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RESEARCH LETTER

The Role of Albumin/Globulin Ratio in Discharged COVID-19 Patients with Re-Positive Nucleic Acid Detection

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Novel coronavirus disease (COVID-19) pandemic is becoming a threat of global public health. Up to Aug 31, 2020, 182 countries and territories have reported a cumulative total of 24,854,140 COVID-19 cases; 838,924 of them have died (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). Recent data noticed that SARS-CoV-2 RNA test results of the recovered COVID-19 patients returned positive, termed "re-positive" phenomenon.[1,2] However, the clinical characteristics and the immune biomarkers of "re-positive" COVID-19 patients are still far from being fully understood. We therefore conducted this retrospective study to clarify the clinical features and possible risk predictors of "re-positive" in discharged COVID-19 patients.

From Jan 17, 2020, to Mar 16, 2020, 503 COVID-19 patients were discharged from eight hospitals in Wenzhou City, Zhejiang Province, China. Patients were discharged if they met the criteria based on the National Health Commission of the People's Republic of China, the diagnosis and treatment plan for the novel coronavirus disease (7th). We followed up 369 COVID-19 convalescent patients. The nasopharyngeal and cloacal swab samples were both detected for SARS-CoV-2 nucleic acid every week in one-month follow-up after discharge. Among them, 23 discharged patients identified positive results again. We collected and analyzed the demographic, clinical characteristics, and critical laboratory findings of 369 discharged COVID-19 patients on the first admission. The demo-graphics and clinical characteristics between COVID-19 patients with and without "re-positive" are presented in Table 1. Recent studies found that young COVID-19 patients are more likely to appear in the "re-positive" phenomenon.[3] As shown in Table 1, there was no significant difference in age and gender distribution. There were no significant differences in initial clinical symptoms and laboratory findings at baseline between Re-positive and Non-re-positive group.

Subsequently, we did correlation analysis to demonstrate whether specific laboratory indicators are related to the critical period of these "re-positive" patients' disease processes (Supplemental Table). These patients had experienced an average of 22 days (IQR: 16–29.5) of hospital stay, while 7 days (IQR: 7–13) of the duration from hospital discharge to positive again. Meanwhile, the mean duration of antivirus treatment was 12 days (IQR: 9–17). The average period from onset of symptoms to the end of antivirus treatment was 16 days (IQR: 11.25–22.75).

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Table 1 Characteristics at Baseline in COVID-19 Patients with and without Re-Positive Findings

Variables	Re-Positive Group (N=23)	Non-Re-Positive Group (N=346)	p
Age (%)			0.8123
≤45	9 (39.1)	150 (44.0)	
>45	14 (60.9)	191 (56.0)	
Sex (%)			1
F	12 (52.2)	171 (50.1)	
M	11 (47.8)	170 (49.9)	
Medical history			
Hypertension - n (%)			0.1063
N	15 (65.2)	271 (81.4)	
Y	8 (34.8)	62 (18.6)	
Diabetes - n (%)			0.7444
N	20 (87.0)	304 (91.3)	
Y	3 (13.0)	29 (8.7)	
Coronary heart disease - n (%)			0.4702
N	22 (95.7)	331 (99.4)	
Y	1 (4.3)	2 (0.6)	
Chronic heart diseases - n (%)			0.5786
N	21 (91.3)	317 (95.2)	
Y	2 (8.7)	16 (4.8)	
Cerebrovascular disease - n (%)			0.7473
N	22 (95.7)	328 (98.8)	
Y	1 (4.3)	4 (1.2)	
Laboratory parameters on fist hospital admission			
Procalcitonin, median [IQR], ng/mL	0.08 [0.05, 0.25]	0.10 [0.05, 0.25]	0.5792
Procalcitonin - n (%)			1
≤0.046	4 (26.7)	63 (24.8)	
>0.046	11 (73.3)	191 (75.2)	
C-reactive protein, median [IQR], mg/L	12.00 [3.42, 32.70]	8.95 [3.51, 25.30]	0.8316
C-reactive protein - n (%)			0.8704
≤8	10 (43.5)	156 (47.6)	
>8	13 (56.5)	172 (52.4)	
White-cell count, median [IQR], 10^9/L	5.09 [4.20, 6.54]	4.71 [3.80, 6.04]	0.32
White-cell count - n (%)			0.8816
[4, 10]	16 (69.6)	213 (65.3)	
<4	6 (26.1)	101 (31.0)	
>10	1 (4.3)	12 (3.7)	
Neutrophil count, median [IQR], 10^9/L	3.20 [2.35, 4.10]	2.90 [2.11, 4.03]	0.32
Neutrophil count - n (%)			0.9241
[1.8, 6.3]	19 (82.6)	258 (79.1)	
<1.8	3 (13.0)	51 (15.6)	
>6.3	1 (4.3)	17 (5.2)	
Lymphocyte count, median [IQR], 10^9/L	1.33 [0.90, 1.53]	1.30 [0.95, 1.58]	0.9395

