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Original Article

An Initiative Report on Hospitalized Pulmonary TB Patients Co-Infected by SARS-CoV-2 during the COVID-19 Pandemic from Tertiary Referral Hospitals in Surabaya

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ABSTRACT

The enduring effect of SARS-CoV-2 pandemic has been experienced throughout the past and ongoing three years. Incidences of SARS-CoV-2 co-infected tuberculosis patients were reported globally, including in Italy and several European countries and resulted in a more complicated disease with severe clinical features and poorer clinical outcomes. To effectively manage this co-infection, it is important to be informed of the prevalence and characteristics of an acute SARS-CoV-2 co-infection on TB and determining factors of severity. Therefore, early warning signs can be recognized, monitored closely and managed. This retrospective study, carried out on hospitalized TB patients in Dr. Soetomo Hospital and Universitas Airlangga Hospital, Surabaya, Indonesia, used medical records from March 2020 to December 2022. Samples were from inpatients with a molecularly-Gene Xpert MTB/Rif-confirmed tuberculosis, and currently experienced respiratory and fever symptoms that resembles the symptoms of SARS-CoV-2 infection or exacerbation of tuberculosis. They are then screened and examined using a molecular diagnostic test, with real-time RT-PCR for SARS-CoV-2. A total of 54 (0.7%) patients had TB-SARS-CoV-2 co-infection among 7,786 suspected to have TB, of which 35 had Rifampicin Sensitive (TB-RS), while 19 had TB Rifampicin Resistant (TB-RR) co-infected with SARS-CoV-2. The remaining 2,586 suspected TB patients had only MTB, based on the detection methods of X-pert MTB/RIF, but with negative RT-PCR of SARS-CoV-2. The clinical severity and mortality of TB-SARS-CoV2 co-infected patients were significantly associated with the number of co-morbidities (p=0.0156), and serum haemoglobin levels (p=0.0672), in which p value < 0.05 is considered significant.

Keywords: TB-SARS-CoV-2 co-infection, clinical severity, Sensitive Rifampicin, Resistant Rifampicin, Tuberculosis

Highlights: The pandemic of SARS-CoV-2 is associated with incidence of SARS-CoV-2 co-infection in tuberculosis patients, leading to a more complex disease activity with severe clinical features. This research aims to strategically enhance services for the management and prevention of SARS-CoV-2 and tuberculosis co-infection.

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INTRODUCTION

The first reported case of novel coronavirus in Wuhan in late 2019 has led to the World Health Organization declaration of global pandemic Corona Virus Disease of 2019 (COVID-19). This existing pandemic has placed a significant concern of Case Fatality Rate as high as 16.7%. This concern is especially felt for those who are more vulnerable and have comorbidities such as elderly and those with underlying lung disease as in Tuberculosis. [1,2]

There have been documented cases of co-infection between Tuberculosis and Severe Acute Respiratory Syndrome Coronavirus 2 (TB-SARS-CoV-2), which occurred globally such as reported by Stochino et.al, 2020 and Tandolini et.al, 2020.[3,4] This previous studies suggested that SARS-CoV-2 infection can occur independently of TB, either before or during, or after the disease[5,6]. However, this study defined co-infection as an endemic underlying Tuberculosis which are then exposed and co-infected with SARS-CoV-2. The tuberculosis disease state with weakened immunity is therefore more susceptible to contracting emerging viral SARS-CoV-2 respiratory disease. This co-infection might further affect the drug resistant TB problem.[7-10]

This study aims to describe the prevalence and characteristics of an acute SARS-CoV-2 co-infection on chronic TB, which primarily affects the lungs. in our region, and determining factors of susceptibility, severity and prognosis. Previous study reported that ages such as the elderly, the highly susceptible host experienced a rapidly fatal illness from a single SARS-CoV-2 infection with the generalized spread of the disease to many organs[3,4]. Meanwhile, at younger ages, which considered more resistant hosts, it can cause a mild COVID respiratory syndrome. Therefore, it could be assumed that a more severe disease may occurred in elderly hosts with weakened immune status due to previous TB infection. An understanding of the vulnerable TB host factor and the pathogenesis of TB-SARS COV2, which is needed to prevent the incidence of co-infection as well as to diminish the severity and fatality. It is also expected to help in compiling a reliable and validated human and environmental health protocol.

