergy. Patients treated with the combination of these three drugs exhibited better OS than those without these three drugs or with single drug, but not better than that of two drugs, which may be related to the small number of high-risk cases in this study. Based on the above results, the combination of oseltamivir, lopinavir/ritonavir and Reduning injection may be a promising treatment for COVID-19 patients with high-risk.

There were some limitations to the present study. Firstly, our study was a retrospective study from one center. As lack of external validation in other population, the generalization of our predicting nomogram should be further validated. Secondly, it is difficult to distinguish the specific efficacy of one single drug as various treatments were applied simultaneously. Thirdly, interpretation of this study is limited by the small size of the cohort.

Conclusions

In summary, the combination of oseltamivir, lopinavir/ritonavir and Reduning may improve survival of COVID-19 patients with high-risk identified by our simple-to-use nomogram. At a time when there are no specific drugs that can treat COVID-19, exploring the combination of drugs may be an alternative. Further, prospective clinical trials are warranted to validate our findings.

Abbreviations

ALT
alanine aminotransferase
APTT
activated partial thromboplastin time
ARDS
acute respiratory distress syndrome
AST

aspartate Aminotransferase
AUC
area under the curve
CHD
coronary heart disease
CI
confidence interval
CK
creatine kinase
CKMB
Creatine kinase-MB
COPD
chronic obstructive pulmonary disease
COVID-19
coronavirus disease 2019
CRP
C-reactive protein
CRRT
continuous renal replacement therapy;
CVD
cardiovascular disease
DBIL
direct bilirubin
DCA
decision curve analysis
DM
diabetes mellitus
HL
Hosmer-Lemeshow
IQR
interquartile
LASSO
least absolute shrinkage and selection operator
LDH
lactate dehydrogenase
NIVV
non-invasive ventilation
OR
odds ratio
PCT

procalcitonin
PT
prothrombin time
ROC
receiver operating characteristic
RT-PCR
reverse transcription polymerase chain reaction
SD
standard deviation
TBIL
total bilirubin
WBC
white blood cell

Declarations

Availability of data and materials

The data are available from the Third People's Hospital of Yichang but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Third People's Hospital of Yichang.

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Ethics declarations

Ethics approval and consent to participate

Since no ethics committee has been set up in the Third People's Hospital of Yichang, this study was approved by the ethics committee of the First Affiliated Hospital of Fujian Medical University, and conducted according to Declaration of Helsinki guidelines. Requirement for written informed consent was waived by the ethics board of the First Affiliated Hospital of Fujian Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Contributions

Drs Z. Zeng, D. Du, G. Chen and D. Kang were responsible for conception and design, interpretation of data, and drafting of the manuscript.C. Wu, Y. Fang, Y. Huang, and M. Li were responsible for acquisition of data and administrative and technical support.Z. Lin and S. Feng were responsible for data analysis. Z. Lin and Y. Ye were responsible for statistical analysis. All authors contributed to the writing of the manuscript and approved the final submitted version.

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Not applicable.

