PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Changes in laboratory value improvement and mortality rates over the course of the pandemic: an international retrospective cohort study of hospitalized patients infected with SARS-CoV-2
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VERSION 1 – REVIEW

REVIEWER	Radovanovic, Dejan Division of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy I have no competing interests to report other than being author and co-author of several manuscript focused on clinical characteristics and therapeutic management strategies of patients with COVID-19 pneumonia
REVIEW RETURNED	21-Nov-2021

GENERAL COMMENTS	This was a retrospective multicenter study designed to investigate changes in hospitalized COVID-19 patients' clinical profiles, mortality rates and improvement rates of lab parameters during the first and second part of the 2020-2021 COVID-19 pandemic wave. As correctly highlighted by the Authors, this represents one of the few studies that addressed the evolution of mortality and in-hospital clinical trends from an international point of view comparing the spring and winter 2020 months of the pandemic. The study was well conducted and has a solid rationale. However the study suffers from two major limitations: First, the lack of important clinical variables that were proven to interact with mortality and chance for clinical improvement such as respiratory failure parameters and in-hospital care setting (e.g. ICU vs. general ward). Second, it appears that the

	objectives and the findings of the study were disconnected form the discussion, in which the focus on the main findings was not maintained. Please see below my concerns and comments 1. Introduction: I agree with the Authors that a limited number of studies addressed changes over time in COVID-19 patients. However, they are missing a couple of important studies that might help also to address the discussion and put data into context (Respir Med 2021; 178:106323 and J Infect 2020;S0163–4453(20):30693) 2. Methods: it is unclear how stratification for mortality risk was carried out. Was it managed “a priori”, or derived from collected data? Moreover, considering a possible (and unpredictable) change in patients’ characteristics from the “first” to the “second” pandemic wave, were these characteristics adapted or were fixed and derived only from the first pandemic wave? Did the Authors considered to apply or to compare their mortality risk models to the ones usually applied for risk stratification in patients with COVID-19 pneumonia? 3. Methods: was treatment (including application of invasive/non invasive ventilation) part of the data collected? Was timing of symptom appearance in respect to hospital admission available for analysis? The latter variable can greatly change patients’ outcomes due to anticipation of monitoring and pharmacological/respiratory management. 4. Methods: were patients coming both from ICUs/ high dependency respiratory units and general wards? 5. Results and Methods: the predictive power for mortality of the lab variables that the Authors found strongly depend upon the variables they had in the electronic charts. Indeed, one of the most important parameters associated with mortality in hospitalized patients with COVID-19 pneumonia is the severity of respiratory failure and the degree of respiratory distress at admission. However, these parameters were not available for the current study. Despite the homogeneity of Authors’ findings, I would be cautious in describing definitive results in this sense. Moreover, available literature on mortality risk factors should be also carefully discussed in the discussion section. 6. Discussion: the first part of the chapter should include the results pertaining the primary and secondary objectives. As reported, the reader is driven directly to the mortality risk factors, and not to the changes in 28-day mortality, as suggested in the Method section 7. Discussion: “Despite few changes in patient demographic and clinical profiles at admission, stratified mortality rates decreased significantly, and patient laboratory profiles displayed faster physiological recovery.” This observation might also be secondary to different healthcare system and population preparedness to the disease, and also different timing for referral to the emergency department. Please consider these observations for discussion. 8. Discussion: “ For example, continuous positive airway pressure reduces the need for mechanical ventilation, and high positive end-expiratory pressure and prone positioning optimizes oxygenation [10,58,59].” This sentence, as places, is quite confusing. The Authors have no data on ventilatory or respiratory support strategies, therefore the role of these interventions can’t be ppreciated. Moreover, the application of noninvasive or invasive respiratory support strategies have been sustained from the beginning of the COVID-19 pandemic, especially in European countries in regard to CPAP or NIV. Lastly, it would be more cautious when addressing the use of high end expiratory pressure in COVID-19 patients, because several reports have suggested the use of low PEEP strategies to manage patients during non invasive respiratory supports, and

	sometime profound differences from traditional ARDS and COVID-ARDS. 9. Discussion, strengths and limitations: please add to the limitation paragraph the issues discussed above

REVIEWER	Carsetti, Rita Bambino Gesù Children's Hospital, Rome, Diagnostic Immunology Unit
REVIEW RETURNED	09-Dec-2021

GENERAL COMMENTS	The manuscript reports an interesting retrospective cohort study of 83,178 hospitalized patients with COVID-19 recruited by the Consortium for Clinical Characterization of COVID-19, including 288 hospitals in the United States and Europe. The Authors find that the mortality rate decreased over time between the first and second wave of the pandemics in all countries.At the same time laboratory values improved. The study and the methods are clearly described. The data is solid and interesting. Tables and figures are clear and informative.