(*Continued*)

Table 1 (Continued).

Variables	Re-Positive Group (N=23)	Non-Re-Positive Group (N=346)	p
Lymphocyte count - n (%)			NaN
[1.1, 3.2]	15 (65.2)	219 (67.2)	
<1.1	8 (34.8)	107 (32.8)	
>3.2	0 (0.0)	0 (0.0)	
Hemoglobin, median [IQR], g/L	135.00 [125.00, 143.50]	134.00 [124.00, 146.00]	0.7933
Hemoglobin - n (%)			0.9017
≤110	1 (4.3)	24 (7.4)	
>110	22 (95.7)	302 (92.6)	
Platelet count, median [IQR], 10^9/L	189.00 [149.00, 219.00]	187.00 [153.00, 235.50]	0.8365
Platelet count - n (%)			1
≤100	0 (0.0)	7 (2.1)	
>100	23 (100.0)	319 (97.9)	
Lymphocyte-to-white-cell ratio, median [IQR]	0.26 [0.19, 0.30]	0.28 [0.21, 0.35]	0.3556
Neutrophil-to-lymphocyte ratio, median [IQR]	2.40 [2.04, 3.46]	2.21 [1.56, 3.30]	0.3545
Platelet-to-lymphocyte ratio, median [IQR]	145.03 [121.64, 195.21]	150.53 [114.09, 205.04]	0.9864
Albumin, median [IQR], g/L	42.20 [37.90, 43.70]	41.00 [37.45, 43.50]	0.4918
Albumin - n (%)			0.6428
>40	12 (63.2)	173 (54.9)	
≤40	7 (36.8)	142 (45.1)	
Globulin, median [IQR], g/L	27.60 [26.50, 32.05]	28.60 [25.55, 31.40]	0.9201
Globulin - n (%)			0.6436
[20, 40]	19 (100.0)	301 (95.6)	
<20	0 (0.0)	7 (2.2)	
>40	0 (0.0)	7 (2.2)	
Albumin-to-globulin ratio, median [IQR]	1.42 [1.29, 1.57]	1.44 [1.26, 1.62]	0.6946
Alanine aminotransferase, median [IQR], IU/L	20.00 [16.00, 29.00]	22.50 [14.00, 34.75]	0.6563
Alanine aminotransferase - n (%)			0.7812
≤69	23 (100.0)	315 (96.6)	
>69	0 (0.0)	11 (3.4)	
Aspartate aminotransferase, median [IQR], IU/L	23.00 [18.25, 28.25]	24.00 [18.00, 34.00]	0.4345
Aspartate aminotransferase - n (%)			0.6405
≤46	23 (100.0)	311 (95.7)	
>46	0 (0.0)	14 (4.3)	
Serum creatinine, median [IQR], μmol/L	61.00 [55.00, 73.00]	63.00 [54.00, 75.30]	0.9513
Creatine kinase, median [IQR], IU/L	63.00 [46.50, 83.40]	67.00 [48.70, 107.50]	0.4705
Creatine kinase - n (%)			0.5435
Abnormal [$]	1 (5.0)	35 (12.2)	
Normal [$]	19 (95.0)	252 (87.8)	
Lactate dehydrogenase, median [IQR], IU/L	218.50 [189.50, 256.75]	211.00 [174.00, 264.00]	0.9627
Lactate dehydrogenase - n (%)			1
≤245	12 (66.7)	187 (67.0)	
>245	6 (33.3)	92 (33.0)	

