PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hospital Bed Occupancy Rate is An Independent Risk Factor for COVID-19 Inpatient Mortality: A Pandemic Epicenter Cohort Study
AUTHORS	Castagna, Francesco; Xue, Xiaonan; Saeed, O; Kataria, Rachna; Puius, Yoram; Patel, Snehal; Garcia, Mario; Racine, Andrew D.; Sims, Daniel; Jorde, Ulrich

VERSION 1 – REVIEW

REVIEWER	VASCO RICOCA FREIRE DUARTE Peixoto Universidade Nova de Lisboa, Nova National School of Public Health
REVIEW RETURNED	27-Oct-2021

GENERAL COMMENTS	The abstract is very sound and the study seems to have a lot of potential and usefulness and I would like to see it published. However when Ilooked at the results I couldn´t find what I expected. I expected some type of multivariable model(logistic regression or other, for the outcome death), using individual level data, while inlcuding "% of hospital occupancy" as exposure as a categorical variable and period of time as a categorical variable; and pharmacological therapy used as other exposures. The presented results in tables or graphs do not support conclusions of the authors. I also expected to see the matching for the other characteristics comparing Lower occupancy levels with higher occupancy levels. Since this is one of the main findings of the study(that occupancy may have an independed impact in the probability of death(although this should be seen by age group; interaction) , i dont think it is adequatly supported by the presented results. Further statistical revision may be needed. I Conclusion : Inpatient mortality from COVID-19 decreased to a degree disproportionate to advances in disease specific therapeutics and was associated with bed occupation. Early reduction in epicenter hospital bed occupation to accommodate acutely ill and resource-intensive patients should be a critical component in the strategic planning for future pandemics." This should inform the strategy. But other aspects of early reduction

	in epicentre bed occupancy should consider other factors.

REVIEWER	Andrew Udy Monash University Faculty of Medicine Nursing and Health Sciences, ANZIC-RC
REVIEW RETURNED	06-Dec-2021

GENERAL COMMENTS	Thank-you for the opportunity to review this paper. The authors present a retrospective cohort study concerning COVID-19 admissions to a single-centre between March 1st 2020 to February 28th 2021. Patients were grouped into 3-month quartiles, with in-hospital mortality decreasing over the course of the year. Adjusted analysis demonstrated that mortality increased by 0.7% per 1% increase in bed occupancy. The paper has an important message, and the results are analysed in a robust fashion. I have the following comments for the authors: 1. Please confirm that no additional beds were opened due to the unprecedented demand for healthcare. E.g. the denominator for bed occupancy remained 1491 through-out the pandemic? 2. I would avoid the use of 'seasons' (e.g. Spring 2020), as for those not residing in the Northern hemisphere, this has different implications. 3. I think the term "bed occupancy" is preferable to "bed occupation". 4. The results of the multi-variable logistic regression, suggests reduced mortality during the second surge, even though bed occupancy was included as a covariate? This would imply additional factors were involved, beyond a lesser degree of strain on the healthcare system. Could you comment? 5. Page 3, Line 9 - "hospital police changes"? 6. Page 5, Line 7 - please close the parentheses 7. Please confirm how many patients in each quartile had 30-day mortality data available? E.g. What proportion were still in hospital receiving treatment at this point, and does this vary between the quartiles? 8. Please clarify what is referred to by "Hospital Bed Saturation"? 9. What is meant by "pandemic specific therapeutic hospital logistic changes"? (Page 6, Line 52)? 10. Page 10, Line 45 - "in-house mortality"? 11. Page 12, Line 36 - "To a similar extend"? 12. Please comment on the impact of COVID-19 vaccination on these data? What proportion of the local population were vaccinated by Feb 28 2021? Would this also account for some of the improvements observed?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Dr. VASCO RICOCA FREIRE DUARTE Peixoto, Universidade Nova de Lisboa
Comments to the Author:

Comment #1: The abstract is very sound and the study seems to have a lot of potential and usefulness and I would like to see it published.
Response: We thank Dr. Vasco Ricoca Freire Duarte for his positive comments.