VERSION 1 – AUTHOR RESPONSE

Suggestion, Question, or Comment from Reviewer 1	Author's Response	Change in the Manuscript (if applicable)
Introduction: I agree with the Authors that a limited number of studies addressed changes over time in COVID-19 patients. However, they are missing a couple of important studies that might help also to address the discussion and put data into context (Respir Med 2021; 178:106323 PubMed and J Infect 2020;S0163–4453(20):30693)	We thank the reviewer for this suggestion. We have now cited the two studies kindly provided by the reviewer along with other relevant studies in the introduction of the manuscript.	Mortality rates among hospitalized patients with SARS-CoV-2 infection have decreased over the course of the COVID-19 pandemic [1–5]. It has been hypothesized that this may reflect a higher proportion of younger patients being hospitalized later in the pandemic, but a recently published study reported significant decreases in mortality after stratification by age group [6,7]. A variety of factors are likely responsible, including, but not limited to, improvements in clinical management, resource allocation, and earlier detection of disease [8–15].
Methods: it is unclear how stratification for mortality risk was carried out. Was it managed "a priori", or derived from collected data? Moreover, considering a possible (and unpredictable) change in patients' characteristics from the "first" to the "second" pandemic wave, were these characteristics adapted or	We thank the reviewer for raising this point. Mortality risk stratification was performed using an estimated mortality risk score for each patient, derived from information recorded in the EHR on the date of hospital admission, which we refer	Using the trained penalized Cox model, we obtained a mortality risk score for each patient constructed using their baseline covariates. The candidate covariates included in the model training were determined according to existing clinical knowledge.

were fixed and derived only from the first pandemic wave? Did the Authors considered to apply or to compare their mortality risk models to the ones usually applied for risk stratification in patients with COVID-19 pneumonia?	to as baseline covariates. In doing this, we sought to demonstrate the ability to stratify patients by their mortality risk using clinical characteristics at the admission date. We have clarified this in the manuscript. The candidate feature set we included was determined based on existing clinical knowledge about COVID-19. The value of the features was extracted for each patient at their respective hospitalization date. In our preliminary analysis, we compared an existing model which only used 3 laboratory values. We refitted the model to one US site and compared its performance to (1) the full model that incorporates all seventeen 4CE laboratory test values, and (2) the common lab model that incorporates selected laboratory tests with missing rates less than 30% at most sites. The results suggest that the literature based model performed worse than the common lab model (7-day AUC =0.808 vs 0.849, P-value=0.0001). Therefore in this paper, we focused on the analysis based on 10 common labs.	
Methods: was treatment (including application of invasive/non invasive ventilation) part of the data collected? Was the timing of symptom appearance in respect to hospital admission available for analysis? The latter variable can greatly change patients' outcomes due to anticipation of monitoring and pharmacological/respiratory management.	Patient-level data for specific treatments was not collected. Along this line, data on invasive/non-invasive ventilation were not collected. The exact timing of COVID-19 symptom onset in respect to the hospital admission date was not available for analysis as we only considered data recorded in the EHR after hospital admission. However, we strongly concur with the reviewer's point that timing of COVID-	A further limitation was the lack of data on patient-specific timing of symptom onset relative to hospital course.

