Clinical Risk Factors for Long-term Hospital Stay in Common Patients with coronavirus disease 2019(COVID-19)

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Research article

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Abstract

Background

This study aimed to investigate the potential risk factors associated with hospital stay in mild patients with COVID-19.

Methods

A total of 109 laboratory-confirmed COVID patients with initial common subtype diseased by real-time RT-PCR that meet discharge standards were retrospectively included from January 16 to March 15 of 2020. Baseline demographic, clinical, laboratory examination was extracted from electronic medical records at the first day of admission and compared between short-term hospital stay and long-term hospital stay. Univariable and multivariable logistic regression methods were used to explore the risk factors associated with hospital stay.

Results

Of 109 COVID-19 patients, 61 patients were short-term stay (≤ 10 days) and 48 patients were long-term stay (> 10 days). The average age of patients in short-term stay were younger than those long-term stay ($P = 0.01$). Hypertension was the most common comorbidity (34%, 21/61), followed by diabetes (15%, 9/61) and Cardiopathy (8%, 5/61). Fever and cough were the typical clinical manifestation in two group. Decreased WBC, Hemoglobin and increased Monocyte, MLR (Monocyte Lymphocyte ratio) and Hypersensitive CRP showed a long-term stay (all $P < 0.05$). The treatment of Resochin and Human immunoglobulin had a shorter hospital stay. Multivariable regression showed that MLR and CRP on admission were risk factors for predicting the hospital stay, with the HR (hazard ratio 2.03, 1.02–5.39; $P = 0.022$) and (1.32, 1.05–3.24, $P = 0.045$) respectively.

Conclusions

The potential risk factors of MLR and CRP may help clinicians to predict the hospital stay of COVID-19 patients.

Background

The 2019 novel coronavirus (SARS-CoV-2) disease (COVID-19) [1–3] is a new and highly contagious respiratory disease, initially outbreaking in the end of 2019 from Wuhan China and quickly spread throughout the world [4–5]. Due to its extremely infectivity, as of 24:00 on April 14, 2020, a total of 1932760 confirmed cases of COVID-19 and a total of 115676 deaths have been reported [6], causing a pandemic worldwide.

To better understand the disease, systematic and effective diagnosis and treatment, several diagnosis and treatment plans and guidelines have been reported [7–8], and the median hospital stay of forty-seven discharged patients was 10 days [9]. Some studies indicated that patients' maximum lung involved peaked at approximately 10 days from the onset of initial symptoms in Wuhan [10]. meanwhile, patients outside Wuhan with symptoms longer than 10 days were less severe than those in Wuhan [11]. Therefore, the hospital stay in COVID-19 patients is one of the prognostic indicators, the estimation of risk factors for hospital stay is important for preventing transmission and facilitating diagnosis to establish the guidelines and criteria.

Here, 109 cases of the hospital with complete diagnostic data that meet discharge standards from January 16 to March 15 of 2020, including clinical features and laboratory examination was included to explore the risk factors of hospital stay for COVID-19 patients.

Methods

Study cohort

This retrospective study was approved by the institutional review board of the hospital and the written informed consents were waived. All hospitalized 109 patients were laboratory confirmed COVID-19 according to WHO interim guidance. Laboratory confirmation of SARS-CoV-2 was performed in certified tertiary care hospitals. RT-PCR assays were performed in accordance with the protocol established by the WHO [12]. The diagnostic criteria and discharge criteria were in line with "The new coronavirus pneumonia treatment program (Trial seventh edition)" issued by the Ministry of Health on March 3, 2020 [13]. The inclusion criteria: a). Positive COVID-19 nucleic acid test (RT-PCR method); b). Admission in the hospital from the first time since onset to discharge; c). The clinical classification was common; d). no lymphatic system disorders or other hematologic diseases to ensure a normal baseline values of blood parameters. Patients with acute coronary syndromes, renal or hepatic failure or systematic inflammatory diseases were excluded. In total, 48 COVID-19 patients suffered from long-term hospital stay and the other 61 short-term patients were collected. The mean age in long-term stay was 55.1 years (ranging from 22 years to 81 years).

