



The (in)significance of TB and COVID-19 co-infection

To the Editor:

We read with great interest the research letter by TADOLINI *et al.* [1], in which they have published the first cohort of 49 cases of tuberculosis (TB) and coronavirus disease 2019 (COVID-19) co-infection. However, a few issues regarding the letter need to be addressed.

The authors categorised the patients with TB and COVID-19 co-infection into 3 groups based on timing of their diagnosis. However, in view of the difference in the natural history of TB (chronic course) and COVID-19 (acute), categorising 14 patients as having COVID-19 prior to TB (median time interval of 4 days between the two diagnosis) and nine as diagnosed simultaneously (within the same week) seems inappropriate. Since TB has an insidious onset, it is obvious that TB was present before COVID-19 infection in both the subgroups, although the diagnosis was made at different times. In fact, it may be right to say that all the three subgroups actually constitute a single group of old/active TB patients who developed COVID-19 infection. COVID-19 has probably just unmasked some of the subtle active TB cases that were responsible for hidden transmission in the general population [2]. Superimposed COVID-19 has brought them to the hospital to get a timely diagnosis.

Considering the high worldwide prevalence of TB and increasing burden of COVID-19, the co-infection seems more likely to be a co-incidental occurrence rather than a causal association. It is likely that patients with active TB will have more time to get exposed to COVID-19 infection due to chronic course of TB. The hypothesis is also supported by a higher percentage of multidrug-resistant TB patients in the present study, as these patients are on a prolonged treatment and harbour TB disease for a longer period of time. However, a well-designed prospective cohort study is required to prove any causal association between the two diseases, as also concluded by the authors.

Apart from assessing association, the other main concern about this co-infection is the mortality associated with it. The present study showed a mortality of 12.3% in the patients with dual infection, which is much higher than isolated COVID-19 [3]. However, this apparent higher mortality cannot be attributed to the dual infection from this cohort as the majority of patients with fatal disease had proven risk factors for mortality (>60 years age and one or more comorbidity) that might have distorted the figures.

Irrespective of the probable temporal association between COVID-19 and TB, both the infectious diseases may have synergistic impact on social and economic impact worldwide. This is because both the diseases are expected to spread in overcrowded areas with poor and undernourished populations [4]. High TB burden countries have a huge number of patients with post TB lung sequelae and the outcome of COVID-19 in such patients is unknown so far. It is important to understand from this analysis that in the fight against COVID-19 pandemic, we should not forget to suspect and manage TB appropriately, which is still one of the leading infectious causes of death worldwide.

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In the fight against COVID-19 pandemic, we should not forget to suspect and manage TB appropriately, as it is still one of the leading infectious causes of death worldwide <https://bit.ly/30FZs9C>

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On tuberculosis and COVID-19 co-infection

From the authors:

We wish to thank A.K. Khurana and D. Aggarwal for their interest in our research letter and comments.

In their correspondence, the authors raised two important issues, namely the possible association between tuberculosis (TB) and coronavirus disease 2019 (COVID-19) (can infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) re-activate TB?), and the effects of TB on early mortality in co-infected patients.

Our research letter reported the first cohort of patients with diagnosis of TB (including post-treatment sequelae) and COVID-19. The article was aimed at reporting what was observed at the beginning of the epidemic among some of the most affected countries. This explains the small numbers described and the countries involved. At the time the article was submitted, several countries in Africa, Europe and Latin America represented in the Global Tuberculosis Network (GTN) had no TB/COVID-19 patients to report.

In the absence of previous cohorts and scientific information on TB/COVID-19 co-infection, we have described the timing of diagnosis of the two diseases, observing that one third had COVID-19 diagnosed prior to TB and 18% were diagnosed simultaneously.

We agree, it is possible that the diagnosis of COVID-19 was made before TB because of acute onset of symptoms caused by SARS-CoV-2 in addition to the alarm generated by the COVID-19 pandemic, which determined rapid access to radiological examinations and subsequent discovery of underlying TB. In fact we commented on this in point 3 of our article [1], and we abstained from making any clear statement about causal association. However, we could not exclude that the infection by SARS-CoV-2 or the drugs utilised might have accelerated the progression of a pre-existing TB infection to disease.

However, apart from the speculation on what disease comes first, it is evident that the co-existence of TB and COVID-19 poses a challenge in differential diagnosis [1].

The study was observational, and based on a relatively small cohort, and therefore we fully agree that larger prospective studies are necessary to shed further light on this to establish whether there is an association or not.



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COVID-19 may boost tuberculosis given infection and mortality, further studies are needed <https://bit.ly/2Z2r5XO>

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A.K. Khurana and D. Aggarwal also raised the important question of whether TB has a real effect or “weight” in increasing the probability of death in COVID-19 patients.

The issue has been described in a second article [2] which reports the findings of 69 patients from our original cohort plus a second cohort [3] which was managed in a reference hospital in Northern Italy.

The patients more likely to die were those of older age with pre-existing comorbidities [2].

It is important to emphasise that the cohort of young migrants without comorbidities reported elsewhere [2, 3] experienced a milder form of COVID-19 with no deaths.

However, in countries where risk factors for mortality are highly prevalent among young individuals (smoking, alcohol and substance abuse, HIV co-infection, among others), particularly in the presence of drug resistance and difficult access to diagnosis (delayed diagnosis), the impact of mortality may be higher. We agree that, in resource-limited settings, poverty and malnutrition might play an important role in increasing morbidity and mortality.

Furthermore, we do agree that the population of individuals with post-TB treatment sequelae deserves further evaluation, given the potential effect of both TB and COVID-19 on quality of life and subsequent need for rehabilitation [4–6].

In order to better understand the implication of TB and COVID-19 co-infection the study is continuing: more countries and a larger sample size will help answering some of the questions left open by our original study [1]. We will be happy to collaborate with all interested colleagues.

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