Stochino et.al, 2020 and Tandolini et.al, 2020 identified the risk factors for severe coinfection of TB-SARS-CoV-2, namely endogenous (host), exogenous (agent of infection), and environmental factors[8,9]. The endogenous components include high-risk age groups (elderly), genetic factors, nutritional status (malnutrition both underweight and overweight), as well as comorbidities, such as underlying TB-endemicity, TB chronicity, and other respiratory diseases. They also consist of immunosuppression conditions, including diabetes, renal function disorder, as well as underlying chronic and progressive viral infections, such as HIV, Hepatitis B, and Hepatitis C. The exogenous components that increase the power of infectious agents' transmission include the similarity of SARS-CoV-2 and MTB transmission through close contacts, airborne, and droplets. They also have a similar mechanism of evading the host immune system by replicating intracellularly within host macrophages and epithelial cells. Consequently, complete viral and bacterial clearance is difficult to achieve. The level of education and awareness in the community is still lacking. There is also a prevalence of ignorance and hesitancy in the community as well as poor environmental health. These components increase the rate of transmission, and they cause higher severity clinical outcomes and mortality in TB co-infected SARS-CoV2 patients[8.9].

Several studies on the co-infection of TB-SARS-CoV-2 showed that TB can significantly reduce SARS-CoV-2 specific response, and it is characterized by low

lymphocyte count[10]. This reduced or absent response to SARS-CoV-2 antigens is caused by massive compartmentalization of the specific T-cells in infectious foci, or by the elimination of effector T-cells when fighting high doses of antigens[11]. The co-morbidity TB-COVID-19 does not have a direct impact on SARS-COV2-specific response, and it is associated with worse clinical outcomes[9]. There is a dual critical impact where COVID-19 pandemic worsened TB epidemic globally due to TB-services fragmentation and the additional pressures on health systems, which weakened the National TB programs [12–15]. RT-PCR (Real time PCR) is a simple, reliable, and rapid test that is widely used for the detection of patients with TB and without TB coinfected with SARS-CoV-2[16–21]. It has a technical limit of detection (LOD) < 10 copies/ reaction and a detection threshold of 3.8 RNA molecules per reaction[22]. These parameters depend on the amplified region as well as the primers and probes used in the RT-PCR platform analysis. Therefore, this study particularly aims to describe the demographic profiles and their clinical characteristics in hospitalized TB patients coinfected with SARS-CoV-2 in two tertiary referral hospitals in Surabaya, followed by an analysis of its correlation with the clinical severity of TB-SARS CoV-2 co-infection.

MATERIAL AND METHODS

Ethics statement

This study was approved by the RSDS ethics committee (Ref. No. 0492/LOE/301.4.2/VI/2021) and RSUA ethics committee (Ref. No. 185/KEP/2021). The data used were collected from documented records and laboratory reports.

Materials

This is a retrospective study, where information and data were collected from medical and laboratory records of hospitalized TB patients in two tertiary referral hospitals, namely Dr. Soetomo Hospital and Universitas Airlangga Hospital, Surabaya, Indonesia during the COVID-19 pandemic between March 2020 and December 2022.

Methods

Incoming patients aged > 18 years who were suspected to have TB were included as participants, and the prediction was confirmed using Xpert MTB/RIF[23]. Children aged < 18 years were excluded in this retrospective study because of the nonspecific clinical and radiologic sign of TB and tend to present in paucibacillary disease. The patients who met the inclusion criteria were then grouped as TB Rifampicin Sensitive and TB Rifampicin Resistant. Subsequently, the confirmed TB inpatients were tested for SARS-CoV-2 coinfection using real-time RT-PCR[12]

The cases were retrospectively recorded using a logbook, including demographics, evidence of SARS-CoV-2 infection, clinical characteristics, co-morbidities, disease course, laboratory, imaging, and recovery/outcomes. Classification of weight was categorized using BMI measurement in adult Indonesian, as described in the Table 1.1.