Laboratory Procedures

PCR re-examination every other day after clinical remission of symptoms (fever, cough, et al) by throat-swab or sputum specimens. The criteria for discharge were absence of fever for at least 3 days, Pulmonary imaging showed significant improvement in acute exudative lesions, Two consecutive negative respiratory tract nucleic acid tests (sampling time at least 24 hours apart) [13]. The hospital stay was the days from admission to discharge (average, 12 days, 6 ~ 28 days). In this study, the optimal cut-off days of hospital stay was 10 days according to previous studies [9–11], and then the patients were classified into short-term hospital stay (≤ 10 days) and long-term hospital stay (> 10 days).

The baseline characteristics including demographics(age, sex, BMI, exposure history, et al), clinical features(typical symptoms(fever, cough, fatigue), comorbidity, et al), routine blood tests(white blood cell count(WBC), Neutrophils, Platelet count, D-dimer, Hemoglobin, Lymphocyte, Monocyte, MLR(Monocyte/Lymphocyte), et al), liver function parameters(LDH, ALT) and treatment strategies(Resochin, Lopinavir, Arbidol, Human immunoglobulin, et al) were collected at the first admission day.

Statistical Analysis

All statistics were analyzed with SPSS (version 25.0, IBM Crop. Armonk, NY, USA) and Medcalc (version 19.0, <https://www.medcalc.org>). Continuous variables were analyzed using student t test (mean $\pm$ standard deviation) and categorical variable with Chi-square (number(percentage)) test, as appropriate to compare differences between short-term and long-term hospital stay. Different parameters between groups($P < 0.05$) were further assessed by univariable and multivariable logistic regression(stepwise). Only independent risk factors with the hospital stay at univariate analysis were included in the multivariable model. The results were shown with hazard ratio (HR) with 95% confidence intervals (CI). The predictive accuracy of the independent factors was quantified by the area under the receiver operator characteristic (ROC) curves (AUC). The statistical significance levels were all two-sided with statistical significance set at 0.05.

Results

Baseline characteristics between short-term and long-term hospital stay

Detail comparison of characteristics in short-term and long-term group were presented in Table 1. The mean age in long-term stay was 55.1 years, significantly older than those in short-term stay($P = 0.01$). Most patients had an exposure history in both group (87%, 95/109), but smaller current smoker (8.2%, 9/109). Hypertension was the most common comorbidity (34%, 21/61), followed by diabetes (15%, 9/61) and Cardiopathy (8%, 5/61). The most common symptoms were fever and cough, followed by fatigue and Vomiting.

Table 1
Demographic, clinical and laboratory findings of COVID-19 patients

Characteristic	Short-term hospital stay (≤ 10 days) (n = 61)	Long-term hospital stay (> 10 days) (n = 48)	P value
Demographics Characteristic			
Age, years	46.4 $\pm$ 12.1	55.1 $\pm$ 11.5	0.01
Sex			
Male	41 (67.2%)	32 (66.7%)	1
Female	20 (32.8%)	16 (33.3%)	
Height	1.6 $\pm$ 0.1	1.62 $\pm$ 0.15	0.476
Weight	62.3 $\pm$ 11.4	64.7 $\pm$ 10.7	0.451
BMI	23.2 $\pm$ 3.1	24.0 $\pm$ 3.4	0.261
Exposure history	52(85.2%)	43(89.6%)	0.701
Current smoker	8(13.1%)	1(2.1%)	0.084
Clinical Characteristic			
Diabetes	6(9.8%)	3(6.2%)	0.745
Hypertension	11(18%)	10(20.8%)	0.902
Cardiopathy	2(3.3%)	3(6.2%)	0.783
COPD	1(1.6%)	1(2.1%)	1
Tuberculosis	1(1.6%)	0	1
Carcinoma	2(3.3%)	0	1
Chronic kidney disease	0	1(2.1%)	0.923
Chronic liver disease	3(4.9%)	1(2.1%)	0.788
Respiratory rate	18.1(0.7%)	17.5(1.0%)	0.321
Fever(temperature $\geq 37.3^{\circ}\text{C}$)	43 (70.5%)	35 (72.9%)	0.948
Cough	28 (45.9%)	26 (54.2%)	0.506
Fatigue	12 (19.7%)	10 (20.8%)	1
Vomiting	14 (23.0%)	11 (22.9%)	1

ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; WBC: white blood cells; IL: interleukin; CRP: C-reactive protein.