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Figures

Fig. 1

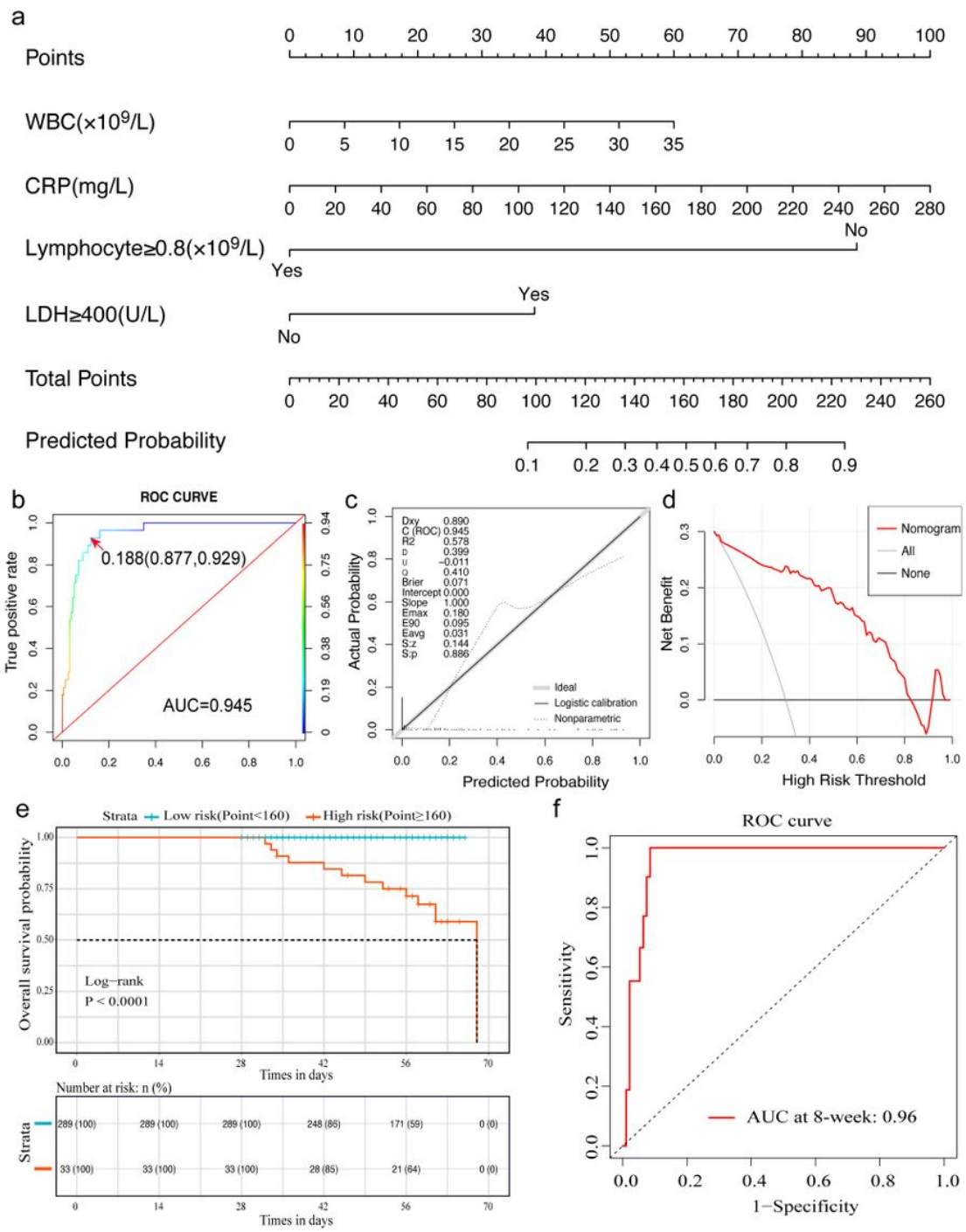

Figure 1

Nomogram for predicting the probability of exacerbation and survival of patients with coronavirus disease 2019 (COVID-19). (a) Nomogram developed in the training cohort; (b) Receiver operating characteristic (ROC) curve analysis for nomogram in the the training cohort; Area under the curve (AUC) of our model was 0.945; (c) Calibration plot for nomogram in the the training cohort; (d) Decision curve analysis for nomogram in the the training cohort. (e) Kaplan-Meier survival curves of overall survival of patients in the total cohort according to high-risk and low-risk defined by the developed nomogram total

points (P<0.0001). Low-risk=Point<160; High-risk=Point≥160; (f) Time-dependentROC curve analysis for developed nomogram predicting survival of patients with COVID-19 in the total cohort.