Notes: [$] Abnormal was defined when creatine kinase was greater than 174 IU/L for male and greater than 140 IU/L for female; normal was defined when creatine kinase was less than or equal to 174 IU/L for male and less than or equal to 140 IU/L for female. Data are presented as count (percentage) for categorical outcomes and as median [quartiles] for continuous outcomes. Groups comparison were using Chi-square test or Fisher's exact test for categorical variables and Kruskal–Wallis rank sum test for quantitative variables. P-values of less than 0.05 was regarded as significant. P-values presented in this table have not been adjusted for multiplicity. No imputation was made for missing data. All statistical analyses were performed with R software (version 3.6.3; www.r-project.org).

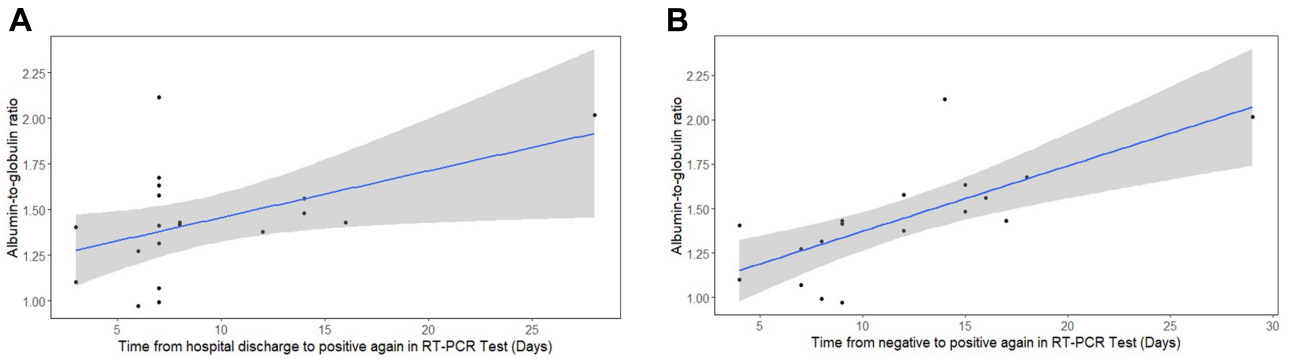

Figure 1 Correlation analysis for albumin/globulin ratio (AGR) and the period from hospital discharge to positive again (**A**) or the duration from last negative to positive again (**B**).

Overall, there were no apparent differences in the two age groups. As shown in Figure 1A, correlation analysis indicated that there was a significant positive correlation existing between AGR at first admission and the period from hospital discharge to positive again in these 23 patients (r=0.49, p=0.0343). We also found that AGR at first admission was markedly positively correlated (r=0.72, p=0.00048) with the duration from last negative to positive again (Figure 1B).

In summary, these 23 "re-positive" patients showed several features as a mild symptom, which is consistent with a previous study.[3] However, there were no more cases in the lower age group in our study. This may be related to the sample size and age stratification of the present study. Hypertension, markedly common in older patients, maybe a host risk factor for severe SARS-CoV-2.[4] AGR combines the nutritional as well as the inflammatory status in one measure, it may be a good indicator reflecting these two factors.[5] It can be regarded as an index for predicting the prognosis of AECOPD and other inflammatory diseases.[6] Recent studies indicated that a low AGR may respect a susceptible state to infection.[5,6] We suggested that "re-positive" patients may not sufficiently apparent the virus. Our results indicated that AGR may potentially have a predictive effect in "re-positive" discharged COVID-19 patients. Further definitive largescale clinical studies are feasible and needed.

Ethics Approval and Consent to Participate

The study complied with the declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Wenzhou Medical University (No.2020-004). Informed consent was obtained from all participants.

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Disclosure

All authors report no potential conflicts of interest for this work.

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