Journal of Clinical and Medical Images

Research Article ISSN 2640-9615|Volume 6

Characteristics of COVID-19 and Tuberculosis Co-Infection: A Cross-Sectional Study in Henan Province, China

Li P[1#], Lu X[1#], Wang H[1], Song X[1], Chen T[1], Lou L[1], Cheng J[1], Gou J[2*] and Zhang G[1*]

[1]Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China

[2]Department of General Surgery, The First Affiliated Hospital of Zhengzhou University, No.1, Jianshe East Road, Zhengzhou, Henan 450052, P.R. China

[*]Corresponding author:

Guojun Zhang,
Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University, No.1, Jianshe East Road, Zhengzhou, Henan 450052, P.R. China,
E-mail: gjzhangzzu@126.com

Jianjun Gou,
Department of General Surgery, The First Affiliated Hospital of Zhengzhou University, No.1, Jianshe East Road, Zhengzhou, Henan 450052, P.R. China, E-mail: goujun64@163.com

Received: 1 Feb 2022
Accepted: 17 Feb 2022
Published: 24 Feb 2022
J Short Name: JCMI

Citation:

Gou J, Zhang G, Characteristics of COVID-19 and Tuberculosis Co-Infection: A Cross-Sectional Study in Henan Province, China. J Clin Med Img. 2022; V6(3): 1-8

[#]Authors Contributions:

Ping Li, Xinhua Lu, These authors are contributed to equally to this article.

Keywords:

COVID-19; Tuberculosis; Co-infection; Characteristics

1. Abstract

1.1. Aims: Coronavirus disease 2019 (COVID-19) and Tuberculosis (TB) are two major infectious diseases posing significant public health threats. This study aimed to investigate the clinical features of COVID-19 and TB co-infected patients.

1.2. Methods: 45 cases with COVID-19 and TB co-infection in Henan Province, China between July 30 2021 to September 17 2021 were included in the study. Demographic, clinical, laboratory, and Computed Tomography (CT) imaging data were dynamically collected since first nucleic acid positive.

1.3. Results: Among all 45 co-infected patients, 100% involved active TB, and males comprised more than females. The number and proportion of COVID-TB patients in the≤48 years and 48+ years age groups were 21 (46.67%) and 24 (53.33%), respectively, with an average age of 49 years. 26.67% patients got vaccinated. 91.11% patients were only with pulmonary TB. A total of 33.33% of the COVID-TB patients had comorbidities, the most common of which were diabetes, hypertension and coronary heart disease. 45 patients were Rh positive group. 37.78% were blood type A, 28.89% type B, 26.67% type O and 6.67% type AB. The main CT imaging of 45 patients were bilateral lesions, infiltrates and ground-glass opacity. Up to September 15 2021, 80.00% patients whose nucleic acid had turned negative, and the virus shedding time was 28 days. The transforming negative time had no correlation with age, and no significant differences between male and female.

1.4. Conclusions: In summary, males, older age and CT imaging features of bilateral lesions, cavities, infifiltrates, ground-glass opacity, nodules, may be the main clinical features of COVID-19 and TB co-infected patients.

2. Introduction

At the end of 2019, a novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), emerged in humans and caused fatal respiratory illness. Following the declaration of the World Health Organization (WHO), the COVID-19 pandemic continues to be a significant global health crisis [1]. As of November 3th, 2021, more than 247 million people have been affected. Reported death has been more than 5 million [2].

Other than Middle East respiratory syndrome coronavirus (MERS-CoV) binds to DPP4 as a key receptor, many studies have reported that SARS-CoV-2 bound to Angiotensin Converting Enzyme 2 (ACE2) [3,4]. ACE2 is found in human cells like in lung alveolar epithelial cells and Intestinal mucosa epithelial cells [5]. In this pathogenic mechanism, this highly contagious pathogen is transmitted by respiratory droplets and aerosols. As described by the

Centers for Disease Control (CDC), the most common symptoms for COVID-19 are cold, fever, and cough, followed by pneumonia, which are similar to other respiratory infections, such as Tuberculosis (TB) and influenza. However, coinfections with common viral, bacterial, and fungal pathogens among COVID-19 patients are not unusual [6-8].