Comment #2: However when I looked at the results I couldn´t find what I expected.
I expected some type of multivariable model(logistic regression or other, for the outcome death), using individual level data, while including "% of hospital occupancy" as exposure as a categorical variable and period of time as a categorical variable; and pharmacological therapy used as other exposures.
Response: The primary statistical method used in this paper is the multivariate Cox proportional hazards model where time to in-hospital death is treated a time to event outcome (instead of a binary outcome) and discharged from the hospital was treated as a competing event. The same model was used in our previous paper for the first wave COVID-19 data (Saeed, Statin Use and In-Hospital Mortality in Patients with Diabetes Mellitus and COVID-19. JAHA 2020). The primary exposure variable is percentage of bed occupancy, as continuous variable. As was initially reported in the Supplemental Material (section “Covariate Selection Method for Multivariable Competing Risk Proportional Hazard Models for Time to In-hospital Death”) and now moved to the main text “The covariates in the multivariable analyses included factors present in > 90% of our dataset, known to be associated with in-hospital COVID-19 mortality based on prior literature1-3, or with a univariate association with in-hospital mortality ($p<0.05$) and a clinical (relative difference >5%) difference between survivors and non survivors (Supplemental Table 2). These variables included: age, sex, body mass index (BMI), vital signs at presentation (temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, pulse oxygen saturation), platelet count, white cell count, potassium, bicarbonate, creatinine, glucose, alanine transaminase, aspartate transaminase, history of hypertension, dyslipidemia, chronic kidney disease (CKD), heart failure, coronary artery disease, asthma/chronic obstructive pulmonary disease, diabetes mellitus and statin use. Additionally, lactic acid level and percent of hospital bed saturation were forced into the model as marker of illness severity and level of hospital stress, respectively.” (Lines 99-110) As suggested, we also repeated the analysis including bed occupancy as a categorical variable using quartiles, the results were similar. We added the sentence: “Consistent results were observed per level increase in bed occupancy quartile, (HR 1.086 [1.026 -1.148], P-value for linear trend = 0.004).” (Lines 190-191)

Comment #3: The presented results in tables or graphs do not support conclusions of the authors.
Response: Results of the competing risk regression analysis are now presented in the new Table 2 to support our conclusions.

Comment #4: I also expected to see the matching for the other characteristics comparing Lower occupancy levels with higher occupancy levels.
Response: We apologize for the confusion. The matching was not for the purpose of comparing bed occupancy levels. In our next analysis, we focused the comparison between spring and winter. Again, as reported in the Supplemental Material (section “Covariate Selection Method for Multivariable Competing Risk Proportional Hazard Models for in-hospital Death between Patients Spring and Winter Patients”) a multivariate Cox proportional hazards model was used to assess the effect of season (as binary variable spring vs winter) while controlling for age, sex, BMI, vital signs at presentation, white cell count, creatinine, glucose, alanine transaminase, history of hypertension, dyslipidemia, chronic kidney disease (CKD), heart failure, coronary artery disease, asthma/chronic obstructive pulmonary disease, diabetes mellitus and statin use. Also in this model, lactic acid level and percent of hospital bed saturation were forced into the model as marker of illness severity and level of hospital stress, respectively. Furthermore, we used a propensity score analysis to compare in-hospital mortality between spring and winter. The purpose of matching is to remove potential confounding due to difference in patient population, treatment, and hospital stress when comparing mortality rate between winter and spring seasons. The primary outcome variable is in-hospital mortality while bed-occupancy level is a potential confounder here. The result from the propensity score analysis was similar to what was obtained from the multivariate Cox model.

