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SHORT COMMUNICATION

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COVID-19 case fatality rate and tuberculosis in a metropolitan setting

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Abstract

In this study, we aimed to assess the relationship between tuberculosis case rate and COVID-19 case fatality rate (CFR) among districts within a tuberculosis-endemic metropolitan area. We analyzed data from 43 districts in Lima, Peru. We used districts as the units of observation. Linear regressions were used to investigate the relationship between COVID-19 CFRs and tuberculosis case rates. The mean COVID-19 CFR in each district for reporting Weeks 5–32 was used as the dependent variable. Independent variable was the mean rate of confirmed pulmonary tuberculosis cases for 2017–2019 period. Analyses were adjusted by population density, socioeconomic status, crowded housing, health facility density, and case rates of hypertension, diabetes mellitus, and HIV infection. The mean COVID-19 CFR in Lima was 4.0% ± 1.1%. The mean tuberculosis rate was 16.0 cases per 10,000 inhabitants. In multivariate analysis, tuberculosis case rate was associated with COVID-19 CFR (β = 1.26; 95% confidence interval: 0.24–2.28; p = .02), after adjusting for potential confounders. We found that Lima districts with a higher burden of tuberculosis exhibited higher COVID-19 CFRs, independent of socioeconomic, and morbidity variables.

KEYWORDS
case fatality rate, COVID-19, Peru, tuberculosis

1 | INTRODUCTION

The novel COVID-19 pandemic is intersecting with other epidemics including tuberculosis. The response to the COVID-19 pandemic has affected tuberculosis prevention and control programs worldwide.[1,2] COVID-19 may occur in patients with active tuberculosis or tuberculosis sequela.[3] There is growing evidence of the effect of tuberculosis on COVID-19 susceptibility and prognosis,[4,5] although a meta-analysis of Chinese studies did not show a significant association between tuberculosis and COVID-19 severity.[6] Clearly, it is urgent to improve our understanding of the intersection between COVID-19 and tuberculosis, especially in countries with a high burden of both diseases.

A setting in the world conducive to studying the confluence of these two scourges is Peru. Tuberculosis is endemic in Peru, accounting for the highest rates of multidrug resistant tuberculosis in Latin America.[7] Moreover, Peru has been one of the countries most affected by the COVID-19 pandemic. By August 2020, Peru ranked second among countries with the highest mortality rate of COVID-19 reported worldwide, with approximately 600,000 confirmed COVID-19 cases and 28,000 COVID-19 related deaths.[8] To provide some insight on the interplay between COVID-19 and tuberculosis, we studied the relationship between COVID-19 case fatality rates (CFRs) and of tuberculosis case rates in Metropolitan Lima, Peru.

2 | METHODS

We conducted an ecological study where the units of observation were individual districts of Metropolitan Lima, which contained a total of 43 districts and approximately 9 million inhabitants living

within a 2670.4 km^2 geographic area. For our analyses, the dependent variable was COVID-19 CFR per 100 COVID-19 cases. The main covariable was the rate of pulmonary tuberculosis cases confirmed by histology or bacteriology (cases per 10,000 inhabitants) for the years 2017, 2018, and 2019. Other morbidity variables included case rates of HIV infection, diabetes mellitus, and hypertension from 2017 to 2019. Sociodemographic covariables included population density (number of inhabitants per km^2), socioeconomic status (proportion of population with fourth and fifth lowest household income group), crowded housing (percentage of population living in houses with >3.4 inhabitants per room), and healthcare facility density (number of healthcare facilities per 10,000 inhabitants).