It is well known that TB had been the most fatal infectious disease in the world for many years [9,10]. Globally, an estimated 10 million people contracted TB and 1.4 million died from TB in 2019 [11]. TB is mainly transmitted through the respiratory droplets and its main target is the lung, which is similar to COVID-19. Due to the high prevalence of both of two infectious diseases, it is unclear whether COVID-19 and TB co-infection patients have different clinical features, a worse prognosis or are more likely to develop severe disease. In July 2021, a new wave of COVID -19 epidemics broke out in Henan Province, China. After sequencing the virus in the laboratory of the Provincial Center for Disease Control and Prevention and comparing and analyzing it with the virus strains of recent imported cases, this epidemic was mainly caused by SARS-CoV-2 (delta variant). Among the confirmed patients, we collected the clinical data of 45 patients with COVID-19 and TB co-infected, and then summarized in detail the clinical characteristics, which is expected to provide valuable clinical evidence and new ideas for the studies of COVID-19 and TB co-infected patients.

3. Materials & Methods

3.1. Patients and Data Collection

45 cases with COVID-19 and TB co-infection in isolated ward of Airport Zone Hospital of Zhengzhou First People's Hospital (Zhengzhou, Henan, China) between July 30, 2021 to September 17, 2021 were included in the study. All clinical data (including basic information, clinical manifestations, laboratory findings, treatments, and outcomes during hospitalization) were obtained from patients' electronic medical records. The mean duration of clinical observation was 36·42±2·148 days, and the longest was 46 days. Patients were diagnosed and treated according to the "Diagnostic and treatment protocol for Novel Coronavirus Pneumonia (the eighth edition)" issued by the National Health Commission of the People's Republic of China [12].

3.2. SARS-CoV-2 RNA Measurement

SARS-CoV-2 RNA load in nasal swabs was measured by real-time reverse transcriptase-polymerase chain reaction assays (RT-PCR) using primers and probes targeting the SARS-CoV-2 ORF1ab and N gene and detected using the 2019-nCoV Nucleic Acid Test Kit (bioperfectus, technologies). cycle threshold (Ct) =37 is the cut-off for a positive result and Ct=40 is a negative sample; Ct=40 was the limit of detection. The diagnostic criteria were in accordance with the recommendations of the National Institute for Viral Disease Control and Prevention in China.

3.3. Statistical Analysis

Continuous variables including hematological and biochemical indicators of each group were described as the median (P25, P75) due to their skewed distribution. The Mann-Whitney U test was used for comparing two groups of continuous data. The mean and standard deviation of the age variable were described. Categorical variables, including age subgroup, gender, blood type, vaccination of COVID-19, type of TB, Computed Tomography (CT) findings, comorbidity and complication, were expressed as frequencies and proportions. Categorical variables were compared using the chi-squared test or Fisher's exact test. A two-sided $P< 0.05$ was considered statistically significant. All statistical analyses were carried out using SPSS (version 22.0).

4. Results

4.1. Clinical Features of COVID-19 and TB Co-infected Patients

Table 1 describes the demographic characteristics. Among all 45 COVID-19 and TB co-infected patients examined, 100% involved active TB, and males comprised more than females, with a ratio of 32 to 13. The number and proportion of COVID-TB patients in the≤48 years and 48+ years age groups were 21 (46.67%) and 24 (53.33%), respectively, with an average age of 49 years (IQR 27-63.5). According to the grading standard of the National Institute for Viral Disease Control and Prevention in China, we defined non-critical patients as mild and moderate types, and critical patients as severe and critical types. Of the 45 patients with COVID-19 and TB co-infection, 33.33% were classified as mild (15/45), followed by moderate type (55.56%, 25/45), severe type (4.44%, 2/45) and critical type (6.67%, 3/45). The median age of mild, moderate, severe and critical group were respectively 38.6, 45.44, 63.50, 65.67 years old(Figure 1a). As a whole, male was the main proportion of 45 COVID-TB patients, and the median age of the critical group was older than that of non-critical group although the difference fell short of statistical significance (Figure 1b). Of the 45 patients, vaccination of COVID-19 coverage was 26.67% (12/45) belong to non-critical group. The proportions of pulmonary TB only, and pulmonary TB/extrapulmonary TB (>1 site possible) were 91.11% (41/45), 8.89% (4/45), respectively. Moreover, 4.44% were combined with central nervous system TB, 2.22% lumbar tuberculosis and 2.22% intestinal tuberculosis. A total of 33.33% (15/45) of the COVID-TB patients had comorbidities, the most common of which were diabetes, hypertension and coronary heart disease followed by asthma, coronary heart disease, gastritis, kidney disease, hyperthyresis, cerebrovascular disease and polymyositis (Table 1).

