Tuberculosis Prevalence Correlation to COVID-19 Mortality in Malaria Free Countries

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Research Article

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Abstract

Background: Both malaria and latent tuberculosis (LTB) are possible factors related to decreased COVID-19 mortality. The malaria endemicity variable is a possible confounder when conducting a study on the correlation of LTB prevalence to COVID-19 mortality. Studies regarding LTB prevalence" according to different studies" did not adjust malaria endemicity as a possible confounder.

Many malaria-endemic countries are high TB prevalent. Malaria-free countries could be: high, moderate, or low in TB prevalence.

The main aim of this study is to look for the influence of TB prevalence on COVID-19 mortality. TB prevalence reflects LTB prevalence in the absence of malaria endemicity as a possible confounding factor in TB studies.

Material and methods: The total chosen countries were 69 non-malaria endemic countries. Countries were classified according to TB prevalence groups into low, moderate, and high prevalent groups. Covid-19 deaths/Million(M) inhabitants were taken as reported on September 2, 2020. "Kendall's-τ Correlation Coefficient", "Kruskal-Wallis test, and Mann-Whitney test were used in statistical analyses.

Results: We found inverse relationships between TB prevalence and COVID-19 deaths/ (M) inhabitants and a highly positive significant correlation coefficient was reported (0.008) in Kendall's-τ correlation coefficient test. Kruskal-Wallis test showed a significant relationship within studied groups. Furthermore, the low TB prevalent group had significant reverse associations with both high and moderate TB prevalent groups in the Mann-Whitney test.

Conclusion: In the absence of possible malaria confounding, TB prevalence in malaria-free countries is inversely related to COVID-19 mortality in a highly significant association.

Introduction

Microorganisms may modulate hosts' protective heterologous cross-immunological reactions, which can last for a long time. This cross-protection can be achieved by inducing the training of innate immune cells. This promotes host resistance against a wide spectrum of pathogens.

Latent TB (LTB): Approximately 2–3 billion people in the world are latently infected with Mycobacterium tuberculosis .The lifetime risk of reactivation of TB is estimated to be around 5–10% of screen positive persons [1].

TB prevalence in countries reflects the LTB prevalence as far as TB prevalence constitutes approximately one-tenth or one-twentieth of TB prevalence. [2]. The incubation period for TB infection is very rarely more than 2 years after infection.. [3] On the other hand, if a person crosses these 2 years without showing manifestation of the disease, immunity "generated by LTB " shows long-time positivity making a person with previous LTB immune from getting the disease . This immunity can be tested by specific

immunologic tests that did not differentiate past infections from recent ones since it did not indicate the presence of live bacteria. This TB immunoreactivity can persist whether a patient is treated by curative treatment or not.[8]

Studies show that LTB infection prevalence is associated with a decrease in COVID-19 mortality. These studies suggested a heterogeneous immune response to COX-COV2 viral infection. ‴. Despite this significant association, some countries are hugely disparate case fatality rates among low % LTBI countries. Also, disparity exists in case fatality rates among high % LTBI countries. This disparity existed despite that these studies have suggested a role of BCG vaccination as far as BCG is a form of mycobacterial species, has heterogeneous immune effects, and was suggested to have an added effect to LTB effect.

These studies did not consider the possible role of malaria in explaining these disparities. We consider malaria's role in this study and restrict the study of TB prevalence to malaria-free countries.

Malaria: Early in this pandemic, malaria-endemic areas were suggested to have a low risk for catching COVID-19. [13,‴] Past malaria exposure was suggested to attenuate monocyte-associated immunopathology induced by SARS-CoV-2 through inducing epigenetic reprogramming of monocytes/macrophages toward a regulatory phenotype that mitigated inflammatory responses. In the same context, another 2 studies founde a significant correlation between malaria endemicity and COVID-19 mortality.'

Material And Methods

Material and methods

Patients or the public were not involved in this work, given that we used related publically published morbidity and mortality statistics. Countries that have achieved at least 3 consecutive years of zero indigenous cases of malaria up to 2019 were selected. The total chosen countries were 69, as shown in (Appendix A) attached to this manuscript. These countries may also eligible to apply for a WHO certification of malaria-free status[i]. Free -malaria countries listed in the supplementary list by WHO were included in our study sample. The supplementary list contains countries where malaria never existed or disappeared years or decades ago and where full WHO certification of malaria elimination is not needed. WHO lists dates of notification in this list rather than elimination dates. We chose the most recent updates published in the following WHO online publications.:

1-Countries and territories certified malaria-free by WHO

Last update: 22 May 2019

WHO | Countries and territories certified malaria-free by WHO

https://www.who.int/malaria/areas/elimination/malaria-free-countries/en/

2- World Health Organization. (1968). SUPPLEMENTARY LIST OF MALARIA-FREE AREA = LISTE SUPPLÉMENTAIRE DES ZONES SANS PALUDISME. *Weekly Epidemiological Record = Relevé épidémiologique hebdomadaire, 43* (05), 82.