Table 1.1 Classification of weight by BMI in adult Indonesia

Classification	BMI (kg/m^2)
Underweight	< 18.5
Normal range	18.5-22.9
Overweight	≥ 23
At risk	23-24.9
Obese I	25-29.9
Obese II	≥ 30

The patients were used for analysis if they are positive for TB using the gene Xpert molecular testing and confirmed with SARS-CoV-2 infection based on WHO criteria, namely a positive PCR[12,21,24]. The severity of TB was then assessed with the Modified

Bandim Score, while that of COVID-19 was evaluated using NIH criteria [23,25,26].

Statistical Analysis

The positivity RT-PCR and clinical characterization data were recorded and further described in the distribution table. A statistical correlation test was used to analyse collected data. The cut off p-value of significance is $p<0.05$.

RESULTS AND DISCUSSION

Between March 2020 and December 2022, 54 (0,7 %) TB co-infection SARS-CoV-2 cases were found among the 7,786 who were examined with the GeneXpert MTB/RIF and RT-PCR SARS-CoV-2. Among these 54 patients, 35 were diagnosed with SR-TB, while 19 had RR-TB, both of which co-infected with SARS-CoV-2.

From Table 1.2, it can be seen that 54 confirmed cases of TB coinfected with SARS-CoV-2 patients, 11 (20%) died (14% from SR-TB, 32% from RR-TB). There were 44 recovered from SARS CoV-2 coinfection. From Table 1.3, mean hemoglobin for coinfected patients was 8.5g/dL for TB-RIF sensitive-mild COVID-19, 10.7g/dL for TB-RIF sensitive-moderate COVID-19, 9.16g/dL for TB-RIF sensitive-severe COVID-19, 11.25g/dL for TB-RIF resistant-mild COVID-19, 11.05g/dL for TB-RIF resistant-moderate COVID-19, 11.1g/dL for TB-RIF resistant-severe covid, for deceased case 8.3g/dL , for recovered case 10.68g/dL. There was a nearly statistically significant association (p=0.06) between the concentration of hemoglobin in the blood and mortality. The mortality rate was found to be higher in individuals with lower hemoglobin levels.

Most 40% confirmed TB-RIF sensitive co-infected with COVID patients had two co-morbid, 37% had one co-morbid, 16% had three co-morbid, 7% had four co-morbid, whereas most 54% confirmed TB-RIF resistant coinfected with COVID patients had three co-morbid, 18% had four co-morbid, 9% had one co-morbid, 18% had two co-morbid. There was a statistically significant association (p=0.01) between number of co-morbid and mortality in which, there was higher mortality rate with the increasing number of co-morbid disease. The most frequent co-morbidities were anemia (39%) and diabetes mellitus type 2 (30%). Compared with survivors, deceased cases showed a higher prevalence of co-morbidities within TB-RIF resistant including anemia(27% vs. 4%), diabetes (27% vs. 9%). Dyspnea (56%), cough (69%), and fever (26%) were the most frequent clinical symptoms.

Table 1.2 Characteristic individuals TB-RS and TB-RR coinfected with SARS-CoV-2

TB Categories	**TB Rifampicin Sensitive (N=35)**			**TB Rifampicin Resistant (N=19)**		
COVID Severity	Mild (N=6)	Moderate (N=22)	Severe(N=7)	Mild (N=2)	Moderate (N=12)	Severe (N=5)
Age (years)	42(21-68)	49(20-69)	44(22-62)	42(29-54)	41(23-61)	46(21-61)
Gender						
Female	3 (50%)	9(41%)	4(57%)	2(100%)	5(42%)	3(60%)
Male	3(50%)	13(59%)	3(43%)	0	7(58%)	2(40%)
Nutritional status (BMI in kg/m^2)						
Normal	3(50%)	15 (68%)	1(14%)	2(100%)	8(67%)	3(60%)
Underweight	2(33%)	5(23%)	2(29%)	0	4(33%)	2(40%)
Overweight	1(17%)	2(9%)	4(57%)	0	0	0

