Early View

Correspondence

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On Tuberculosis and COVID-19 co-infection

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Take home message: COVID-19 may boost tuberculosis given infection and mortality, further studies are needed

Key words: TB, COVID-19, mortality, quality of life, rehabilitation

Text 572 words
Dear Editor,

we wish to thank, Alkesh Khurana and Deepak Aggarwal [1] for their interest in our research letter and comments [1].

In their correspondence, the Authors raised two important issues, namely the possible association between tuberculosis (TB) and COVID-19 (can infection by 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 the 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 was made before TB because of acute onset of symptoms caused by SARS-CoV2 in addition to the alarm generated by the COVID-19 pandemic, which determined rapid access to radiological examinations and subsequent discovery of underlying tuberculosis. In fact we commented this in point 3 of our article [2], 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 utilized 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 [2].

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.

The Authors [1] also raised the important question 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 [3] which reports the findings of 69 patients from our original cohort plus a second cohort [4] which was managed in a reference hospital in Northern Italy.

The patients likelier to die were those of older age with pre-existing co-morbidities [3].

It is important to emphasise that the cohort of young migrants without co-morbidities reported elsewhere [3,4] 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 [5-7].

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 [2]. We will be happy to collaborate with all interested colleagues.

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References

1) Khurana A, Aggarwal D. The (in)significance of TB and COVID-19 co-infection. Eur Respir J 2020; xxxx

2) Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, Andréjak C, Bachez P, Bart PA, Belilovski E, Cardoso-Landivar J, Centis R, D'Ambrosio L, De Souza-Galvão ML, Domínguez-Castellano A, Dourmane S, Jachym MF, Froissart A, Giacomet V, Goletti D, Grard S, Gualano G, Izadifar A, Le Du D, Royo MM, Mazza-Stalder J, Motta I, Ong CWM, Palmieri F, Rivièrè F, Rodrigo T, Rossato Silva D, Sánchez-Montalvá A, Saporiti M, Scarpellini P, Schlemmer F, Spanevello A, Sumarokova E, Taberner E, Tambyah PA, Tiberi S, Torre A, Visca D, Muguiro MZ, Sotgiu G, Migliori GB. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. Eur Respir J. 2020 May 26;2001398. doi: 10.1183/13993003.01398-2020.

3) Motta I, Centis R, D’Ambrosio L, García-García JM, Goletti D, Gualano G, Lipani F, Palmieri F, Sánchez-Montalvá A, Pontali E, Sotgiu G, Spanevello A, Stochino C, Tabernero E, Tadolini M, van den Boom M, Villa S, Visca D, Migliori GB. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. Pulmonology. 2020 May 14. doi: 10.1016/j.pulmoe.2020.05.002

4) 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 Jun 1;2001708. doi: 10.1183/13993003.01708-2020.

5) Visca D, Zampogna E, Sotgiu G, Centis R, Saderi L, D’Ambrosio L, Pegoraro V, Pignatti P, Muñoz-Torrico M, Migliori GB, Spanevello A. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. Eur Respir J. 2019 Mar 14;53(3):1802184. doi: 10.1183/13993003.02184-2018.

6) Zumla A, Marais BJ, McHugh TD, Maeurer M, Zumla A, Kapata N, Ntoumi F, Mfinanga S, Centis R, Cirillo DM, Petersen E, Hui DS, Ippolito G, Leung CC, Tiberi S, Migliori GB. The increasing threat of respiratory tract infections to global health security – COVID-19 and Tuberculosis. Int J Tuberc Lung Dis 2020; in press
7) Visca D, Tiberi S, Pontali E, Spanevello A, Migliori GB. Tuberculosis in the time of COVID-19: quality of life and digital innovation. Eur Respir J. 2020 Jun 8:2001998. doi: 10.1183/13993003.01998-2020.