Pneumonia mortality, comorbidities matter? Authors' answer

Dear Editor,

Thank you for inviting me to reply to the letter published in Pulmonology journal by H. Ito ''Potential survival paradox in pneumonia''[1] concerning the recent published article in Pulmonology ''Pneumonia Mortality, comorbidities matter?''

Thanks for reading and commenting our article, ''Pneumonia Mortality, comorbidities matter?''

Regarding the results described in your letter to the editor,one comment and some matters for concern raised about the results described in our paper.[2] The comment refers to the possible high proportion of pneumococcal pneumonia identified in the etiology of pneumonia in Portugal, pointing to its possible relationship with vaccination policy. In fact, in Portugal the target populations for pneumococcal vaccination are people under five and older than 64, and patients with any kind of immunodeficiency. Interestingly, most of pneumococcal isolates we obtained in our study, were identified with young-adult patients with no comorbidities, which are not usually included in the target population for pneumococcal vaccination. This is probably one of the explanations for the fact that, that this etiology was not associated with a higher mortality risk.

The concerns are linked to the fact that in our study, smoking habits, obesity, COPD and diabetes are not associated with an increased risk of dying of pneumonia, whereas these comorbidities are usually associated with an increased risk of death from pneumonia. However, the studies[3–5] used to justify the doubts raised in our research, have very different designs, populations, methodologies and analyses, so they can hardly serve for comparison.

In our study, all patients admitted to National Health Service (NHS) hospitals with pneumonia or sepsis with pneumonia, during 2015, were evaluated. The NHS hospitals are responsible for the overwhelming majority of hospitalizations in Portugal. The evaluation and classification of inpatient episodes is permanently carried out, prospectively, by medical doctors specialized in disease coding. This data was used in our study and, whenever necessary, electronic patient records of pneumonia episodes were evaluated. It is not possible, when the investigation is carried out on a retrospective basis, to eliminate all types of bias, due to information/recall or if a particular patient characteristic was included or not in the protocol. However, we believe this was controlled by the nature of our data and by the negligible number of missing values of the 36,366 patients we studied. The risk of misclassification, as we pointed out in the article, is impossible to eliminate completely and we assume that it existed. However, we think that these limitations do not explain the results. The prevalence of severe limiting comorbidities, such as the high number of bedridden patients, patients with stroke, sequelae, dementia, cachexia, cancer and patients living in Care Homes, accounting, in that year, for about 50% of the pneumonia mortality requiring hospital admission. The interpretation of ''non concordant'' results from different research designs, seeking the same goals, but using different data, is not unusual.[6] One way of dealing with this, is using Bayesian approach for interpretation of to the data and results.[7,8] This way of thinking, requiresnot only current data assessment, but also, use of ''prior knowledge'' of the context where the study was conducted, using the prevalence of the patients characteristics in the study population, the way of living and the access to medical care. The variable distribution and prevalence are determinant in the subsequent interpretation of the results and their external validity. The data we used included the great majority of the hospital admissions for pneumonia during 2015 in Portugal. The main goal of the study was to seek for explanations for the high mortality rate for pneumonia in our country,[9,10] and in our view, comorbidities play an important role in this. Using the available data from lastyears,[9,10] it is easy to conclude that chronic illnesses appear early, limiting quality of life. Our study allowed us to identify the coexistence, in a large number of patients, of multiple comorbidities (eg.: smoker + obese + diabetic + COPD + stroke sequelae + bedridden, ...) highly limiting. The impact of any comorbidity, will always depend on their prevalence but also, if in each patient, it exist alone or in combination with others, leading to a different impact in the outcome we are studying.

The results we obtained must be interpreted according to the particularities of the studied population and the access to health care. The large number of elderly patients with concomitant multiple serious comorbidities and the universal access to NHS facilities, may justify the results we found. In fact in other study in our country, the authors found that hospital mortality was particularly related to the aging process and unfavorable socioeconomic conditions[11].The risk model obtained will be tested prospectively in the near future, so we hope to be able to validate the results obtained for this population.

Conflicts of interest

The authors have no conflicts of interest.

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Interleukin-6 blockade with tocilizumab in COVID-19: Does it live up to its hype?

A recent systematic review by Cortegiani et al.[1] reviewed the evidence and appraised the quality of evidence concerning the use of tocilizumab in patients with coronavirus disease 2019 (COVID-19). Despite a thorough appraisal of a large number of clinical studies (n = 28) on tocilizumab in patients with COVID-19, Cortegiani et al.[1] concluded that there is still insufficient evidence on its clinical efficacy in patients with COVID-19 because these studies are associated with a high risk of bias and poor quality. We would like to complement the discussion on the evidence of tocilizumab use in patients with COVID-19.

Interleukin (IL)-6 blocking agents such as tocilizumab have been touted as the potential treatment for COVID-19 since the recognition of the cytokine storm associated with a severe course of COVID-19, which involves increased levels of several cytokines where one of them is IL-6. However, a more pressing question is ''Do increased concentrations of an IL-6 imply that its neutralisation will be effective in COVID-19?'' While a recent observational study[2], not included in the systematic review, demonstrated mortality benefits associated with the use of COVID-19, the two recent randomized controlled trials[3,4] did not replicate the findings. The randomized, double-blinded, placebo-controlled COVACTA trial[3] among hospitalized patients with COVID-19 reported no difference in 28-day mortality between the tocilizumab arm and placebo arm (19.7% and 19.4%, respectively). Furthermore, based on the results released on September 18, 2020, from the randomized, double-blind, placebo-controlled EMPACTA trial[4], there was no statistical difference in 28-day mortality between patients who received tocilizumab and patients who received a placebo (10.4% and 8.6%, respectively).

The findings from randomized controlled trials have proved that the use of tocilizumab in COVID-19 did not live up to the hype, where the increased concentration of IL-6 does not imply that its neutralization will be effective in COVID-19. There is a possibility that the wrong cytokine was targeted to dampen the cytokine storm in COVID-19. A recent prospective study by Blot et al.[5] compared the concentrations of IL-6 between 27 patients with COVID-19 pneumonia and 36 patients with non-COVID-19 pneumonia. It was reported that the plasma concentrations of IL-6 were significantly lower in the patients with COVID-19 pneumonia compared to the patients with pneumonia other than COVID-19 (121.0 pg/mL versus 460.4 pg/mL).

The findings of this prospective study, coupled with the findings from two randomized controlled trials that failed to detect mortality benefits with tocilizumab, suggest that IL-6 may not be the cytokine that drives the progression of COVID-19. The use of tocilizumab is not harmless since it may predispose patients to the development of secondary infections. We suggest a shift in focus and to target other mediators of hyperinflammatory state in patients with COVID-19.

Conflicts of interest

The authors have no conflicts of interest.

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