Fig. 2

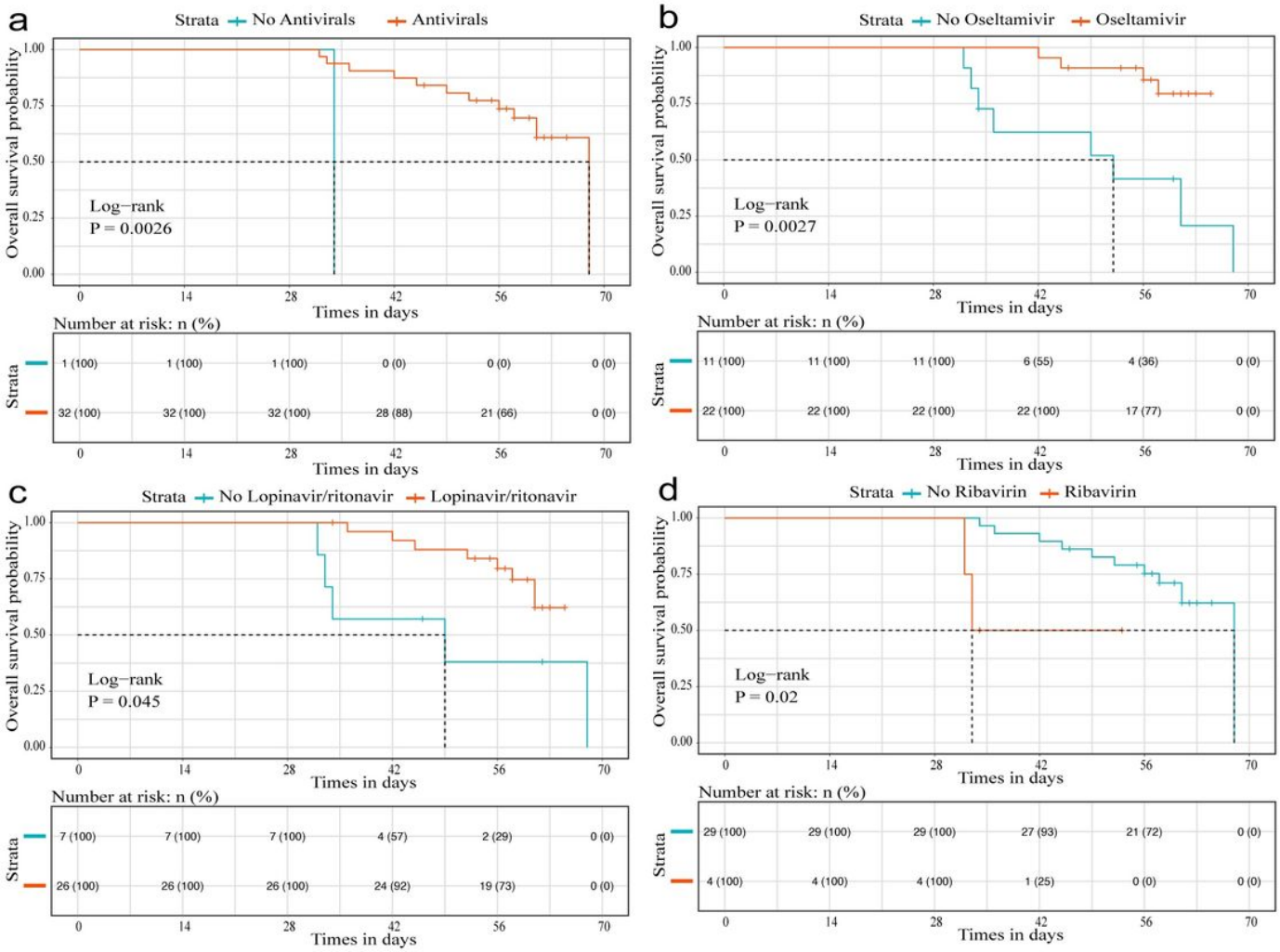

Figure 2

Effects of antiviral drugs on the survival of coronavirus disease 2019 (COVID-19) patients with high-risk identified by the developed nomogram. (a) Antivirals; (b) Oseltamivir; (c) Lopinavir/ritonavir; (d) Ribavirin.