Characteristic	Short-term hospital stay (≤ 10 days) (n = 61)	Long-term hospital stay (> 10 days) (n = 48)	P value
Hemoptysis	2(3.3%)	3(6.2%)	0.904
Chest pain	4(6.6%)	5(10.4%)	0.707
Digestive Symptoms	4(6.6%)	4(8.3%)	1
Time from onset to admission	5.5 $\pm$ 3.5	6.5 $\pm$ 4.0	0.232
Laboratory findings			
WBC, $10^3/\text{mm}^3$	4.8 $\pm$ 0.3	4.3 $\pm$ 0.4	0.015
Neutrophils, $10^3/\text{mm}^3$	3.3 $\pm$ 1.4	4.1 $\pm$ 3.2	0.138
Hemoglobin, g/L	135.6 $\pm$ 13.1	128.0 $\pm$ 22.3	0.036
Lymphocyte, $10^3/\text{mm}^3$	1.3 $\pm$ 0.5	1.3 $\pm$ 0.9	0.739
Monocyte, $10^3/\text{mm}^3$	0.3 $\pm$ 0.01	0.4 $\pm$ 0.03	0.028
MLR (Monocyte Lymphocyte ratio)	0.28 $\pm$ 0.05	0.32 $\pm$ 0.03	0.030
Platelet count, $10^9/\text{L}$	212.9 $\pm$ 75.4	207.2 $\pm$ 67.7	0.681
Troponin, ng/mL			
> 28	22(36.1%)	20(41.7%)	0.691
D-dimer, $\mu\text{g}/\text{L}$	0.4 $\pm$ 0.1	0.5 $\pm$ 0.3	0.231
ESR, mm/Hour	65.6 $\pm$ 8.7	60.4 $\pm$ 5.1	0.191
Hypersensitive CRP, mg/L	17.4 $\pm$ 3.1	20.7 $\pm$ 1.8	0.024
LDH	225.8 $\pm$ 17.1	212.4 $\pm$ 6.2	0.159
ALT	24.9 $\pm$ 4.5	28.6 $\pm$ 3.1	0.320
Procalcitonin, ng/ml	0.03 $\pm$ 0.01	0.035 $\pm$ 0.02	0.233
IL-2, pg/mL	1.1 $\pm$ 0.7	1.9 $\pm$ 0.8	0.186
IL-4, pg/mL	2.0 $\pm$ 0.7	2.1 $\pm$ 0.8	0.473
IL-6, pg/mL	6.7 $\pm$ 2.3	9.1 $\pm$ 1.7	0.165
IL-10, pg/mL	3.4 $\pm$ 2.0	4.9 $\pm$ 1.8	0.115
ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; WBC: white blood cells; IL: interleukin; CRP: C-reactive protein.			

In blood routine tests, The WBC, Hemoglobin were decreased, and Monocyte, MLR (Monocyte Lymphocyte ratio) and Hypersensitive CRP were all increased in long-term stay ($P = 0.015$, $P = 0.036$, $P = 0.028$, $P = 0.03$ and $P = 0.024$, respectively). There was no statistical difference between Neutrophils, Lymphocyte, Platelet count, Troponin, lactate dehydrogenase (LDH), interleukin (IL), et al ($P > 0.05$, Table 1).

Five treatment strategies were used in the hospital, including Resochin, Lopinavir, Arbidol, Recombinant Human Interferon, Hormonotherapy and Human immunoglobulin (Table 2). Lopinavir (100%) and recombinant Human Interferon (almost 100%) were most used in two groups. More patients were treated with Resochin and Human immunoglobulin in short-term hospital stay compared to long-term stay ($P < 0.001$).