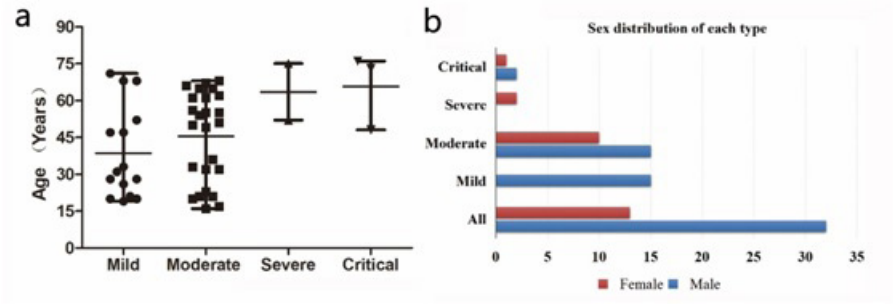

Figure 1: Age and sex distribution in different types of 45 COVID-TB patients. (a.The median age of mild, moderate, severe and critical group were respectively 38.6, 45.44, 63.50, 65.67 years old.
b. Sex distribution of each type, and male was the main proportion of 45 COVID-TB patients, and the median age of the critical group was older than that of non-critical group although the difference fell short of statistical significance.)

Table 1: Clinical characteristics of 46 patients with COVID-19 and TB co-infection

	All (n=45)	Mild (n=15)	Moderate (n=25)	Severe （n=2）	Critical (n=3)
Age,years					
Average	49.00（27,63.5）	38.60±18.82	45.44±18.23	63.50±16.26	65.67±15.37
≤48(n,%)	21 (46.67%)	11 (73.33%)	9 (36.00%)	0 (0%)	1 (33.33%)
>48(n,%)	24 (53.33%)	4 (26.67%)	16 (64.00%)	2 (100%)	2 (66.67%)
Gender					
Male	32 (71.11%)	15 (100%)	15 (60.00%)	0 (0%)	2 (66.67%)
Female	13 (28.89%)	0 (0%)	10(40.0%)	2 (100%)	1 (33.33%)
Vaccination					
Yes	12 (26.67%)	5 (33.33%)	7 (28.00%)	0 (0%)	0 (0%)
No	33 (73.33%)	10 (66.67%)	18 (72.00%)	2 (100%)	3 (100%)
Site					
Pulmonary TB only	41(91.11%)	13(86.67%)	23 (92.00%)	2(100%)	3(100%)
Pulmonary TB and/or extrapulmonary TB (>1 site possible)	4 (8.89%)	2(13.33%)	2 (8.00%)	0(0%)	0(0%)
Coexisting disorders					
Any (n=45/15/15/15/15)	15(32.61%)	3(20.00%)	9(60.00%)	2(13.33%)	1(6.67%)
Diabetes	3	1	2	0	0
Hypertention	3	2	0	0	0
Asthma	1	0	1	0	0
Coronary heart disease	1	0	1	0	0
Gastritis	1	0	1	0	0
Kidney disease	2	0	2	0	0
Hyperthyresis	1	0	1	0	0
Cerebrovascular disease	2	0	0	2	0
Polymyositis	1	0	1	0	0