Fig. 3

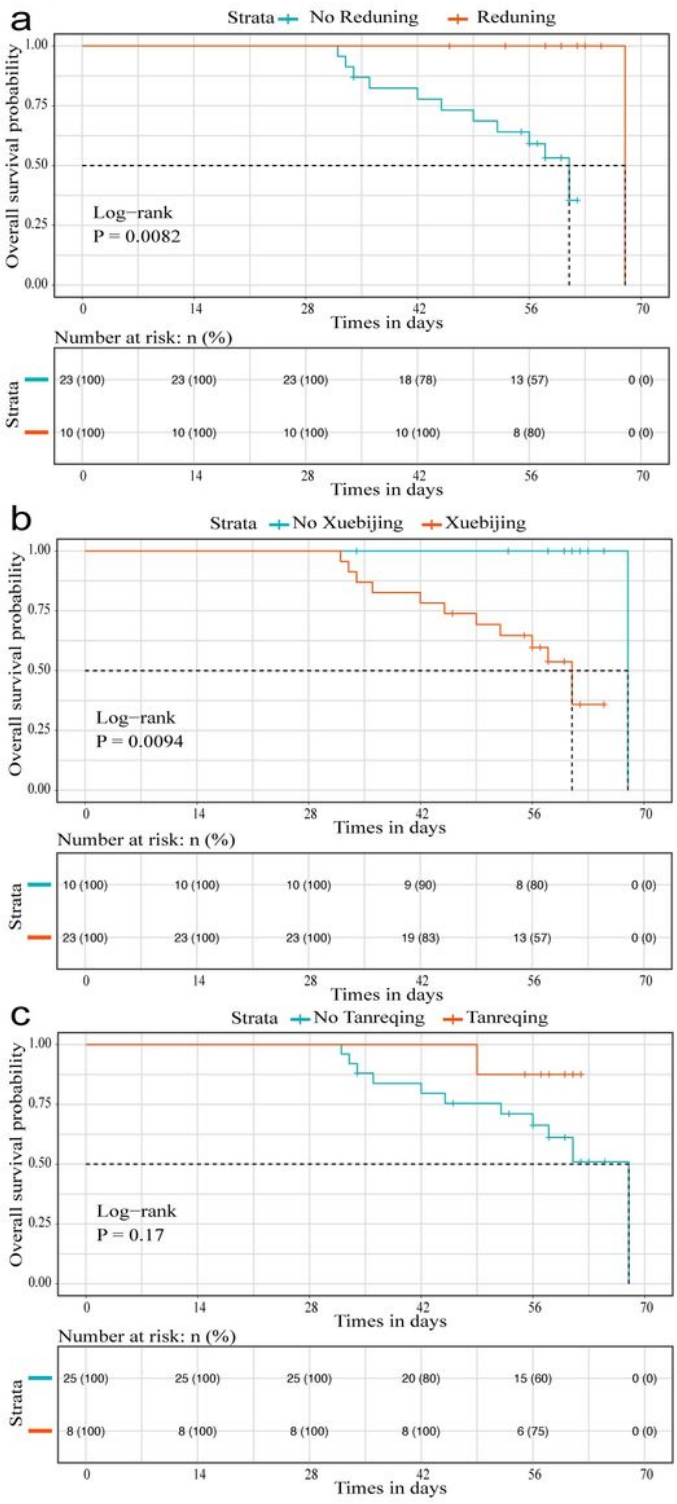

Figure 3

Effects of Chinese patent medicine injections on the survival of coronavirus disease 2019 (COVID-19) patients with high-risk identified by the developed nomogram. (a) Reduning; (b) Xuebijing; (c) Tanreqing.

