Journal of Clinical Toxicology
ISSN: 2161-0495
OPEN ACCESS Freely available online
Research Article

High Rate of Increased Level of Plasma Angiotensin II and its Gender Difference in Covid-19: An Analysis of 55 Hospitalized Patients with Covid-19 in a Single Hospital, Wuhan, China

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ABSTRACT

Aim: 2019 Novel coronavirus disease (COVID-19) is turning into a pandemic globally lately. There were few reports illustrated the circulating levels of Angiotensin II (AngII) in COVID-19. This study aimed to demonstrate the circulating levels of AngII in COVID-19 and how it correlated to the disease.

Methods and results: We enrolled 55 patients with COVID-19 admitted to Renmin Hospital of Wuhan University from January 21st to February 21st, 2020. Demographic data were collected upon admission. COVID-19 nuclear acid, plasma AngII, Renin and aldosterone in the lying position without sodium restriction, and other laboratory indicators were together measured by the laboratory department of our hospital. Of the 55 patients with COVID-19, 34(61.8%) had an increased level of AngII. A high level of AngII was identified in male patients and in critically ill patients. The level of blood lymphocyte, PCT, ALT, and AST were remarkably severe with patients of normal level of AngII ($p<0.05$). CD4/CD8 cells ratio was significantly higher in patients of normal level of AngII ($p<0.05$). The results of binary logistic regression analysis showed that the severity of COVID-19 (OR=4.123) and CD4/CD8 ratio(OR=4.050) were the co-directional impact factor while female(OR=0.146) was inverse impact factor of elevated AngII level.

Conclusion: High rate of increased level of AngII and its gender differences were detected in COVID-19 patients. Elevated AngII level were correlated with the severity of COVID-19 and CD4/CD8 ratio.

Keywords: 2019 Novel coronavirus disease (COVID-19); Angiotensin II (AngII); CD4/CD8 cells

ABBREVIATIONS

COVID-19: 2019 Novel coronavirus disease; AngII: Angiotensin II; ACE2: Angiotensin-converting enzyme 2; SARS-Cov-2: Severe Acute Respiratory Syndrome Corona-virus 2; AT1R: Angiotensin II Type 1 Receptor; RT-PCR: Real-time reverse-Transcriptase Polymerase-Chain-Reaction; IQR: Inter Quartile Range; PaO2: Alveolar Oxygen Partial Pressure; FiO2: Fraction of Inspiration O2; ALD: Aldosterone; AARR: Aldosterone/ Renin Ratio; Ly: Lymphocyte; HB: Hemoglobin; PLT: Platelet Count; CRP: C-reactive Protein; PCT: Procalcitonin; BUN: Blood Urea Nitrogen; sCr: Serum Creatinine; ALT: Aspartate Amino Transferase; AST: Alanine Amino Transferase; ALB: Albumin; LDH: Lactate Dehydrogenase; CK: Creatinine Kinase; DD:D-Dimer; APTT: Activated Partial Thromboplastin Time; CD: Cluster of Differentiation; CD3+ Count: CD3 Positive Cells Count; CD3+CD4+ Count: CD3 Positive CD4 Positive Cells Count; CD3+CD8+ Count: CD3 Positive CD8 Positive Cells Count; CD4+/CD8+: CD4+/CD8+ Ratio; CD56+CD16+CD3- count: CD56 positive CD16 positive CD3 negtive cells count; CD19+CD3- count: CD19 positive CD3 negative cells count; Ang-(1-7): Angiotensin-(1-7)

BACKGROUND

2019 Novel coronavirus disease (COVID-19) was rampant in China since December 2019 and spread worldwide gradually [1-5]. Angiotensin-converting enzyme 2 (ACE2) is identified as an important functional receptor for SARS-Cov-2 [6,7]. The host receptor ACE2 degrades after binding to SARS-Cov-2, leading to ACE2 loss and prompting the target oragns injury [6]. ACE2

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Received: March 02, 2021; **Accepted:** March 16, 2021; **Published:** March 23, 2021

Citation: Liu N, Hong Y, Chen R, Zhu H (2021) High Rate of Increased Level of Plasma Angiotensin II and its Gender Difference in Covid-19: An Analysis of 55 Hospitalized Patients with Covid-19 in a Single Hospital, Wuhan, China. J Clin Toxicol. S16:001.