4.2. The Distribution of Different Blood Types in COVID-19 and TB Co-infected Patients

Some studies reported that ABO and Rhesus (Rh) blood groups were associated with risk for SARS-CoV-2 infection [13]. To analyse the distribution of different blood types in COVID-19 and TB co-infected patients, we collected the blood types of all the 45 patients, of which 45 were Rh positive group. 37.78% (17/45) had blood type A, 28.89% (13/45) had type B, 26.67% (12/45) had type O and 6.67% (3/45) had type AB. There were no significant differences among different blood types in different COVID-19 and TB co-infected patients (P>0.05). Figure 2 presents the distribution of different blood types in different COVID-19 and TB co-infected patients (Figure 2).

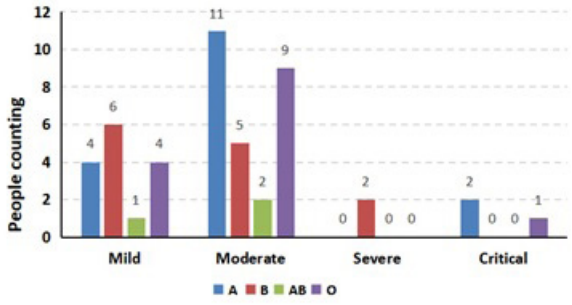

Figure 2: ABO blood type distribution in different types of COVID-19 and TB co-infected patients. There were no significant differences among different blood types in different COVID-19 and TB co-infected patients (*P*>0.05)

4.3. Lung Imaging Features of COVID-19 and TB Co-Infected Patients

Features of lung imaging among the 45 patients were as follows (Table 2): 80.00% (36/45) had bilateral lesions, and 20.00% (9/45) had unilateral lesions. The most common imaging features included cavities (31.11%), infiltrates (71.11%), ground-glass opacity (66.67%), nodules (48.89%), patchy shadows (35.56%), calcific lesions (33.33%), fibrous stripes (40%). In general, COVID-19 and TB co-infected patients had bilateral lesions, infiltrates, ground-glass opacity features. We exhibited two representative chest Computed Tomography (CT) images of COVID-19 and TB co-infected patients which revealed that lesions absorption gradually disappear, followed by timely and effective treatment therapies (Table 2)(Figure 3).

Table 2: Chest CT features of 45 patients with COVID-19/TB co-infection

	All	Mild	Moderate	Severe	Critical
CT findings (n)					
Cavities	14	4	9	0	1
Infifiltrates	32	7	21	2	3
Ground-glass opacity	30	6	19	2	3
Nodules	22	6	14	1	1
Pleural effusion	6	3	3	0	0
Patchy shadows	16	5	10	1	0
Miliary	2	0	1	0	1
Calcific lesions	15	3	8	2	2
Pleural thickening	9	2	5	1	1
Lymphadenopathy	4	1	3	0	0
Minimal signs of interstitial thickening	2	1	0	1	0
Tree in bud	3	0	3	0	0
Air bronchogram	4	1	1	0	2
Fibrous stripes	18	9	8	1	0
Bilateral	36	10	21	2	3
Unilateral	9	5	4	0	0