	19 symptoms can greatly change patients' outcomes due to monitoring and clinical management. We therefore considered variables recorded on the date of hospitalization such as the Charlson score to account for comorbidities and 10 laboratory values to account for patient pathophysiology at admission.	
Methods: were patients coming both from ICUs/ high dependency respiratory units and general wards?	Yes, our study population consisted of hospitalized patients with COVID-19. A sub-population of these patients may very well have been from ICUs or high dependency respiratory units. However, this information was not available in the curated datasets. We have added this important point to the limitations section.	This study has several limitations. First, similar to other EHR-based studies, the current study might have included patients with incidental COVID-19 hospitalization (i.e.,who were either hospitalized due to COVID-19 or had a positive test for SARS-CoV-2 when admitted for an unrelated medical condition). Further, information regarding each patient's in-hospital care settings, such as admission to intensive care units and their specific respiratory status was not available.
Results and Methods: the predictive power for mortality of the lab variables that the Authors found strongly depend upon the variables they had in the electronic charts. Indeed, one of the most important parameters associated with mortality in hospitalized patients with COVID-19 pneumonia is the severity of respiratory failure and the degree of respiratory distress at admission. However, these parameters were not available for the current study. Despite the homogeneity of Authors' findings, I would be cautious in describing definitive results in this sense. Moreover, available literature on mortality risk factors should be also carefully discussed in the discussion section.	We thank the reviewer for raising the point regarding predictive power of lab variables, and we agree that we should be cautious in describing results in a definitive sense. We have edited the language in the discussion section surrounding the predictiveness of lab variables to reflect this. We have also added more discussion of COVID-19 mortality risk factors from the literature into the discussion section as kindly suggested by the reviewer to demonstrate that our results are supported by other studies.	Our study suggests that older age, male sex, higher CCI, low albumin and lymphocyte count values, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT were significantly associated with higher mortality risk. While male sex, older age, and existing comorbidities are established major risk factors for COVID-19-related mortality, our observations of the associations between higher AST/ALT, ALT, and bilirubin with mortality [63–66] are unique. While derangements in liver function tests are well described in prior studies of patients with COVID-19, the patterns of liver dysfunction associated with worse outcomes have been inconsistent [67,68].
Discussion: the first part of the chapter should include the results pertaining the primary and secondary	This is a great point, and we thank the reviewer for raising it. We have gladly	See Discussion section.

objectives. As reported, the reader is driven directly to the mortality risk factors, and not to the changes in 28-day mortality, as suggested in the Method section	re-structured the discussion to first focus on changes in mortality rates across time with subsequent discussion on laboratory value-based physiological recovery.	
Discussion: “Despite few changes in patient demographic and clinical profiles at admission, stratified mortality rates decreased significantly, and patient laboratory profiles displayed faster physiological recovery.” This observation might also be secondary to different healthcare system and population preparedness to the disease, and also different timing for referral to the emergency department. Please consider these observations for discussion.	We appreciate the reviewer’s suggestion, and we have added that differences in healthcare systems, population preparedness, and timing for referral to the emergency visits all may contribute to the observed decreases in mortality and improved laboratory profiles across the COVID-19 waves.	Potential explanations for the differences between the two waves include timing for emergency visits and hospital admission, iterative improvement in management strategies of the severe cases, and increased preparedness of healthcare systems in the latter stages of the pandemic. As diverse healthcare systems and populations in different countries learned to improve the care of COVID-19 patients through diverse experiences, knowledge rapidly disseminated. For example, hospitals may also have benefited from improved resource allocation strategies and management of smaller surges in hospitalizations [63].
Discussion: “ For example, continuous positive airway pressure reduces the need for mechanical ventilation, and high positive end-expiratory pressure and prone positioning optimizes oxygenation [10,58,59].” This sentence, as places, is quite confusing. The Authors have no data on ventilatory or respiratory support strategies, therefore the role of these interventions can’t be appreciated. Moreover, the application of noninvasive or invasive respiratory support strategies have been sustained from the beginning of the COVID-19 pandemic, especially in European countries in regard to CPAP or NIV. Lastly, it would be more cautious when addressing the use of high end expiratory pressure in COVID-19 patients, because several reports have suggested the use of low PEEP strategies to manage patients during non invasive respiratory supports, and sometime profound differences from traditional ARDS and	We thank the reviewer for their thoughtful feedback on this important point. We deleted this sentence to avoid confusion.	Sentence deleted: “ For example, continuous positive airway pressure reduces the need for mechanical ventilation, and high positive end-expiratory pressure and prone positioning optimizes oxygenation [10,58,59].”

COVID-ARDS.		
Discussion, strengths and limitations: please add to the limitation paragraph the issues discussed above	We thank the reviewer for pointing out limitations in the study, and we have gladly expanded our limitations section to include the relevant points from the reviewer.	This study has several limitations. First, similar to other EHR-based studies, the current study might have included patients with incidental hospitalization (i.e., a positive test for SARS-CoV-2 when admitted for an unrelated medical condition)[72]. Further, information regarding each patient's in-hospital care settings, such as admission to intensive care units and their specific respiratory status was not available. Second, most 4CE participating healthcare systems were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality occurs in the hospital[1] , and most discharged patients would have post-discharge follow-up visits, which would reasonably capture 28-day mortality. A further limitation was the lack of data on patient-specific timing of symptom onset relative to hospital course. Additionally, our study may have potential time-dependent bias given that 4CE defines a first hospital admission that occurs between 7 days before and up to 14 days after the first positive SARS-CoV-2 PCR test. This may also affect the results stratified by duration of hospitalization. Future analyses accounting for medication administration and procedure use and the subsequent effect on inflammatory markers and creatinine are necessary to infer why these outcomes improved in the second wave.