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and ACE are homologues with opposite functions in the renin–angiotensin system [8,9]. ACE converts angiotensin I into a vital vasoactive peptide called angiotensin II (AngII), whereas ACE2 hydrolyzes AngII into a series of vasodilators. Theoretically, the loss of ACE2 may reduce degradation of AngII and cause vasoconstriction and oxidative stress. Recently, a small sample study found that plasma angiotensin II levels were significantly increased and linearly associated to viral load and lung injury in COVID-19 [10]. However, the sample size was too small to observe the exact relationship with the disease. Therefore, this study aimed to demonstrate the expression of angiotensin II in COVID-19 and how it correlated to the disease.

METHODS

Study design and participants

This was a single center, retrospectively and observational analysis. We enrolled 55 patients with COVID-19 admitted to Renmin Hospital of Wuhan University from January 21st to February 21st, 2020. All patients hadn't taken any angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor (AT1R) blockers, and diuretics two weeks before and during hospitalization. The diagnosis of hypertension and diabetes were based on 2018 ESC/ESH Guidelines for the management of arterial hypertension and 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed incollaboration with the EASD.COVID-19 was diagnosed based on the Diagnosis and Treatment Scheme for New Coronavirus Pneumonia (Pilot Edition 5, Revised version) published by the National Health Commission of China [11]. A confirmed case with COVID-19 was defined as a positive result to real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasal and throat swab specimens. All patients had imaging pneumonia. Critically ill COVID-19 was defined as meeting either one of the flowing criteria:

- Respiratory distress with respiratory rate more than 30 times/min
- Oxygen saturation ≤ 93% in resting state
- PaO2/FiO2 ≤ 300 mmHg (1 mmHg=0.133 kPa)
- Respiratory failure requires mechanical ventilation
- Shock
- Combining other organ failures requires ICU monitoring and treatment. The study was approved by the ethics committee of Renmin Hospital of Wuhan University (Application ID: [WDRY2020-K114]).

Clinical and laboratory data collection

Demographic data including age, gender, and previous medical history were collected. Laboratory assessments consisting of plasma AngII, renin and aldosterone in the lying position without sodium restriction, complete blood count, blood chemistry, coagulation test, liver and renal function, electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase and creatine kinase were tested by the laboratory department.

Statistical analysis

All statistical analyses were performed by SPSS for mac software, version 23.0. Continuous variables were presented as the means and standard deviations or medians and interquartile ranges (IQR) as appropriate. Categorical variables were summarized as the counts and percentages in ehach category. Independent-Samples T test or the Mann-Whitney U test were applied to continuous variables, chi-square tests and Fisher's exact tests were used for categorical variables as appropriate. Predictors of AngII anomaly were analyzed by logistic regression. A value of $p<0.05$ was considered statistically significant.

RESULTS

By Feb 21st, 2020, 55 confirmed cases of COVID-19 were included in this study. All of them had data on plasma AngII, renin and aldosterone in the lying position without sodium restriction. 34(61.8%) cases had an increased level of AngII while most patients had normal levels of renin and aldosterone (Table 1). The critically ill patients had higher level of AngII than the non-critically ill patients (Table 2).

Table 1: The baseline value of RAS system in COVID-19 patients.

RAS system parameter	Normal range	Total (N=55)	Abnormality, N(%)
AngII(pg/ml, IQR)	25-129	134.2(117.8,155.3)	34(61.8)
Renin(pg/ml, IQR)	45383	10.9(6.3,16.9)	11 (20)
ALD(pg/ml, IQR)	10-160	129.5(112,149.8)	9(16.4)
AARR(IQR)	/	12.3(7.6,19.2)	/

Abbreviations: Ang II: angiotensin II, ALD: aldosterone, AARR: aldosterone/Renin ratio

To further analyze the demographic, clinical and laboratory characteristics of the patients with increased AngII level, we divided the patients into the AngII increased group and the AngII normal group. No difference was seen in renin and aldosterone values between the two groups (Table 3). To our interest, as shown in Table 4, the patients with increased level of AngII were more severe than those with normal level of AngII [18(52.9%) vs. 5(23.8%), p=0.033]. Significant gender differences were found between the two groups. In addition, there was no significant difference in the history of hypertension and the use of vasoactive drugs such as norepinephrine and dopamine in the two groups.