The number of confirmed SARS-CoV-2 cases and deaths were collated using publicly available data from the Peruvian Ministry of Health between March 3 and November 20, 2020.[9] Socioeconomic variables (socioeconomic status, population density and crowded housing) were obtained from the National Institute of Statistics and Informatics.[10–12] Healthcare facility density, and the number of notified cases of tuberculosis, HIV infection, diabetes mellitus and hypertension were available from the Ministry of Health public information system. Population projections from 2017 to 2019 were available through the National Institute of Statistics and Informatics,[13] and were used to calculate the case rates of tuberculosis, HIV infection, diabetes mellitus and hypertension for each district per year. To account for the possibility of different start dates in COVID-19 testing and reporting by district, we calculated the CFR for each district starting from the date of the first confirmed COVID-19 case at each particular district. We excluded COVID-19 data from the first 4 weeks due to inconsistent reporting.

Bivariate and multivariate linear regressions were conducted to determine the factors associated with COVID-19 CFR. Normal distribution was assessed by Shapiro's test. To control the skewness and reach statistical model assumptions, the analysis was performed with log-transformation of covariables (tuberculosis, HIV infection, diabetes mellitus and hypertension rates). Statistical analysis was performed using R software version 3.6.1. This analysis was determined not to be human subject research (IRB# 2020-1116) as it involved existing, deidentified, publicly-available data, and thus did not require additional Institutional Review Board review.

3 | RESULTS

The overall COVID-19 CFR mean among districts in Metropolitan Lima was 4.0% ± 1.1%. The mean tuberculosis case rate was 16.0 cases per 10,000 inhabitants (log-transformed mean: 1.1 ± 0.4). The mean log-transformed rate of HIV infection was 0.6 ± 0.2, whereas the mean rates of diabetes mellitus and hypertension were 1.8 ± 0.4, and 1.7 ± 0.4, respectively. The mean population density was 10,524.9 ± 8489.9 inhabitants per km^2, the mean healthcare facility density was 1.2 ± 1.2 facilities per 10,000 inhabitants. The mean proportion of the population within the lowest socioeconomic status was 31.4 ± 31.4, and the average proportion of population living in houses considered to be in the crowded housing category was 7.5 ± 3.5.

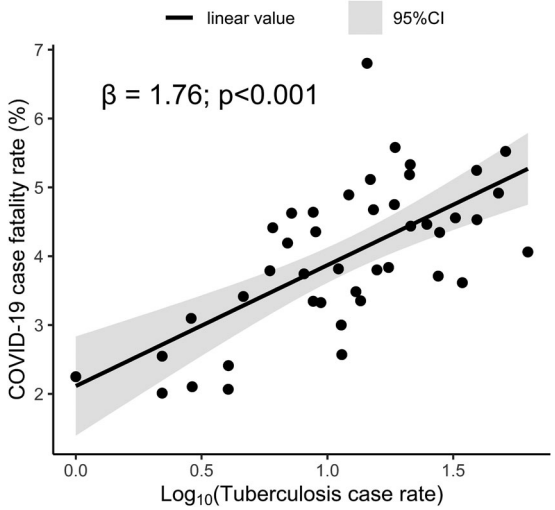

FIGURE 1 Association between COVID-19 CFR mean of Weeks 5–32 and mean of log-transformed tuberculosis case rate in 2017–2019 period. Each point represents an individual district of Metropolitan Lima, Peru

In bivariate analysis, tuberculosis case rate was associated with COVID-19 CFR ($\beta = 1.76$; 95% confidence interval [CI]: 1.13–2.39; $p < .001$; Figure 1). Population density, crowded housing, and case rates of diabetes mellitus, hypertension, HIV infection were also associated with COVID-19 CFR (Table 1). In multivariate analysis, tuberculosis case rate remained associated with COVID-19 CFR ($\beta = 1.26$; 95% CI: 0.24–2.28; $p = .02$; Table 1), as well as population density ($\beta = 5.2 \times 10^{-5}$; 95% CI: 0.5×10^{-5}–9.9×10^{-5}; $p = .03$; Table 1). No mediation effects nor significant interaction were detected (Tables S1 and S2a–g)