Outcome						
Survive	5(83%)	21(95%)	4(57%)	0	10(83%)	3(60%)
Nonsurvive	1(17%)	1(5%)	3(43%)	2(100%)	2(17%)	2(40%)
>1 co-morbid	5(83%)	14(64%)	6(86%)	0	6(50%)	5(100%)
Anemia	5 (83%)	8(36%)	1(14%)	0	2(17%)	3(60%)
DM type 2	2(33%)	6(27%)	3(43%)	0	4(33%)	3(60%)
Hypertension	0	1(5%)	1(14%)	0	1(8%)	1(20%)
Hyperthyroid	0	0	0	0	0	1(20%)
HIV	1(17%)	1(5%)	0	0	0	1(20%)
Hep B	0	0	1(14%)	0	1(8%)	1(20%)
Hep C	0	0	0	0	1(8%)	0
Acute Kidney Failure	0	2(9%)	1(5%)	0	0	0
Chronic Kidney Failure	0	1(17%)	0	0	0	1(20%)

Table 1.3 Comparison of mean laboratory values among TB-RS and TB-RR coinfected with SARS-CoV-2.

TB categories	**TB Rifampicin Sensitive (N=35)**			**TB Rifampicin Resistant (N=19)**		
COVID-19 severity	Mild (N=6)	Moderate (N=22)	Severe(N=7)	Mild (N=2)	Moderate (N=12)	Severe (N=5)
Laboratory results						
WBC (µL)	7,947	10,735	11,911	5,960	7,550	9,394
NLR	7.88	13.15	19.92	4.31	5.56	8.19
Monocyte (µL)	826	797	833	585	716	834
CRP (µg/mL)	7.02	24.53	13.51	2.62	2.8	3.325
Length of positive CT value (days)	25.5	15.5	12.29	15	29	9.4

Table 2. Correlation Analysis of Several Determining Factors and Mortality Outcome

Determining Factors	***p values, significant if p < 0.05***
Age	p = 0.6106
Gender	p = 0.6418
Nutritional status	p = 0.1092
Co-morbidity	**p = 0.0156**
Haemoglobin	**p = 0.0672**
WBC	p=0.5537
NLR	p=0.2201
Monocyte	p=0.2283
CRP	p=0.1088
TB category	p=0.1369
COVID severity	p=0.4580

In this study has been shown in Table 2., the two most common co-morbid diseases were anemia and type 2 diabetes mellitus. The most common co-morbidity in TB-SARS-CoV-2 co-infection, being present in about 41% of coinfected patients, was anemia. This association, which seems to be more frequent in women, was directly influenced by aging and concomitant presence of CKD. More importantly, TB-SARS-CoV-2 co-infected patients with anemia had an approximately higher risk of death (p=0,0672) in the short-term period compared to those without. Our findings are in accordance with the results presented by Al-Jarallah et al. (2021) who reported that COVID-19 patients having a hemoglobin > 10 g/dL had lower odds of dying than those who were considered anemic (i.e., Hb < 10 g/dL). From a pathophysiological perspective, Hb concentration represents one of the most important markers of oxygen-carrying capacity in the bloodstream. Therefore, anemia can further reduce oxygen delivery to

peripheral tissue in COVID-19 patients who have an increased oxygen demand due the interstitial pneumonia [7,23,24,35]. Another major contributing role could have been played by the impairment of iron metabolism due to the underlying infection, resulting in the reduced availability of the metal for erythropoiesis and the production of Hb.[8,35] Whereas, diabetes mellitus type 2 has a typical adult-onset of insulin resistance, and manifest as increased blood glucose level. If the elevation in blood glucose level is uncontrolled, it can lead to a decrease in neutrophil function, response from T cell lymphocyte, antioxidant status function, and altered secretion of proinflammatory cytokines. This defect in modalities of systemic immune functions increases the virulence of opportunistic pathogens. In addition, the condition of high blood sugar also provides nutrition for microbes, thereby further increasing the virulence of microbial infection, including opportunistic bacterial and candida infections.[27,28] Whereas patient with co-morbidities of other viral infection, such as HIV, Hepatitis B, Hepatitis C, are prone to be underweight, carbohydrate-fat and protein deficiency, depleted lymphocyte and T-cell counts, decreased immunomodulatory effects and so might contribute to exacerbation of coinfection manifestation thus, increases the risk of mortality. Another study revealed that the presence of impaired nutritional status increased the risk of an abnormal and chronic inflammation with higher level of oxidant. Failure to eliminate agents of coinfection can aggravate clinical outcomes of TB-RS and TB-RR with SARS-CoV-2. The presence of Rifampicin resistant TB can cause an obscure clinical manifestation of coinfection exacerbation. This is due to failure in eradicating rifampicin resistance tuberculosis bacilli and it is more difficult to activate optimal immune response to an acute SARS-CoV2 infection agent in Tuberculosis infected macrophage [11,17,19,32–34].