RAS system	Normal range	Total (N=55)	Non-critically ill group(n=32)	Critically ill group(n=23)	p value
AngII(pg/ml, IQR)	25-129	134.2(117.8,155.3)	127.4(93.5,145.6)	147.4(131.5,169.5)	0.009*
Renin(pg/ml, IQR)	45383	10.9(6.3,16.9)	10.2(5.8,16.2)	14.7(6.5,19.7)	0.232
ALD(pg/ml, IQR)	10-160	129.5(112,149.8)	133.4(115.1,168.1)	115.9(104.8,135.7)	0.05
AARR(IQR)	/	12.3(7.6,19.2)	14.1(10.1,21.5)	9.1(6.2,18.7)	0.028*

Abbreviations: Ang II: angiotensin II, ALD: aldosterone, AARR: Aldosterone/Renin Ratio

Table 2: Comparison of RAS system between non-critically ill and critically ill patients with COVID-19.

RAS system	Normal Range	Total (N=55)	Ang II increased group(n=34)	Ang II normal group(n=21)	p value
AngII(pg/ml, IQR)	25-129	134.2(117.8,155.3)	149.7(137.8,165.1)	99.4(84.5,119.1)	0
Renin(pg/ml, IQR)	45383	10.9(6.3,16.9)	11.1(6.0,19.5)	10(6.5,16.9)	0.842
ALD(pg/ml, IQR)	10-160	129.5(112,149.8)	133.4(112.4,142.1)	121.8(106.9,163.5)	0.591
AARR(IQR)	/	12.3(7.6,19.2)	12.3(7.0,19.9)	12.4(9.3,19.5)	0.665

Abbreviations: Ang II: angiotensin II, ALD: aldosterone, AARR: aldosterone/Renin ratio

Table 3: Comparison of RAS system between COVID-19 patients grouped by Ang II level.

Demographic and clinical characteristics	Total (N=55)	Ang II increased group(n=34)	Ang II normal group(n=21)	p value
Gender female, n(%)	20(36.4)	7(12.7)	13(21.7)	0.002*
Age(year, IQR)	53(45,66)	56(44.75,66.5)	52(45.5,67)	0.0822
History of chronic disease, n(%)	25(45.5)	18(32.7)	7(12.7)	0.156
History of hypertension, n(%)	16(29.1)	13(23.6)	3(5.5)	0.057
History of diabetes, n(%)	8(14.5)	7(12.7)	1(1.8)	0.136
Newly-onset hypertension, n(%)	10(18.2)	6(10.9)	4(7.3)	1
Systolic pressure(mmHg, IQR)	129(122,141)	134(122,141)	126(123,140)	0.64
Diastolic pressure(mmHg, IQR)	81(76,90)	80(73,91)	83(72,96)	0.641
The severity of COVID-19	-	-	-	-
Non-critically ill, n(%)	32(58.2)	16(29.1)	16(29.1)	0.033*
Critically ill, n(%)	23(41.8)	18(32.7)	5(9.1)	-
Usage of vasoactive drugs , n(%)	7(12.7)	5(9.1)	2(3.6)	0.696

Critically ill COVID-19 was defined as meeting either one of the flowing criteria: 1) Respiratory distress with respiratory rate more than 30 times/min; 2) Oxygen saturation ≤93% in resting state; 3) PaO2/FiO2 ≤ 300 mmHg (1 mmHg=0.133 kPa).4) Respiratory failure requires mechanical ventilation; 5) Shock; 6) Combining other organ failures requires ICU monitoring and treatment.

Vasoactive drugs included norepinephrine, dopamine, Adrenaline and Isoproterenol.

Table 4: Comparison of Demographic and clinical characteristic between COVID-19 patients grouped by Ang II level.