4 | DISCUSSION

We found a positive correlation between district tuberculosis case rate and COVID-19 CFR in a metropolitan area with high COVID-19 and tuberculosis burden, independent of district socioeconomic status, population density, crowded housing and morbidity variables, including case rates of diabetes mellitus, hypertension, and HIV infection. Our findings support the possibility of an important synergy between tuberculosis and COVID-19. The mechanism remains speculative. Tuberculosis may be a marker of individual comorbid or socioeconomic conditions known to increase the risk of progression to severe COVID-19.[14] In addition, it is possible that tuberculosis could affect clinical outcomes of COVID-19 patients through direct pathogenic effects,[15] as both infections share common disease pathways.[16] Although a meta-analysis of Chinese studies did not find an association between tuberculosis and COVID-19 severity,[6] it is important to note that these results may have been affected by the clinical heterogeneity of tuberculosis cases and sample size limitations. Moreover, another systematic review recently reported an association between tuberculosis and COVID-19, independent of HIV

TABLE 1 Factors associated with COVID-19 case fatality rate in Lima, Peru

	Bivariate				Multivariate			
	95% CI				95% CI			
	β	Lower	Upper	*p*	*β*	Lower	Upper	*p*
Population density	4.2×10^{-5}	0.4×10^{-5}	8.0×10^{-5}	.03*	5.2×10^{-5}	0.5×10^{-5}	9.9×10^{-5}	.03*
Socioeconomic status	7.5×10^{-3}	-3.0×10^{-3}	18.1×10^{-3}	.16	0.5×10^{-2}	-1.0×10^{-2}	2.1×10^{-2}	.50
Tuberculosis[a]	1.76	1.13	2.39	<.001*	1.20	0.18	2.22	.02*
Hypertension[a]	0.97	0.21	1.73	.01*	1.64	−0.31	3.58	.10
HIV infection[a]	2.02	0.05	3.98	.04*	−0.20	−2.42	2.01	.85
Diabetes mellitus[a]	0.99	0.26	1.73	.01*	−1.55	−3.60	0.50	.13
Health facility density	−0.34	−0.60	−0.09	.01*	−0.17	−0.47	0.13	.26
Crowded housing	0.12	0.04	0.21	.01*	0.02	−0.11	0.15	.76

Abbreviations: *β*, coefficient; CI, confidence interval; *p* values estimated by linear regression.

[a]log10 transformed.

*$p < .05$; adjusted $R^2 = 45.5\%$.

status, suggesting that tuberculosis patients may be more susceptible to severe COVID-19 and death.[17] Therefore, more studies with well-characterized tuberculosis phenotypes and COVID-19 coinfection are needed.[18]

Our study had limitations. Since our analysis had an ecological design and the units of observation were the districts of Metropolitan Lima, these results are not readily applicable to individual patients. Whether the population-based association observed between tuberculosis case rates and COVID-19 deaths is a manifestation of what happens at the individual patient level needs to be further studied. It is possible that COVID-19 cases and deaths could have been underreported due to limitations in SARS-CoV-2 testing and reporting. However, underreporting, if it occurred, is unlikely to have biased associations in a specific direction. Although we adjusted our results for important sociodemographic, healthcare facility density, and morbidity factors, we recognize that it is not feasible to account for all potential confounders of the relationship between tuberculosis and COVID-19 in our analyses.

In conclusion, our findings indicate that districts with a higher burden of tuberculosis may also be the most affected by COVID-19 CFRs in metropolitan settings, independently of socioeconomic characteristics, and morbidity rates from other diseases. Tuberculosis hotspots might need to be prioritized in COVID-19 control strategies. Research is needed to better understand the interplay between COVID-19 and tuberculosis at individual and aggregate levels.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

6 | AUTHOR CONTRIBUTIONS

Daniel Rojas-Bolivar: Design of the study, data collection, data management, analysis, and interpretation, writing and review of manuscript. Claudio Intimayta-Escalante: Data collection, management and interpretation, review of manuscript. Ariana Cardenas-Jara: Data collection, data management and interpretation, review of manuscript. Roman Jandarov: Interpretation and final approvement of manuscript. Moises A. Huaman: Interpretation and final approvement of manuscript. All authors read and approved the manuscript.