Further references are listed in appendix (C) within the supplementary file attached to this manuscript.

https://apps.who.int/iris/handle/10665/216419

Countries and territories with less than 1 million populations were excluded. Appendix (D)

Data for TB prevalence are publically available through:

1-http://www.bcgatlas.org/ttp://www.bcgatlas.org/

2- https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&lan=%22EN%22&iso2=%22AU%22

Data for COVID-19 mortality are available through public the site :

WHO Coronavirus (COVID-19) Dashboard

WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data

TB prevalence was taking from available data for up to 10 years ago (2011-2017) we took the highest available figure. COVID-19 deaths/million(M) inhabitant reported as it was on September 2, 2020.

Data regarding to TB Prevalence groups were classified as: (low, moderate, and high where (Low: ≤ 15), (Moderate: 16-49) and (High: ≥ 50) (appendix A).

We used the following methods:

"Kendall's-τ Correlation Coefficient", "Kruskal-Wallis test, and Mann-Whitney test". Also we used "Stem-Leaf" plot for exploring data behavior concerning COVID-19 mortality/ (M) inhabitant in relation to different TB prevalence groups.

All statistical operations were performed through using the ready-made statistical package SPSS, ver. 22.

Results And Findings

Table (1) represents "Kendall's-τ Correlation Coefficient" and P-values for studied the amount and the direction concerning relationships among the studied markers.

Results showed there was a strong relationship among studied markers (Covid-19 deaths/M and TB prevalence) as the number of deaths increased with lowering the prevalence of tuberculosis and too

highly positive significant correlation coefficient was reported (p-value = 0.008). This indicates that the research hypothesis is fulfilled in general with a highly significant p-value.

Table (1): "Kendall's-τ correlation coefficient" for studied the amount and the direction of relationships among the studied markers

Markers	Correlation Coeff. and P-value	TB prevalence
Covid-19 Deaths/M 2/August	Correlation Coefficient	-0.251 **
	Sig. (2-tailed)	0.008
	No.	69
** Correlation is significant at the 0 .01 level (2-tailed).		

Table (2) represents summary statistics of (COVID-19 deaths/M) among studied groups. These statistics include 5% trimmed mean, median, minimum, maximum readings, range, and interquartile range). Maximum figures of mortalities were among the low TB prevalence group and minimum within the high TB prevalence group. Furthermore, the 5% trimmed mean is shown to be higher within low TB prevalence group compared to moderate and high TB prevalence groups. Kruskal-Wallis Test showed a p-value of 0.021 which is less than the significance level of 0.05, hence we rejected the null hypothesis and conclude that the medians are not all equal. Significant comparisons among TB prevalence categories using the Mann-Whitney test were significant regarding the relations between a low TB prevalence group with both groups high TB prevalence and moderate TB prevalence.

Table (2): Descriptive Statistics of (COVID-19 Deaths/M on September 2, 2020) and testing of all probable combinations of TB prevalence categories

Statistics	TB prevalence categories		
	Low	Moderate	High
5% Trimmed Mean	235	82	68
Median	110	47	60
Minimum	6	5	0
Maximum	853	591	250
Range	847	586	250
Interquartile Range	445	168	97
Kruskal-Wallis Test C.S. P-value	Chi-Square = 7.740 P=0.021 (S)		
Mann-Whitney test			
Low X Moderate	Z = -2.276; P=0.023 (S)		
Low X High	Z = -2.418; P=0.016 (S)		
Moderate X HIGH	Z = -0.437; P=0.662 (NS)		

S: Sig. at P<0.05; NS: Non Sig. at P>0.05.

The shape of the distribution. of the recorded COVID-19 deaths within TB prevalence groups is well shown in stem-leaf graphical plots (figure 1). This illustration shows clearly how COVID-19 deaths were highest within the low TB prevalence group and lowest within the highest TB prevalence group. In the moderate TB prevalence group. The mortality was between the other two groups.