As presented in Tables 5 and 6, there were statistical difference in the level of blood lymphocyte[0.66(0.36,1.03) vs. 1.02 (0.68, 1.42), p=0.021], PCT[0.07 (0.03, 0.12) vs. 0.03 (0.02, 0.07), p=0.007], CD4/CD8 cells ratio[2.35 (1.86, 3.22) vs.1.55 (1.11, 2.5), p=0.015], ALT[27 (21, 44) vs. 19 (13,34), p=0.03], AST[24.5(18.5,36) vs. 18(14,22.5), p=0.028], CD3+CD8+ cells [128(51,206) vs. 218(123,322), p=0.016], CD3+CD8+ cells proportion [20.1(14,25.6) vs. 25.4 (20.9,35.7),p=0.011], CD56+CD16+CD3- cells [81(56,102)/111(66,171) p=0.031] between the AngII increased group and the AngII normal group. The rate of Lymphopenia [27(79.4%) vs. 11(52.4%), p=0.035] were remarkably higher in Patients with elevated AngII level.

Furthermore, we evaluated the effect of various clinical and laboratory indicators on elevated AngII level with binary regression analysis. During the analysis, we applingII elevated or not as dependent variables, while applying the severity of COVID-19, gender, lymphocyte, PCT, CD4/CD8 cells ratio,CD3+CD8+ cells count, CD3+CD8+ cells proportion, CD56+CD16+CD3- cells count as independent variables, among these independent variables. The results showed that the severity of COVID-19 [OR=4.123, 95%CI(1.07-15.877), p=0.040] and CD4/CD8 ratio[OR=4.050, 95%CI(1.207-13.588), p=0.024]was the co-directional impact factor while female[OR=0.146,95%CI(0.035-0.603), p=0.008] were reverse impact factor of elevated AngII level (Figure 1).

DISCUSSION

As COVID-19 outbreak continues to spread globally, the newly discovered infectious disease may cause global public health crisis. It was reported that on February 28th, the World Health Organization raised the global risk of transmission and impact of COVID-19 to "very high" level [12]. Although some literatures have been published, as a new epidemic infectious disease, the epidemiological and clinical characteristics of COVID-19 are not well known. Human ACE2 is confirmed to be the receptor and a gateway for SARS-CoV-2 [6]. ACE2 is a zinc metalloproteinase homologous to ACE, which can directly convert Ang II to Ang-(1-7), thus acting as a negative regulator of the renin-angiotensin system. Therefore, it could be hypothesized that a decrease in ACE2 caused by SARS-CoV-2 infection will reduce the degradation of Ang II, thereby causing an increase in Ang II [8-9]. A recently published small sample study not only confirmed this hypothesis, but also found that angiotensin II levels were linearly associated to viral load and lung injury in COVID-19 [10]. This study reported a high rate of increased level of AngII in COVID-19 patients, which could be verified with the study above. There was no significant difference in the history of hypertension and the use of vasoactive drugs such as norepinephrine and dopamine in the two groups, which means that abnormality of AngII cannot be blamed to a history of hypertension and the use of vasoactive drugs.

Laboratory assessments	Normal range	Total (N=55)	Ang II increased group(n=34)	Ang II normal group(n=21)	p value
WBC(109/L,IQR)	3.5-9.5	6.76(5.25,9.36)	6.98(4.77,10.06)	6.67(5.67,8.23)	0.952
Ly (109/L,IQR)	1.1-3.2	0.74(0.49,1.19)	0.66(0.36,1.03)	1.02(0.68,1.42)	0.021*
HB(g/L,IQR)	130-175	128(114,142)	127.5(112,142.8)	128(114,140)	0.959
PLT(109/L,IQR)	125-350	198(142,263)	189(122.3,263.8)	238(171,274)	0.225
CRP(mg/L,IQR)	0-8	7.73(2.88-26.36)	11.2(3.67,44.99)	7.03(1.53,21.20)	0.253
PCT (ng/mL,IQR)	0-0.09	0.06(0.03,0.1)	0.07(0.05,0.12)	0.03(0.02,0.07)	0.007*
ALT(U/L,IQR)	18507	26(18,38)	27(21,44.3)	19(13,34)	0.030*
AST (U/L,IQR)	15-40	21(16,32)	24.5(18.5,36)	18(14,22.5)	0.028*
ALB(g/L,IQR)	40-55	33.9(30.1,37.4)	33.6(30.1,36.1)	36(29.8,38.9)	0.253
BUN(mmol/L,IQR)	3.2-8.0	4.9(3.0,7.5)	4.95(3.1,8.38)	4.3(2.85,6.45)	0.287
sCr(umol/L,IQR)	Male:57-97	60(48.2,67.4)	61.3(54.6,70.3)	55.2(45.7,65.8)	0.203
	Female:41-81				
LDH(U/L,IQR)	120-250	214(179,354)	244(188.3,400)	201(176.5,258)	0.057
CK(U/L,IQR)	50-310	39(26,57)	38(26.8,59)	40(25,59)	0.972
Na(mmol/L,IQR)	137-147	135(132.1,138.7)	134.9(131.6,137.5)	136.3(134,138.9)	0.194
K(mmol/L,IQR)	3.5-5.3	4.01(3.70,4.61)	3.99(3.64,4.62)	4.2(3.82,4.63)	0.55
DD(mg/L,IQR)	0.01-0.55	1.96(0.69,4.92)	3.46(0.82,6.56)	1.2(0.63,30.2)	0.121
APTT(s,IQR)	25-31.3	26.5(23.8,29.1)	26.1(24.0,28.1)	26.8(23.5,30.2)	0.808
Urine protein positive, n(%)	/	7(12.7)	6(10.9)	1(1.8)	0.232
Urine RBC positive, n(%)	/	3(5.35)	2(3.64)	1(1.8)	1
Ly<1.1, n(%)	/	38(69.1)	27(49.1)	11(20)	0.035*
PCT>0.09, n(%)	/	15(27.3)	12(21.8)	3(5.5)	0.123