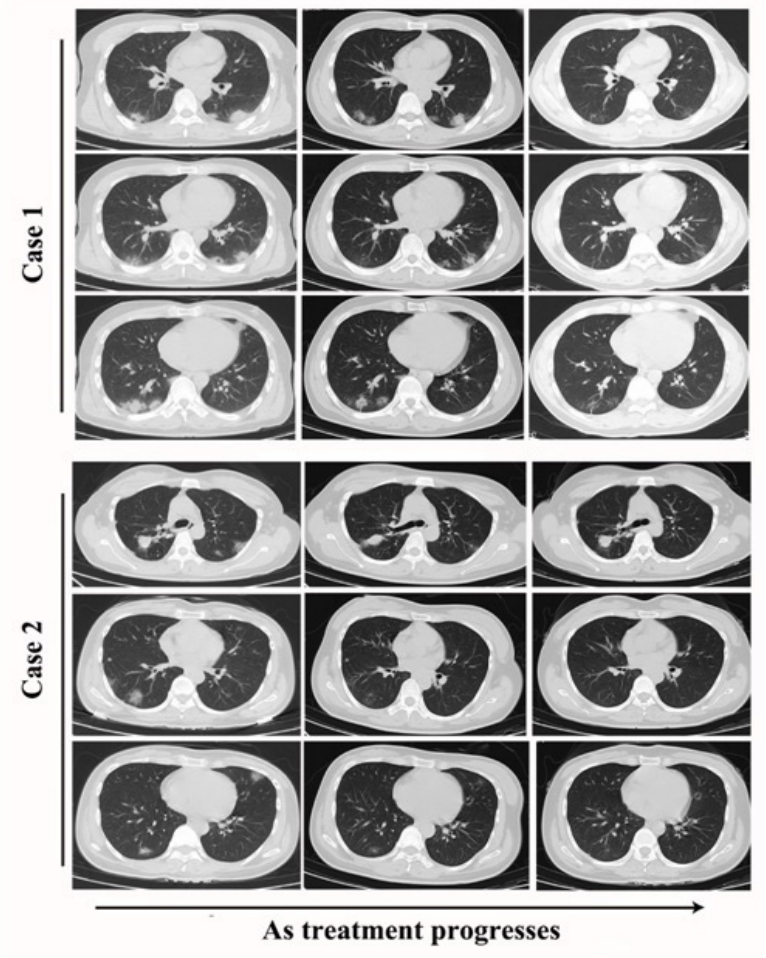

Figure 3: Evolution of the lesions on chest CT of two patients with COVID-19 and TB co-infection (Case1 is a male patient and case 2 was a female patient). As treatment progresses.

4.4. Dynamic Change of SARS-CoV-2 Delta Variant Viral Load

All patients received nasopharyngeal swab sampling at regular intervals. Since SARS-CoV-2 nucleic acid initially testing positive, we tracked and analyzed average Ct value in all patients every day. In mild and moderate groups, we found low Ct value for about 18 days, indicating the median viral load was greater for a long period (Figure 4a,b). In severe and critical groups, average Ct values maintained at a lower level and with high viral load (Figure 4c,d).

Up till September 15 2021, there was 80.00% (36/45) patients whose nucleic acid had turned negative, and the virus shedding time was 28 days (IQR, 17-34 days). Among 36 patients with negative nucleic acid, 33.33% (12/36) were mild, followed by 55.56% (20/36) moderate cases, 3.03% (1/36) severe cases and 8.33% (3/36) critical cases (Figure 4e). About the transforming negative time, there were no significant differences among four types of COVID-19 and TB co-infected patients (Mann-Whitney U test, P=0.275). The correlation of between the transforming negative time and age is r=-0.546 (P=0.564), indicating that age has nothing to do with transforming negative time (Figure 4f). Moreover, there was no significant differences between male and female about the transforming negative time (Mann-Whitney U test. P=0.346) (Figure 4g).