Pathophysiology of co-infection TB-SARS-CoV-2 depends on the number of initial viral load, ability to evade from the host immune system by replicating intracellularly within macrophages, and the severity of underlying chronic TB infection. It can also be influenced by the presence of endogenous risk factors, inflammatory responses of the host innate, and adaptive immune system in eliminating coinfection effectively. Severity of clinical outcome is often affected by hyperactivity of the host immune response, and it is characterized by the production of cytokine storms, which cause systemic organ hyperinflammation and destruction.

Consequently, there was no significant difference in the time length of positivity for the E, N, ORF1ab gene of SARS-CoV-2 in TB-RR group lasted within 9-15 days was needed to clear SARS-Cov-2. In cases of new TB patient with Rifampicin Sensitivity, 12-25 days were required. Early detection of TB-SARS-CoV-2 coinfection using E, N, ORF1ab gene, as well as RdRp and Helicase gene gave the same accuracy in indicating active replication and ongoing pathogenicity[31].

This study highlights the importance of concomitant molecular detection pathway for TB patients experienced exacerbation of symptoms during their antituberculosis medication regimen, using Gene Xpert MTB/RIF and RT-PCR SARS-CoV-2 for effective both SR/RR-TB-SARS-CoV-2 co-infection case findings and then delivering early treatments. It can also help to prevent further or break the transmission chain of SR-TB-SARS-CoV-2 co-infection and RR-TB-SARS-CoV-2 co-infection.

STRENGTH AND LIMITATION

The strength of this study was the first preliminary study carried out from two referral hospitals in Surabaya that reported incidences of TB-SARS-CoV-2 coinfection based on detection of SARS-CoV-2 gene using molecular RT-PCR methods in diagnosed and hospitalized TB patients. This

study has limitations. The reporting system relies on consecutive sampling which included a limited 54 TB patients with SARS-CoV-2 coinfection from 7,786 suspected TB patients collected during the peak exponential COVID-19 pandemic. Therefore, the result of this research study, needed to be confirmed with larger samples of clinical study.

CONCLUSIONS

Small incidences of 54 cases of TB-SARS-CoV-2 co-infection was found in two tertiary referral hospitals in Surabaya using molecular RT-PCR assays. There was no significance difference in profile prevalence of gene specific SARS-CoV-2 detection or CT value between TB-RR and TB-RS groups. As all confirmatory gene specific SARS-CoV-2 are detected, in both methods using E, N, ORF1ab gene as well as methods using RdRp and Helicase gene detection. There was a significant difference between 35 patients of SR-TB and 19 patients of RR-TB in terms of their clinical severity and mortality outcomes. The clinical severity level and mortality of TB-SARS-CoV-2 co-infected patients were significantly associated with the number of co-morbidities (p=0.0156) and serum hemoglobin concentration (p=0.0672). Thus these comorbidities and the level of serum hemoglobin need to be considered as warning signs, monitored closely and managed.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

LE, NMM, SS, PDE have equally contributed to the designing, data analysis, interpretation of data, drafting or revision of critically important intellectual content, given final approval of the version to be published.