Comment #5: Since this is one of the main findings of the study(that occupancy may have an independed impact in the probability of death(although this should be seen by age group; interaction) , i dont think it is adequatly supported by the presented results. Further statistical revision may be needed.
Response: The primary study question of this paper is to examine if there is difference in in-hospital mortality over time using a multivariate statistical model while controlling for potential difference in patient population, treatment strategies, and hospital conditions. A significant difference in in-hospital mortality was shown particularly between spring and winter after controlling for these potential cofounders. In addition, we showed that the percentage of bed occupation as a measure of hospital stress is an independent risk factor for mortality.
The occupancy level is not the main focus and it is a secondary finding of the paper. Despite the independent effect of bed occupancy on mortality, we still found a significant difference in mortality between seasons. We have revised the paper throughout to clarify the emphasis of the paper, presenting the results of the multivariable regression in the new Table 2.

Comment #6: Conclusion
: Inpatient mortality from COVID-19 decreased to a degree disproportionate to advances in disease specific therapeutics and was associated with bed occupation. Early reduction in epicenter hospital bed occupation to accommodate acutely ill and resource-intensive patients should be a critical component in the strategic planning for future pandemics."

This should inform the strategy. But other aspects of early reduction in epicentre bed occupancy should consider other factors.

Response: We agree with the reviewer that this point should be better clarified. We added to following paragraph to the discussion: “In light of these results, strategies to minimize the bed occupancy for non-Covid-19 patients or non-life-saving admission should be adopted to diverge resources to improve the outcome of admitted Covid-19 patients.” (Lines 280-282)

Reviewer #2

Dr. Andrew Udy, Monash University Faculty of Medicine Nursing and Health Sciences
Comments to the Author:
: Thank-you for the opportunity to review this paper. The authors present a retrospective cohort study concerning COVID-19 admissions to a single-centre between March 1st 2020 to February 28th 2021. Patients were grouped into 3-month quartiles, with in-hospital mortality decreasing over the course of the year. Adjusted analysis demonstrated that mortality increased by 0.7% per 1% increase in bed occupancy. The paper has an important message, and the results are analysed in a robus't fashion. I have the following comments for the authors:

Response: We thank Dr. Udy for his positive comments.

Comment #1. Please confirm that no additional beds were opened due to the unprecedented demand for healthcare. E.g. the denominator for bed occupancy remained 1491 through-out the pandemic?
Response: as stated in the introduction (Lines 64-65) “[…] Montefiore Einstein, with its three principal teaching hospitals and combined adult bed capacity of 1,491 […]” and on lines 140-142 “[…] On April 8, 2020, peak of the spring season, the total numbers of simultaneously adult patients admitted to our hospital (including those admitted to emergency adult wards at our children’s hospital21) was 1,762 (118% of nominal bed capacity) […]”, showing that our institution opened additional beds to meet the unprecedented demand.

Comment #2. I would avoid the use of 'seasons' (e.g. Spring 2020), as for those not residing in the Northern hemisphere, this has different implications.
Response: We have clarified that we are referring to North American seasons adding the sentence “based on northern hemisphere calendar” (Line 83). We believe that keeping the word “season” would improve the readability. We are however willing to replace the word “season” with quarter or “trimester” and defer to editorial guidance in this matter.

Comment #3. I think the term "bed occupancy" is preferable to "bed occupation".
Response: “bed occupation” have been changed to “bed occupancy” throughout all the manuscript

Comment #4. The results of the multi-variable logistic regression, suggests reduced mortality during the second surge, even though bed occupancy was included as a covariate? This would imply additional factors were involved, beyond a lesser degree of strain on the healthcare system. Could you comment?
Response: We thank the reviewer for providing this important comment. The following paragraph has been added: “The cumulative effect of these therapeutic changes, in combination with a better preparedness to respond to a pandemic, can be estimate from the different mortality between the first surge (spring) and the second surge (winter). After matching the two groups for demographic and clinical variables, as well as for elements indicative of hospital distress (bed occupancy), a significant reduction of mortality was observed during the winter trimester.” (Lines 267-270)
Comment #5. Page 3, Line 9 - "hospital police changes"?
Response: it has been changed to “hospital policy changes”

Comment #6. Page 5, Line 7 - please close the parentheses
Response: parentheses closed

Comment #7. Please confirm how many patients in each quartile had 30-day mortality data available? E.g. What proportion were still in hospital receiving treatment at this point, and does this vary between the quartiles?