Table 2
Treatments of COVID-19 patients in two groups

Characteristic	Short-term hospital stay (≤ 10 days) (n = 61)	Long-term hospital stay (> 10 days) (n = 48)	P value
Treatments			
Resochin	45(73.8%)	37(77.1%)	< 0.001
Lopinavir	61(100.0%)	48 (100.0%)	0.213
Arbidol	55(90.2%)	47 (97.9%)	0.212
Recombinant Human Interferon	61(100.0%)	47 (97.9%)	0.904
Hormonotherapy	6 (9.8%)	8(16.7%)	0.441
Human immunoglobulin	44(72.1%)	31(68.9%)	< 0.001
Time from onset to fever	1.0 ± 1.0	1.0 ± 1.0	0.360
Time from onset to cough	2.0 ± 1.0	1.0 ± 1.0	0.190
Time from onset to COVID-19 negative	7.0 ± 4.0	20.0 ± 6.0	< 0.001
Time from onset to discharge	9.0 ± 3.0	21.5 ± 7.0	< 0.001

So, significant differences between the groups were found for patient's age, blood routine markers (WBC, Hemoglobin, Monocyte and MLR), treatment scheme (Resochin and Human immunoglobulin), the mean time from illness onset to COVID-19 negative, 7 days in short-term stay and 20 days in long-term stay. The mean time from onset to discharge was 9.0 days in short-term stay and 21.5 days in long-term stay (Table 2).

Identifying Independent Risk Factors for short-term and long-term hospital stay

Clinical variables including age, blood routine markers (WBC, Hemoglobin, Monocyte, MLR and CRP), were included in the univariable analysis. As shown in Table 3, all above parameters except Hemoglobin were independent predictors associated with higher risk of long-term hospital stay. Multivariate logistic regression analysis showed that MLR and CRP were significantly correlated with long-term stay for COVID-19 patients (HR = 2.03, 95%CI = 1.02–5.39; P = 0.022 and HR = 1.32, 95%CI = 1.05–3.24, P = 0.045, respectively, Table 3).

Table 3
Risk factors associated with long-term hospital stay of COVID-19 patients

Variables	Univariable		Multivariable	
	OR (95%CI)	P value	OR (95% CI)	P value
Age, years	1.09(1.01–1.21)	0.047	NA	NA
WBC	1.12(1.09–1.35)	0.028	NA	NA
Hemoglobin	1.03(0.96–1.06)	0.053	NA	NA
MLR	2.65(1.64–11)	0.016	2.03(1.02–5.39)	0.022
CRP	1.58(1.04–3.68)	0.038	1.32(1.05–3.24)	0.045

Predictive Performance Of Independent Predictors

The Accuracy, AUC, sensitivity, specificity of MLR for predicting long-term hospital stay were 0.7, 0.72, 68.9% and 70.8%, respectively (Table 4 and Fig. 1), with the optimal cutoff value 0.31. The optimal cutoff value of CRP was 19.3 mg/L. The Accuracy, AUC, sensitivity, specificity was 0.69, 0.67, 65.6% and 72.9%, respectively (Table 4 and Fig. 2).

Table 4
Performance of MLR and CRP for long-term hospital stay in COVID-19 patients

Variables	Accuracy	AUC (95%CI)	Sensitivity	Specificity	Youden	P value
CRP	0.69	0.67(0.61–0.76)	65.6%	72.9%	0.38	0.012
MLR	0.70	0.72(0.65–0.80)	68.9%	70.8%	0.40	0.003

Discussion

This retrospective cohort study identified several risk factors for long-term hospital stay with COVID-19 patients, which suggested the feasibility of this new methodology as a potential tool for COVID-19 evaluation in clinical outcome. In particular, higher MLR and CRP on admission were associated with the higher risk of longer hospital stay in COVID-19 patients with initial diagnosis of common type disease at

admission. Additionally, older age, decreased WBC, more treatment scheme of Resochin and Human immunoglobulin were more commonly seen in long-term hospital stay.