REFERENCES

1. Kementerian Dalam Negeri RI. *Pedoman Umum Menghadapi Pandemi COVID-19 Bagi Pemerintah Daerah*. Jakarta; 2020. https://covid19.kemkes.go.id/protokol-covid-19/pedoman-umum-menghadapi-pandemi-covid-19-bagi-pemerintah-daerah/.
2. National Institute of Health (NIH). Clinical Spectrum of SARS-CoV-2 Infection. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Published 2022. Accessed August 1, 2022.
3. Stochino C, Villa S, Zucchi P, Parravicini P, Gori A, Raviglione MC. Clinical characteristics of COVID-19 and active tuberculosis co-infection in an Italian reference hospital. *Eur Respir J*. 2020;56(1). doi:10.1183/13993003.01708-2020.
4. Tadolini M, Codecasa LR, García-García J-M, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J*. 2020;56(1):2001398. doi:10.1183/13993003.01398-2020.
5. WHO. *Global Tuberculosis Report 2021*. Geneva, Switzerland; 2021. https://www.who.int/publications/i/item/9789240037021.
6. Petrone L, Petruccioli E, Vanini V, et al. Coinfection of tuberculosis and COVID-19 limits the ability to in vitro respond to SARS-CoV-2. *Int J Infect Dis*. 2021;113(January):S82-S87. doi:10.1016/j.ijid.2021.02.090.

7. World Health Organization (WHO). Indonesia Commitment to eliminate TB by 2030 supported by the highest level government. https://www.who.int/indonesia/news/detail/28-11-2021-indonesia-commitment-to-eliminate-tb-by-2030-supported-by-the-highest-level-government. Published 2021. Accessed August 29, 2022.
8. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob*. 2020;19(1):21. doi:10.1186/s12941-020-00363-1.
9. Peraturan Presiden. *LEMBARAN NEGARA REPUBLIK INDONESIA: Penanggulangan TBC*. Indonesia; 2021. http://www.peraturan.go.id/peraturan/view.html?id=f724fa6c8f6c0eb70b99a3c24f92db14.
10. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: Current State of the Science. *Immunity*. 2020;52(6):910-941. doi:10.1016/j.immuni.2020.05.002.
11. Sheerin D, Abhimanyu, Peton N, et al. Immunopathogenic overlap between COVID-19 and tuberculosis identified from transcriptomic meta-analysis and human macrophage infection. *iScience*. 2022;25(6):104464. doi:10.1016/j.isci.2022.104464.
12. Magro P, Formenti B, Marchese V, et al. Impact of the SARS-CoV-2 epidemic on tuberculosis treatment outcome in Northern Italy. *Eur Respir J*. 2020;56(4):2002665. doi:10.1183/13993003.02665-2020.
13. Marimuthu Y, Nagappa B, Sharma N, Basu S, Chopra KK. COVID-19 and tuberculosis: A mathematical model based forecasting in Delhi, India. *Indian J Tuberc*. 2020;67(2):177-181. doi:10.1016/j.ijtb.2020.05.006.
14. Keddy KH, Migliori GB, Van Der Walt M. Developing health policies in patients presenting with SARS-CoV-2: consider tuberculosis. *Lancet Glob Heal*. 2020;8(11):e1357-e1358. doi:10.1016/S2214-109X(20)30413-7.
15. Ong CWM, Migliori GB, Raviglione M, et al. Epidemic and pandemic viral infections: impact on tuberculosis and the lung. *Eur Respir J*. 2020;56(4):2001727. doi:10.1183/13993003.01727-2020.
16. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. *N Engl J Med*. 2020;382(13):1278-1280. doi:10.1056/NEJMc2001899.
17. Feng S, Song F, Guo W, et al. Potential Genes Associated with COVID-19 and Comorbidity. *Int J Med Sci*. 2022;19(2):402-415. doi:10.7150/ijms.67815.
18. Zóka A, Bekő G. Does the E gene provide additional information in SARS-CoV-2 PCR? *J Infect Chemother*. 2021;27(11):1676-1677. doi:10.1016/j.jiac.2021.08.017.
19. Ponti G, Pastorino L, Manfredini M, et al. COVID-19 spreading across world correlates with C677T allele of the methylenetetrahydrofolate reductase (MTHFR) gene prevalence. *J Clin Lab Anal*. 2021;35(7):1-7. doi:10.1002/jcla.23798.
20. Binnicker MJ. Can Testing Predict SARS-CoV-2 Infectivity? The Potential for Certain Methods To Be Surrogates for Replication-Competent Virus. Humphries RM, ed. *J Clin Microbiol*. 2021;59(11):e0046921. doi:10.1128/JCM.00469-21.
21. Fenaux H, Ghelfenstein-Ferreira T, Salmona M, et al. Interpretation of single target positivity among SARS-CoV-2 RT-PCR result tests. *J Clin Virol Plus*. 2021;1(1-2):100021. doi:10.1016/j.jcvp.2021.100021.
22. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus

(2019-nCoV) by real-time RT-PCR. *Eurosurveillance*. 2020;25(3). doi:10.2807/1560-7917.ES.2020.25.3.2000045.