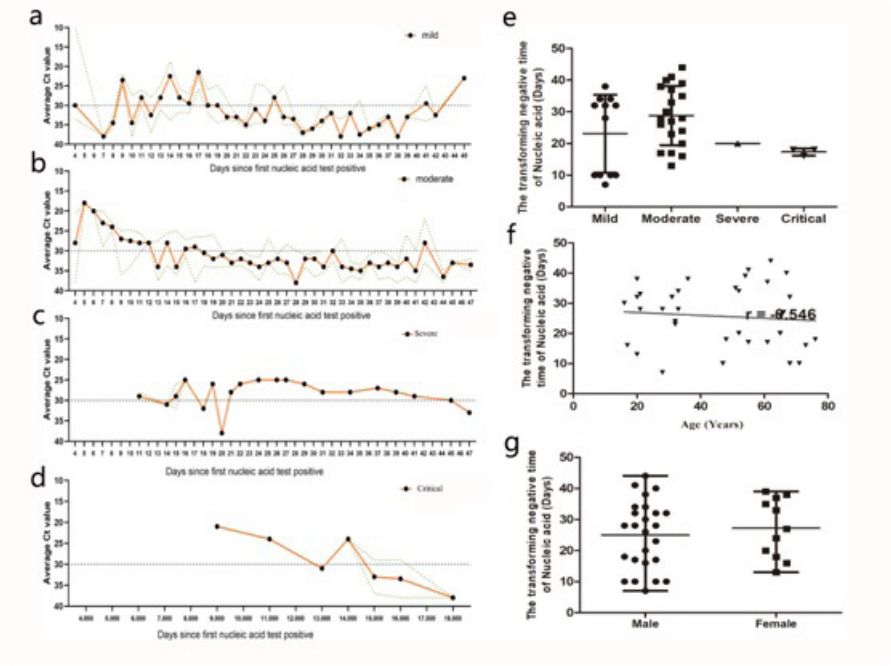

Figure 4: Changes in the Ct value and the transforming negative time in different types of COVID-19 and TB co-infected patients. Ct=37 is the cut-off for a positive result and Ct=40 is a negative sample; Ct=40 was the limit of detection. (a Mean Ct value of targeting at SARS-CoV-2 nucleic acid from mild group at the different time.

b Mean Ct value of targeting at SARS-CoV-2 nucleic acid from moderate group at the different time.

c Mean Ct value of targeting at SARS-CoV-2 nucleic acid from severe group at the different time.

d Mean Ct value of targeting at SARS-CoV-2 nucleic acid from critical group at the different time.

e Distribution of 36 patients with negative nucleic acid in different types of COVID-19 and TB co-infected patients.

f The correlation of between the transforming negative time and age.

g Comparison of the transforming negative time between male and female.

4.5. Treatment of COVID-19 and TB Co-Infected Patients

In terms of treatment, 55.56% of the 45 COVID-19 and TB co-infected patients received anti-TB therapy. Most of 45 patients received some medicine to enhance your immune function as thymopolypeptides or traditional Chinese medicine. There was no patient to receive corticosteroids. Three critical patients also received medication of BRII/196 and BRII/198 and convalescent plasma followed by best support care. Therefore, the viral load of 3 critical patients decreased and then to turn negative in a relatively short period. These treatments did not differ significantly between patients whose nucleic acid had turned negative and Non-negative patients.

5. Discussion

During the COVID-19 pandemic, several respiratory pathogens co-infections were reported, including TB, bacterial and fungal pathogens [14-16]. The incidence of TB is slowly declining but remains a significant issue worldwide (ranked as the ninth leading cause of death worldwide and the leading cause of a single infectious agent, especially in most middle-income and emerging-economy countries [9,10]. Recent studies have indicated that individuals with either latent or active TB may be more susceptible to infection with SARS-CoV-2, and it is likely that COVID-19 may worsen the epidemiological situation of tuberculosis, at least in TB endemic areas where poverty greatly contributes to the TB

prevalence [17,18].

We collected all COVID-19/TB co-infected patients in this epidemic for analysis and research, providing evidence to guide clinical practice and future research. In our study, we found that the majority of the COVID-19/TB co-infected patients (＞80%) were mild or moderate types, which was as the references mentioned that the disease is self-limiting in the majority of patients but about 5% of the infected symptomatic patients develop acute respiratory distress syndrome and require oxygen supplementation through intubation and other invasive procedures [19]. Our study partly reflects COVID-19/TB co-infection has not increased the proportion of severe case. To biological sex and age, our study found males were the main proportion of 45 COVID/TB patients, and the median age of the critical group was older than that of non-critical group, although there was no statistically significant difference in the different type. Most likely cause is a progressive decline in the adaptive immunity in men and in the elderly response to pathogen [20-22]. Certainly, some other studies speculated the possible mechanism were related to altered expression of ACE2 and other molecules involved in the pathogenesis of COVID-19 [26,30]. As to vaccination, vaccination coverage of the 45 patients was 26.67% (12/45) belong to non-critical group. Previous investigation emonstrated that the vaccine provided complete protection to non-human primates by triggering effective humoral immunity responses to combat the systemic spread of SARS-CoV-2[19,23,24]. Therefore, it is necessary to get vaccinated against COVID-19 if health permitted, especially in the elderly or with other inflammatory diseases such as TB. Apart from the factors as age, biological sex and vaccine, preexisting medical conditions, such as bronchial asthma, cardiovascular and cerebrovascular disease or diabetes have been reported to associate with the clinical presentation of COVID-19[25]. Our study also observed patients with many complications had longer hospital stay which have been reported to associate with the clinical presentation of COVID-19.