Abbreviations: Ly: Lymphocyte; HB: Hemoglobin; PLT: Platelet Count; CRP: C-Reactive Protein; PCT: Procalcitonin; BUN: Blood urea nitrogen; sCr: serum creatinine; ALT: Aspartate Aminotransferase; AST: Alanine Aminotransferase; ALB: Albumin; LDH Lactate Dehydrogenase; CK: Creatinine Kinase; DD:D-dimer; APTT: Activated Partial Thromboplastin Time

Table 5: Comparison of laboratory assessments between COVID-19 patients grouped by Ang II level.

Lymphocyte marker	Normal Range	Total (N=46)	Ang II increased group(n=27)	Ang II normal group(n=19)	p value
CD3+ count (/uL;IQR)	1185-1901	561(274.3;776.3)	439(178;741)	669(448;841)	0.073
CD3+ (%;IQR)	64.19-75.77	68.9(60.75;77.93)	69.1(55.5;82.1)	68.7(66.4;77.6)	0.51
CD3+CD4+ count (/uL;IQR)	561-1137	335.5(157.8;488.3)	298(122;488)	390(234;504)	0.16
CD3+CD4+ (%;IQR)	30.09-40.41	44.9(34.4;51.1)	47.4(34.5;56.2)	41.2(34;47.9)	0.212
CD3+CD8+ count (/uL;IQR)	404-754	163(74.8;243.5)	128(51;206)	218(123;322)	0.016*
CD3+CD8+ (%;IQR)	20.74-29.42	23.0(17.1;29.3)	20.1(14;25.6)	25.4(20.9;35.7)	0.011*
CD4+/CD8+	1.36-2.61	2.05(1.47;2.55)	2.35(1.86;3.22)	1.55(1.11;2.54)	0.015*
CD56+CD16+CD3- count (/uL;IQR)	175-567	86.5(62.8;125.5)	81(56;102)	111(66;171)	0.031*
CD56+CD16+CD3- (%;IQR)	10.04-19.78	13.75(7.95;20.73)	12.9(7;24)	13.8(8.3;18.9)	0.832
CD19+CD3-count (/uL;IQR)	180-324	91(55.8;155.8)	73(46;131)	134(59;170)	0.072
CD19+CD3-(%;IQR)	10.12-15.42	13.8(8.5;21.7)	14.1(5.7;24.4)	13.5(9.6;19.5)	0.422

CD: cluster of differentiation; CD3+ count: CD3 positive cells count; CD3+CD4+ count: CD3 positive CD4 positive cells count; CD3+CD8+ count: CD3 positive CD8 positive cells count; CD4+/CD8+: CD4+/CD8+ ratio; CD56+CD16+CD3-count: CD56 positive CD16 positive CD3 negtive cells count; CD19+CD3-count: CD19 positive CD3 negtive cells count

Table 6: Comparison of Lymphocyte classification between COVID-19 patients grouped by Ang II level.