Previously, older age has been reported as an important independent predictor for COVID-19 death [14], due to the stronger host innate responses to virus infection leading to deficiency control of viral replication and more prolonged proinflammatory responses, which may lead to poor outcome [15]. The white blood cell slightly decreased due to the lymphocyte abnormality after the novel coronavirus infection by invading the human body immune system, which may lead to a longer hospital stay. The antiviral treatment Resochin recommended by Chinese guidelines [13] and Human immunoglobulin by improving the immunity might improve clinical outcomes for shorter hospital stay in COVID-19. The time from illness onset to COVID-19 negative in long-term stay (21.5 days) was longer than short-term group (9.0 days), which consistent with the discharge time.

In this study, MLR was significantly higher in long-term hospital stay patients than short-term group. Previous evidence demonstrated that monocytes were susceptible to human coronavirus (HCoV)-229E infection by strongly restricted OC43 replication [16]. After infection by HCoV-OC43, monocytes still could alive for more than 6 days and no apoptosis [17]. These studies suggested that monocytes might be stable in function during HCoV infection (SARS and COVID-19). Meanwhile, SARS-CoV often attacks cytotoxic T lymphocytes [18–19]. Lymphopenia is one of hematological abnormalities, which could predict the severity and clinical outcomes of COVID-19 patients [20]. Previous study showed that lymphocytes were significantly decreased in SARS patients, with more remarkable CD4 + and CD8 + lymphopenia in severe clinical illness or died patients [20]. Similar with SARS-CoV, COVID-19 infection also was associated with lymphocytes loss, it was supported by Chinese guidelines [13]. So, the MLR increased especially in long-term stay patients with a predicting AUC value of 0.72. Further research needed to be continued.

C-reactive protein (CRP) is an indicator of systemic inflammatory response. Lobo SM [21] reported that higher CRP levels reflected a stronger inflammatory response, may be associated with severe acute respiratory illness (SARI) evolving to acute respiratory distress syndrome (ARDS) and the death in patients with influenza A (H1N1) viral pneumonia. Therefore, it is not surprising that CRP was identified as an independent risk factor for severe condition in COVID-19 patients [22–24], which suggested that elevated CRP early in the course maybe a potential biomarker associate with risk of longer hospital stay. In this study, AUC of CRP was 0.67. Future research with multicenter and more sample size is needed to be researched.

The findings of this study should be interpreted in the light of potential limitations. Firstly, the small sample size is relatively small. Second, only common type of COVID-19 was included, and severe type and mild types were excluded in this analysis. Third, the prognosis values for MLR and CRP didn't have powerful performance, a combination of clinical parameters and CT findings are suggested in clinical practice. Four, the clinical and biochemical signs was retrospective collected from January 16 to March

15, treatment drugs and regimens were immature, which may influence the result. Large-scale independent prospective multicenter study is needed for further analysis and validating the results.

Conclusion

We found several risk factors for long-term hospital stay with COVID-19 patients. higher MLR and CRP on admission were associated with the higher risk of longer hospital stay in COVID-19 patients with initial diagnosis of common type disease at admission. The information from the current study can be used to might assist clinicians in making appropriate decisions and optimizing the use of hospital resources, recognize those with high risk of longer hospital stay even at the first outpatient visit, and facilitate early implementation of more appropriate interventions to decrease the risk of longer stay in COVID-19 patients initially diagnosed with common disease.

Declarations

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to an IRB decision which was made in the interest of ensuring patient confidentiality but are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethics approval

This study was approved by the ethics committee of Hwa Mei Hospital, University of Chinese Academy of Sciences; the informed consent requirement was waived.

Consent for publication

Not applicable

Funding

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Authors' contributions

WL, JF and YJ were involved in the study conception and the study design. YJ obtained the funding. WL and JF implemented the study. WL and JF were involved in data management and planning the analysis. WL and JF did the analysis. All authors were involved in interpreting the data. WL and JF wrote the first draft. All authors read and approved the final manuscript.

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Figures

Figure 1

The ROC curves of MLR for diagnosis short-term and long-term hospital stay in COVID-19 patients.

Figure 2

The ROC curves of CRP for diagnosis short-term and long-term hospital stay in COVID-19 patients.