23. Pandey O, Paudyal B, Basnyat B. Gene-Xpert: Diagnosis of Pulmonary Tuberculosis in a Sputum Smear Negative Patient. *J Nepal Health Res Counc*. 2019;17(1):125-127. doi:10.33314/jnhrc.2013.
24. Vanaerschot M, Mann SA, Webber JT, et al. Identification of a Polymorphism in the N Gene of SARS-CoV-2 That Adversely Impacts Detection by Reverse Transcription-PCR. Caliendo AM, ed. *J Clin Microbiol*. 2020;59(1):1-4. doi:10.1128/JCM.02369-20.
25. Dewi DNSS, Mertaniasih NM, Soedarsono. Severity of TB Classified by modified BANDIM Scoring associates with the specific sequence of ESXA genes in MDR-TB patients. *African J Infect Dis*. 2020;14(1):8-15. doi:10.21010/ajid.v14i1.2.
26. Rudolf F, Joaquim LC, Vieira C, et al. The Bandim tuberculosis score: reliability and comparison with the Karnofsky performance score. *Scand J Infect Dis*. 2013;45(4):256-264. doi:10.3109/00365548.2012.731077.
27. Sheerin D, Abhimanyu, Wang X, Johnson WE, Coussens A. Systematic evaluation of transcriptomic disease risk and diagnostic biomarker overlap between COVID-19 and tuberculosis: a patient-level meta-analysis. *medRxiv Prepr Serv Heal Sci*. November 2020. doi:10.1101/2020.11.25.20236646.
28. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. *Thorax*. 2021;76(4):412-420. doi:10.1136/thoraxjnl-2020-216243.
29. Crisan-Dabija R, Grigorescu C, Pavel C-A, et al. Tuberculosis and COVID-19: Lessons from the Past Viral Outbreaks and Possible Future Outcomes. *Can Respir J*. 2020;2020:1-10. doi:10.1155/2020/1401053.
30. Syafa'ah I, Yudhawati R. Peran Imunitas Mukosa terhadap Infeksi Mycobacterium Tuberculosis. *J Respirasi*. 2019;2(2):61. doi:10.20473/jr.v2-I.2.2016.61-68.
31. Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021;19(3):141-154. doi:10.1038/s41579-020-00459-7.
32. Zhang L, Guo H. Biomarkers of COVID-19 and technologies to combat SARS-CoV-2. *Adv Biomark Sci Technol*. 2020;2(January):1-23. doi:10.1016/j.abst.2020.08.001.
33. Kant S, Tyagi R. The impact of COVID-19 on tuberculosis: challenges and opportunities. *Ther Adv Infect Dis*. 2021;8:204993612110169. doi:10.1177/20499361211016973.
34. Luke E, Swafford K, Shirazi G, Venketaraman V. TB and COVID-19: An Exploration of the Characteristics and Resulting Complications of Co-infection. *Front Biosci*. 2022;14(1):6. doi:10.31083/j.fbs1401006.
35. Zuin, M.; Rigatelli, G.; Quadretti, L.; Fogato, L.; Zuliani, G.; Roncon, L. Prognostic Role of Anemia in COVID-19 Patients: A Meta-Analysis. *Infect. Dis. Rep.* **2021**, *13*, 930-937. https://doi.org/10.3390/idr13040085
36. Al-Jarallah, M.; Rajan, R.; Al Saber, A.; Pan, J.; Al-Sultan, A.T.; Abdelnaby, H.; Alroomi, M.; Dashti, R.; Aboelhassan, W.; Almutairi, F.; et al. In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: A retrospective study. eJHaem 2021, 2, 335–339.