Some studies reported type O blood may protect against SARS-CoV-2 infection [26,27]. Unfortunately, there were no significant differences among different blood types of different COVID-19 and TB co-infected patients in our study. Maybe studies involving larger samples are needed to explore the association between ABO and Rh blood groups and SARS-CoV-2 infection or severe COVID-19 illness.

To observe CT features of 45 patients with COVID-19/TB co-infection, we found that the features included bilateral involvement, peripheral distribution, mixed ground glass opacity and consolidation, and vascular thickening [28], which were in line with the findings of previous studies [29]. Thus, clinicians should take COVID19 and TB co-infection into consideration upon encountering the above CT imaging features in the future instead of just focusing on one disease.

In this study, the virus shedding time (turn negative time) was calculated for these patients, with an average of 28 days (IQR, 17-34 days), longer than the turn negative time (21 days) for COVID-19 patients without infection with TB [30,31]. Age and sex had nothing to do with the virus shedding time. 3 critical patients decreased and then to turn negative in a relatively short period because of the use of BRII/196 and BRII/198 and convalescent plasma followed by best support care. BRII-196 can completely block viral entry and neutralize live SARS-CoV-2 infection in cell culture assays, and BRII-198 binds to a different epitope on the spike protein and has additive to synergistic effect when combined with BRII-196. Both of them have the potential of becoming an effective therapy against the COVID-19 pandemic [32]. Several studies showed a shorter hospital stay and lower mortality in patients with COVID-19 treated with convalescent plasma than those who were not treated with convalescent plasma [33-35]. So detection and screening convalescent plasma and early application to severe and critical patients are expected to improve the efficacy of convalescent plasma.

Our study also has limitations. Firstly, although the information available on the patients recently admitted was accurate, some details on previous TB were incomplete, and some examinations were not performed either because the medical limitations or the patients' condition was too severe. Secondly, this is a retrospective observational study with a limited sample size, particularly in the case of the co-infection subgroups. Lastly, the representative longitudinal observations with a larger sample size, conducted in a COVID-19 pandemic-affected area, is necessary, so as to evaluate the interactions between COVID-19 and TB.

6. Conclusion

In summary, males, older age and CT imaging features of bilateral lesions, cavities, infifiltrates, ground-glass opacity, nodules, may be the main clinical features of COVID-19 and TB co-infected patients. It is necessary to get vaccinated against COVID-19 if health permitted, especially in the elderly or with other inflammatory diseases such as TB. Further researches are needed to explain the association between ABO and Rh blood groups and COVID-19/TB co-infection. BRII/196 and BRII/198 and convalescent plasma followed by best support care early application to severe and critical patients are expected to improve the condition and shorten the hospitalization time.

7. Acknowledgments

We wish to thank all participants for their sincere answers.

8. Funding

This work was funded by Science and Technology Department of Henan Province (Emergency research project for prevention and control of COVID-9, No.201100311000).

9. Ethics Approval and Consent to Participate

This study has been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University on February 19, 2020 (approval number: Draft- 2020-KY-001). All participants agreed to participate in the study.