Fig. 4

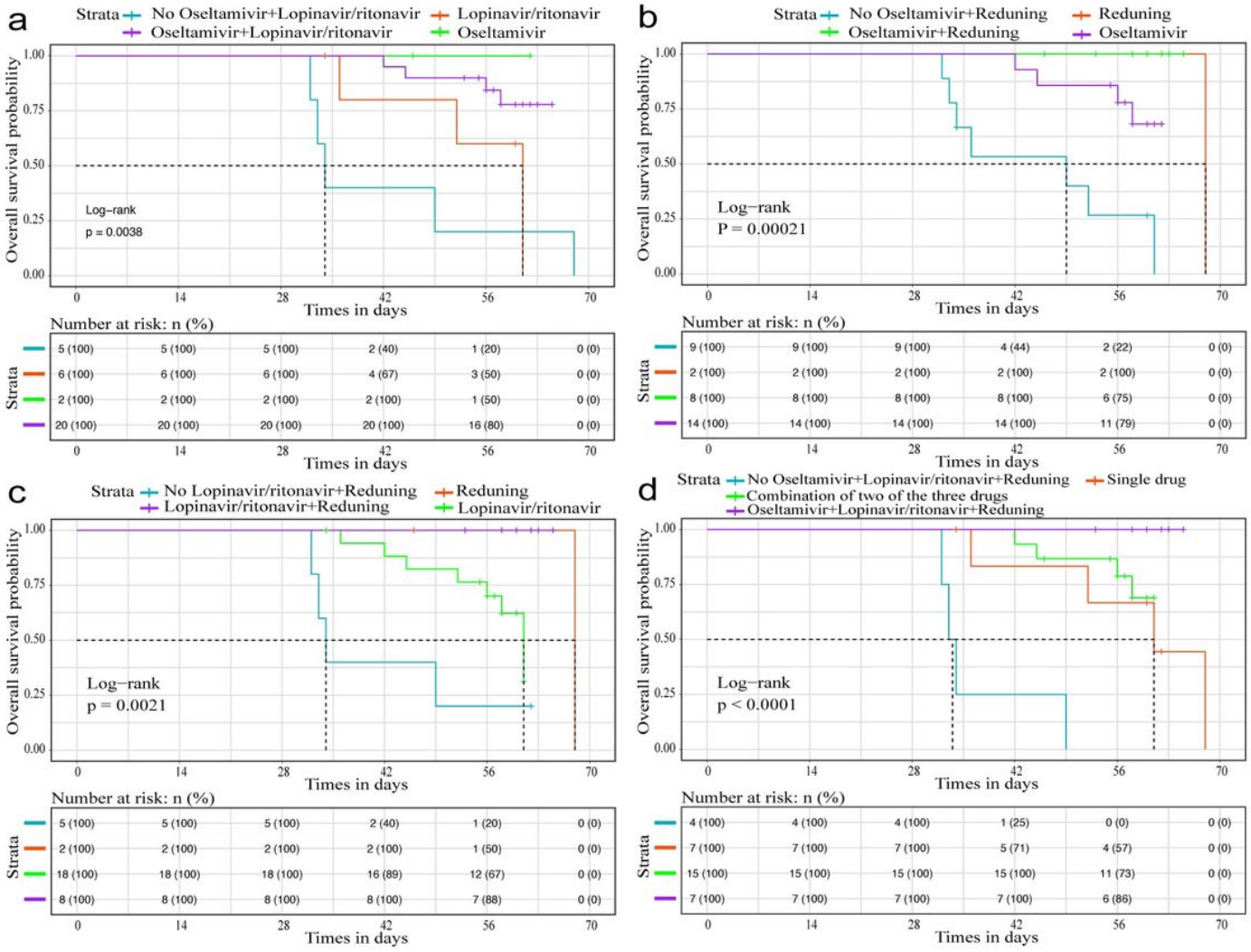

Figure 4

Effects of the different combinations of oseltamivir, lopinavir/ritonavir, and Reduning injection on the survival of coronavirus disease 2019 (COVID-19) patients with high-risk identified by the developed nomogram. (a) The combination of oseltamivir with lopinavir/ritonavir; (b) The combination of oseltamivir with Reduning injection; (c) The combination of lopinavir/ritonavir with Reduning injection; (d) The combination of oseltamivir, lopinavir/ritonavir, and Reduning injection.