VERSION 2 – REVIEW

REVIEWER	Radovanovic, Dejan Division of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy
REVIEW RETURNED	22-Mar-2022

GENERAL COMMENTS	This is a retrospective multinational study involving >80.000 covid-19 patients admitted during the first year of the COVID pandemic. The study was aimed at investigating the mortality trend, risk factors for mortality and blood biomarkers changes during the two pandemic waves were the primary and secondary outcomes. The Authors found that mortality rates were reduced going further into the pandemic, paralleled with an improvement of inflammatory and organ-specific biomarkers, while the severity of patients apparently did not change. The study was well conducted and planned, although the major limitation is represented by the lack of knowledge of the pharmacological treatments and respiratory support used in different countries. Overall, the manuscript has general and epidemiological interest in the COVID-19 epidemic analysis. I have only minor comments, please find them below: - Abstract, design: the intention to compare to different periods (two pandemic waves) is unclear. Please provide some details (e. g. the periods selected) in the methods. Moreover, first sentence: before and after …what time lag? - Methods: Italy, although heavily struck by the covid-19 pandemic wave, was excluded from mortality calculations because reported mortality was too low. Was it due to the lack of reporting? I doubt this was due to a real low mortality rate. This should be clarified - Discussion: the Authors state that “Given that no new major effective pharmacologic therapies were introduced between the two waves…”. I do not completely agree with this idea. The majority of countries substantially and organically introduced the use of systemic steroids in the pharmacological treatment algorithm for patients hospitalized with COVID-19 pneumonia. This is correctly discussed later in the discussion. I would recommend changing the wording of the sentence mentioning that were no “new therapies” but some already implemented therapies were managed differently. Moreover, the use of ventilatory support, the higher proportion of patients managed without mechanical ventilation, probably contributed in improving patients’ management and resource allocation.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer #1

Comments to the Author:

This is a retrospective multinational study involving >80.000 covid-19 patients admitted during the first year of the COVID pandemic. The study was aimed at investigating the mortality trend, risk factors for mortality and blood biomarkers changes during the two pandemic waves were the primary and secondary outcomes. The Authors found that mortality rates were reduced going further into the pandemic, paralleled with an improvement of inflammatory and organ-specific biomarkers, while the severity of patients apparently did not change. The study was well conducted and planned, although the major limitation is represented by the lack of knowledge of the pharmacological treatments and respiratory support used in different countries. Overall, the manuscript has general and epidemiological interest in the COVID-19 epidemic analysis.

Minor comments:

1. Abstract, design: the intention to compare to different periods (two pandemic waves) is unclear.

Please provide some details (e. g. the periods selected) in the methods. Moreover, first sentence: before and after …what time lag?

Response: Thank you for pointing this out. We have now added the following details in the Abstract section: (1) the truncation date of the first (March 1 to June 30, 2020) and the second wave (July 1, 2020 to January 31, 2021); (2) our intention to compare the changes of laboratory value improvement and mortality rate over time between the two waves of the pandemic; (3) time lag information for defining the study cohort, that is being admitted between seven days before or fourteen days after polymerase chain reaction-confirmed SARS-CoV-2 infection.

2. Methods: Italy, although heavily struck by the covid-19 pandemic wave, was excluded from mortality calculations because reported mortality was too low. Was it due to the lack of reporting? I doubt this was due to a real low mortality rate. This should be clarified

Response: Thank you for pointing out the lack of clarification. We agree that the small number of deaths contained in Italy data was more likely due to the lack of reporting, rather than a real low mortality rate. We have now clarified it in the Methods Section.

3. Discussion: the Authors state that "Given that no new major effective pharmacologic therapies were introduced between the two waves…". I do not completely agree with this idea. The majority of countries substantially and organically introduced the use of systemic steroids in the pharmacological treatment algorithm for patients hospitalized with COVID-19 pneumonia. This is correctly discussed later in the discussion. I would recommend changing the wording of the sentence mentioning that were no "new therapies" but some already implemented therapies were managed differently. Moreover, the use of ventilatory support, the higher proportion of patients managed without mechanical ventilation, probably contributed in improving patients' management and resource allocation.

Response: Thank you for the constructive suggestion. We have now revised the sentence in the comments as suggested, mentioning that the different ways of managing existing therapies, the use of ventilatory support, the higher proportion of patients managed without mechanical ventilation, probably contributed in improving patients' management and resource allocation.