Discussion

A confounding factor (third variable) may mask an actual association or falsely demonstrate an apparent association between the study variables where no real association exists. If confounding factors are not measured and considered, bias may result in the conclusion of the stud. Confounding occurs when a measure designed to assess a particular construct inadvertently measures something else as well. [22]

The confounding factor can interfere with the real effect. For this reason, the etiological importance of a variable needs to be prevented or removed as much as possible. Confounding may be prevented by the use of randomization, restriction, or matching.[24] The term restriction is used when a researcher chooses only one variation of a participant to restrict the possibility of including a confounding variable. As far as malaria is a possible confounding factor suggested to create a cross heterogeneous effect towards COX-Cov2, We designed this study to exclude this factor by restricting the study sample to malaria-free

countries. Literature raised the question of unknown contribution factors regarding COVID-19 mortality variances.[25] Some of the literature raised the possibility of malaria as one factor in explaining the variances in COVID-19 mortalities.[13,15,16,17 ,18 , 19,20] . One of these studies found that malaria has an added effect on TB prevalence effect in decreasing the COVID-19 deaths in malaria-endemic areas. [19] Countries are classified as either malaria-free or malaria-endemic countries. All malaria-free countries have a certain TB prevalence. In general, countries might be classified as low, intermediate, and high TB incidence countries. Malaria endemic countries are usually highly endemic in TB.[25],[26] This might lead to confounding when testing relation of TB or malaria against COVID-19 mortality.

Previous studies testing TB influence on COVID-19 mortality fail to control this factor.

In this study by using Kendall's-τ correlation coefficient test, there was a high reverse-directional significant correlation between COVID-19 mortality rates and TB prevalence (in absence of suggested confounded factor of malaria endemicity) with a reported p- value (0.008) (table 1).

Kendall's τ has been classically used to test the significance of cross-correlation between two variables when their distributions significantly deviate from the normal distribution. In that case, a significance test based on the distribution-free τ, which is a function of the ranks of the variates rather than their actual values, offers more power than other parametric tests.[27]

The finding in this study of TB prevalence influence on COVID-19 mortality in malaria-free countries is strongly in agreement with a previous study in malaria-endemic countries.[19] Furthermore, it consolidates other studies on the relation of LTB to covid-19 mortality.[10,11,12,,13 ,14,[28] .

A second test conducted in this study was the Kruskal-Wallis Test. It is a non-parametric method used for testing whether samples originate from the same distribution or not by determining whether the medians of two or more groups are different.[29],[30] It was conducted among different TB prevalence groups. It showed that the Chi-Square result equals 7.740 with P-value equals 0.021 (S)These results signify that there are differences among the groups, but as Kruskal-Wallis Test is an omnibus test statistic and doesn't tell which group is different from other groups. It is used for comparing two or more independent samples of equal or different sample sizes. The Kruskal–Wallis test is a rank-based test that is similar to the Mann–Whitney U test but can be applied to one-way data with more than two groups. It is a non-parametric alternative to the one-way ANOVA test, which extends the two-samples Wilcoxon test.

However, like most non-parametric tests, the Kruskal-Wallis test is not as powerful as the ANOVA but, assumptions of one-way ANOVA are not met in our sample.

A Mann-Whitney U test (another non-parametric test) was used to compare the differences between two independent samples as far as the sample distributions are not normally distributed as shown before.

It showed that the low TB prevalent group when tested against groups moderately TB prevalent and highly prevalent group show significant association with decreased mortality from covid-19 (table 2).

The non-significant association between moderate and high TB prevalent groups (table 2) needs further consideration. The test fails to find a significant association due to possible existing confounding factors. A possible one is the malaria elimination date since faster progress was achieved in malaria elimination recently, compared to TB control in many countries. According to WHO, the malaria elimination net is widening. Furthermore, more countries are moving towards zero indigenous cases: The number of countries with fewer than 100 indigenous cases was 17, 25, and 27 in 2010, 2017, and,2018 respectively, which is a strong indicator that elimination is within reach. .[31]

Despite other significant associations, some countries are disparate fatality rates / M inhabitants among low TB prevalence countries. Also, a disparity exists in fatality rates among high TB prevalence countries. We suggest other possible confounding factors in addition to malaria residual immunity already mentioned which include but are not restricted to BCG policy of country and BCG coverage, other mycobacterial cross-reaction or effects by other vaccines population size measures taken, habits, some LAVs which have induced a broad, nonspecific, protection against unrelated pathogens and decreased mortality from conditions other than the targeted infectious diseases. [32]. Furthermore, this study was done without any regard for income, healthcare facilities.