7.1 | PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jmv.26868

7.2 | DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Husain AA, Monaghan TM, Kashyap RS. Impact of COVID-19 pandemic on tuberculosis care in India. *Clin Microbiol Infect*. 2020. https://doi.org/10.1016/j.cmi.2020.08.014
2. Hogan AB, Jewell BL, Sherrard-Smith E, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. *Lancet Glob Health*. 2020;8:e1132-e1141. https://doi.org/10.1016/S2214-109X(20)30288-6
3. Tadolini M, Codecasa LR, García-García JM, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J*. 2020;56(1):2001398. https://doi.org/10.1183/13993003.01398-2020
4. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19.

Infect Dis. 2020;52(12):902-907. https://doi.org/10.1080/23744235.2020.1806353
5. Boulle A, Davies MA, Hussey H, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa1198
6. Gao Y, Liu M, Chen Y, Shi S, Geng J, Tian J. Association between tuberculosis and COVID-19 severity and mortality: a rapid systematic review and meta-analysis. *J Med Virol*. 2020. 93(1):194–196. https://doi.org/10.1002/jmv.26311
7. WHO. World Tuberculosis Report 2019. 2020. Geneva: WHO.
8. Jhons Hopkins Coronavirus Resource Center. Mortality analyses US: Jhons Hopkins University; 2020. https://coronavirus.jhu.edu/data/mortality. Accessed December 6, 2020.
9. Gobierno del Perú. Plataforma Nacional de Datos Abiertos Lima: Gobierno del Perú; 2020. https://www.datosabiertos.gob.pe/. Accessed December 6, 2020.
10. Instituto Nacional de Estadística e Informática. Perú: mapa de necesidades básicas insatisfechas (NBI), 1993, 2007 y 2017 Lima: INEI; 2018. https://www.inei.gob.pe/media/MenuRecursivo/publicaciones_digitales/Est/Lib1588/. Accessed December 6, 2020.
11. Instituto Nacional de Estadística e Informática. Planos estratificados de Lima Metropolitana a nivel de manzanas 2020: según ingreso per cápita de hogar. Lima: INEI; 2020.
12. Instituto Nacional de Estadística e Informática. Perú: resultados definitivos de los censos nacionales 2017. Lima: INEI; 2018.
13. Instituto Nacional de Estadística e Informática. Perú: estimaciones y proyecciones de población por departamento, provincia y distrito, 2018-2020. Lima: INEI; 2020 Report No.: Boletín Especial N°26.
14. Saunders MJ, Evans CA. COVID-19, tuberculosis and poverty: preventing a perfect storm. *Eur Respir J*. 2020;56(1):2001348. https://doi.org/10.1183/13993003.01348-2020
15. Udwadia ZF, Vora A, Tripathi AR, Malu KN, Lange C, Sara Raju R. COVID-19—Tuberculosis interactions: when dark forces collide. *Indian J Tuberc*. 2020;67:S155-S162. https://doi.org/10.1016/j.ijtb.2020.07.003
16. Rosa BA, Ahmed M, Singh DK, et al. IFN signaling and neutrophil degranulation transcriptional signatures are induced during SARS-CoV-2 infection. *bioRxiv*. 2020. https://doi.org/10.1101/2020.08.06.239798
17. Tamuzi JL, Ayele BT, Shumba CS, et al. Implications of COVID-19 in high burden countries for HIV/TB: a systematic review of evidence. *BMC Infect Dis*. 2020;20(1):744. https://doi.org/10.1186/s12879-020-05450-4
18. Motta I, Centis R, D'Ambrosio L, et al. Tuberculosis, COVID-19 and migrants: Preliminary analysis of deaths occurring in 69 patients from two cohorts. *Pulmonology*. 2020;26(4):233-240. https://doi.org/10.1016/j.pulmoe.2020.05.002

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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