References

1. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020; 181: 281-92.
2. Who. WHO Coronavirus (COVID-19) Dashboard.2021.
3. Wang N, Shi X, Jiang L, Zhang S, Wang D, Tong P, et al. Structure of MERS-CoV spike receptor-binding domain complexed with human receptor DPP4.Cell Res. 2013; 23: 986-93.
4. Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013; 495: 251-4.
5. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol. 2020; 251: 228-48.
6. Rawson T, Moore L, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support covid-19 antimicrobial prescribing. Clin Infect Dis. 2020; 71: 2459-68.
7. Lin D, Liu L, Zhang M, Hu Y, Yang Q, Guo J, et al. Co-infections of SARS CoV-2 with multiple common respiratory pathogens in infected patients. Sci China Life Sci. 2020; 63: 606-9.
8. Tadolini M, Codecasa L, García-García J, Blanc F, Borisov S, Alffenaar J, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. Eur Respir J. 2020; 56: 2001398.
9. Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. Indian J Tuberc. 2020; 67: 295-311.
10. Kalsdorf B, Strassburg A, Greinert U, Lotz J, Lange C. Clinical features and diagnosis of tuberculosis. Pneumologie. 2008; 62: 284-94.
11. World Health Organization. Global Tuberculosis Reports. 2020.
12. China NHCO. Guideline for Diagnosis and Treatment of SARS-CoV-2 (the eighth edition) .2021.
13. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness:A Population-Based Cohort Study. Ann Intern Med. 2021; 174: 308-15.
14. Bandyopadhyay A, Palepu S, Bandyopadhyay K, Handu S. COVID-19 and tuberculosis co-infection: a neglected paradigm. Monaldi Arch Chest Dis. 2020; 90.
15. Ma L, Wang W, Le Grange JM, Wang X, Du S, Li C, et al. Coinfection of SARS-CoV-2 and Other Respiratory Pathogens.Infect Drug Resist. 2020; 13: 3045-53.
16. Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi HAA, Jeda AS, et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020; 72: 2097-111.
17. Singh A, Prasad R, Gupta A, Das K, Gupta N. Severe acute respiratory syndrome coronavirus-2 and pulmonary tuberculosis: convergence can be fatal. Monaldi Arch Chest Dis. 2020; 90(3).
18. Yang H, Lu S. COVID-19 and Tuberculosis. J Transl Int Med. 2020; 8: 59-65.
19. Marian AJ. Current state of vaccine development and targeted therapies for COVID-19: impact of basic science discoveries. Cardiovasc Pathol. 2021; 50: 107278.
20. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020; 20: 442-7.
21. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health. 2020; 8: 152.
22. Chen Y, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, et al. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev. 2021; 65: 101205.
23. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; 369: 77-81.
24. Rawat K, Kumari P, Saha L. COVID-19 vaccine: A recent update in pipeline vaccines, their design and development strategies. Eur J Pharmacol. 2021; 892: 173751.
25. Rashedi J, Mahdavi Poor B, Asgharzadeh V, Pourostadi M, Samadi Kafil H, Vegari A, et al. Risk Factors for COVID-19. Infez Med. 2020; 28: 469-74.
26. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, Ng MH, et al. ABO blood group and sus ceptibility to severe acute respiratory syndrome. JAMA.2005; 293:1450-1.
27. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship Between the ABO Blood Group and the Coronavirus Disease 2019 (COVID-19) Susceptibility. Clin Infect Dis. 2021; 73: 328-31.
28. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. AJR Am J Roentgenol. 2020; 214: 1072-7.
29. Song WM, Zhao JY, Zhang QY, Liu SQ, Zhu XH, An QQ, et al. COVID-19 and Tuberculosis Coinfection: An Overview of Case Reports/Case Series and Meta-Analysis. Front Med (Lausanne). 2021; 8: 657006.
30. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020; 26: 672-5.
31. Lou B, Li TD, Zheng SF, Su YY, Li ZY, Liu W, et al. Serology characteristics of SARS-CoV-2 infection after exposure and post-symptom onset. Eur Respir J. 2020; 56: 2000763.
32. Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature. 2020; 584: 115-9.

33. Altuntas F, Ata N, Yigenoglu TN, Bascı S, Dal MS, Korkmaz S, et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci. 2021; 60: 102955.

34. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020; 20: 398-400.

35. Chen S, Lu C, Li P, Wang L, Wang H, Yang Q, et al. Effectiveness of convalescent plasma for treatment of coronavirus disease 2019 patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020; 32: 1293-8.