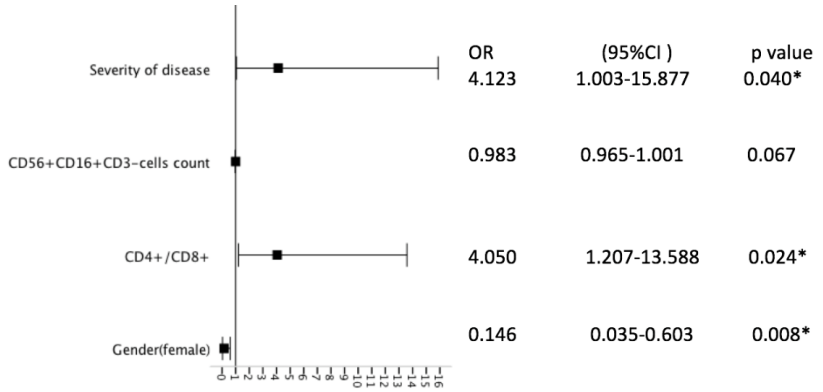

Figure 1: The effect of clinical and laboratory indicators on elevated AngII level with binary regression analysis.

This study showed a significant difference in the severity of COVID-19 in the elevated AngII group, and the severity of COVID-19 was a risk factor of increased AngII level. When grouped according to disease severity, AngII was remarkably higher in critically ill patients than those with mild disease. That implied that AngII level was closely related to disease severity.

Furthermore, this study found that the level of blood lymphocyte, CD3+CD8+ cells, CD56+CD16+CD3- cells, CD3+CD8+ cells proportion were dramatically lower and the CD4/CD8 cells ratio was higher in the elevated AngII group than the normal AngII group. In addition, CD4/CD8 cells ratio was a risk factor of increased AngII level. As we know, CD3+CD8+ cells, CD56+CD16+CD3- cells are killer cells that can recognize and eliminate virus-infected cells. This finding suggested that elevated AngII level may be associated with a reduction in killer cells. Accumulating evidences showed that CD8+ T cells are mediators of hypertension. Hypertension in response to AngII treatment was reduced by ~50% in Cd8−/− mice [13-15]. These studies may provide clues to explain the finding that there was no statistically significant difference in the proportion of new hypertension in the two groups grouped by angiotensin levels. In addition, According to literature reports and our clinical observations, patients with COVID-19 often suffer from immune disorders and even immune storms [16]. What role AngII plays in immune disorders in COVID-19 needs further concern.

There is no gender difference in the mean baseline values for plasma Ang II among normal population [17]. However, this study revealed significant gender differences in the mean baseline values for plasma Ang II among COVID-19 patients. Since ACE2 gene is located on the X chromosome, and estrogen increases ACE2 expression, ACE2 expression is higher in female than male [18]. Considering the gender differences in ACE2 expression, the gender differences in AngII level might deduce less loss of ACE2 in female patients. However, the exact mechanism needs to be further explored.

CONCLUSION

In summary, high rate of increased level of AngII was detected in COVID-19 patients. AngII level seemed to relevant to the severity of the disease, gender differences and immune disorder. This study was a single-center, retrospective analysis of a small sample with many confounding factors. Therefore, the conclusions above need to be verified by strict prospective or experimental research.

ACKNOWLEDGEMENT

We would like to thank all patients with COVID-19 who provided us with biological specimens for free. These patients gave us the courage and motivation to fight the disease. We are grateful to all the medical staff who treated patients with COVID-19 for their selfless dedication.

AUTHOR CONTRIBUTIONS

Heng-Mei Zhu was responsible for the conception and design, analysis and assembly of data as well as interpretation, financial support and manuscript writing. Na Liu was responsible for the application for this study, the collection of data and manuscript writing. Yan Hong was responsible for the collection and analysis of data and manuscript writing. Ren-Gui Chen was responsible for the application for this study and data collection. Na Liu and Yan Hong contributed to the work equally. Everyone participated in the final approval of the manuscript.

FUNDING

This work was supported by Basic Research Project of Shenzhen Science and Technology Innovation Commission (JCYJ20160429181842402) and Jiangxi Natural Sciences Youth Science Foundation-Youth Fund Project (20202BAB216007).

ETHICS APPROVAL

The study was approved by the ethics committee of Renmin Hospital of Wuhan University (Application ID: [WDRY2020-K114]).

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