Controlled clinical studies need to be conducted before further considering reviewing global strategies for the prevention and treatment of TB and malaria. According to global strategy in the treatment of TB, the main goal is to treat the active cases in areas with a high incidence of TB, but in areas with a low incidence of TB, the goal also includes prophylactic treatment for LTBI[33]

Whoever, in recent years, studies have gradually narrowed down to the preventive treatment of LTBI for high-risk target groups. Targeted TB testing and treatment programs in USA and many European countries conducted among high-risk groups.[34],[35]. It was questionable that chasing after LTB infection treatment a time before[36].If prophylaxis is provided for all LTBI patients, it will result in an enormous waste of resources and increase the likelihood of anti-TB drug resistance.[33] Added to that we raised the possible role of LTB on decreasing COVID-19 mortality.

TB prevalence in this study was taken as the highest available figure for up to 10 years ago (since 2011 outward) as far as the immunity created by latent or active TB infection last for a long time. The major dilemma is that there is no test to assure that every person diagnosed with an immune reaction to LTB treatment can be guaranteed free from the active form of infection, although it has been agreed that reactivation is unlikely after 2 years.

We considered 10 years the least time for immune-reaction to wane as far as it is well known that a related Mycobacterium which is Mycobacterium Bovis (BCG), waned by at least by 10 years..[37] A longer time for immune reaction time after natural infection is possible, but the exact time for waning such immunity is unknown yet.

Conclusions

TB prevalence is inversely related to COVID-19 mortality in high significance association.

Low TB prevalence countries have significantly different statistical COVID-19 mortalities in relation to both moderate and high TB prevalent countries.

Recommendations: clinical trials are recommended for any updating global strategies for the prevention and treatment of TB and malaria.

Declarations

• Ethics approval and consent to participate: 'Not applicable

• Consent for publication: I certify that

this study has not been previously published. The publisher has my permission to publish this study. With the consent, I give the publisher copyright license •

Availability of data and materials: We used publically available data. Patients were not involved.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

• Competing interests: There is no conflict of interest to be declared.

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• Author contributions: The author wrote the manuscript and provided data, conducted the statistical analyses, and reviewed the final manuscript.

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Figures

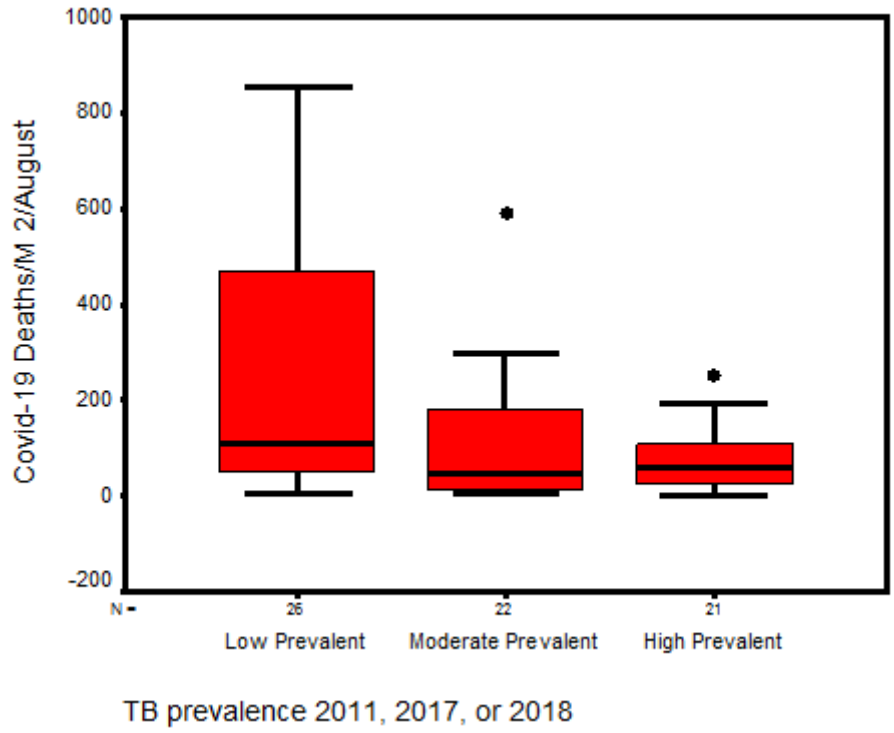

Figure 1

Stem-Leaf plots of (COVID-19 deaths/M) according to TB prevalence categories.

Supplementary Files

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- suppnonmalarious.docx