Response: all patients in each trimester had 30-day mortality data. For the first trimester 194/4495 (4.3%) were still admitted at end of the 30-day follow up; for the second trimester 6/264 (2.3%); for the third trimester 15/377 (4.0%); and for the fourth trimester 103/2254 (4.6%). To better clarify this point, the distribution of different outcomes at the end of follow-up has been added to Table 1. We decided to utilize a multivariable competing risk proportional hazard model to account for the different types of failure (still admitted, dead, or discharged)

Comment #8. Please clarify what is referred to by "Hospital Bed Saturation"?
Response: The sentence “We defined bed saturation the percentage of bed occupation calculated from the ratio between the number of admitted patients over the nominal bed capacity of our institution (1,491)” has been added to clarify this point (Lines 185-186)

.Comment #9. What is meant by "pandemic specific therapeutic hospital logistic changes"? (Page 6, Line 52)?
Response: In order to clarify the concept, we changed the sentence to “public health polices, specific therapeutic approaches, and hospital management changes had been implemented.” (Lines 114-115)
Comment #10. Page 10, Line 45 - "in-house mortality"?
Response: The term has been changed to “in-hospital mortality”

Comment #11. Page 12, Line 36 - "To a similar extend"?

Response: It has been changed to “similarly”

Comment #12. Please comment on the impact of COVID-19 vaccination on these data? What proportion of the local population were vaccinated by Feb 28 2021? Would this also account for some of the improvements observed?

Response: Unfortunately, “single-patient data on vaccination status are not available. 13.8% of the population of New York State received at least one dose and 7.4% received two doses. Given the heterogeneous distribution of vaccination within the state (and the city of New York), it is impossible to meaningfully account for these parameters.” This point has been added in the limitation section (Lines 312-316)

VERSION 2 – REVIEW

REVIEWER	VASCO RICOCA FREIRE DUARTE Peixoto Universidade Nova de Lisboa, Nova National School of Public Health
REVIEW RETURNED	03-Jan-2022

GENERAL COMMENTS	Abstract -Conclusions Make it clearer "Higher hospital occupancy was associated with higher mortality after adjustment." However the use of new therapeutics has contributed to lower mortality after the first wave." Discussion : "Second, we describe - for the first time - hospital bed occupationoccupancy as an independent risk factor for inpatient mortality from COVID-19." Second ? or is this the main findings? How did public health measures may have contributed to reduction in hospital case fatality rate beyond new therapuetic approaches? Non pharmacological measure for COVID prevention may reduced inicial viral load into the respiratory tree, allowing more time for the immune system to react before wide spread infection of the respiratory mucosa and lungs? "Although randomized controlled trials have shown morbidity benefits with the use of remdesevir7 and mortality reduction with steroids8, the magnitude of these effects cannot explain the more than 50% reduction in mortality we observed." - What else could explain it? "Change in Hospital Stress Load " -It should be clear that after multivarible analysis considering all other relevant factors associated with mortality and after PSM you found an associtation between occupancy and mortality. This is in my opinionthe most relevant findings of the study. However, did you adjust for Pandemic periods : 1st ; 2nd wave? This can be a proxy for other things that changed... . It must be present in the discussion that more widespread use of masks and social distancing adoption may have contribute to reduction in severity due to lower initial viral inoculates. "it is conceivable that an uptrend in mortality observed late in the pandemic with established treatment paradigms could be due to new viral strains or a sicker patient population" - Winter effect in the frail?

	"Lastly, single-patient data on vaccination status were not available. At the conclusion of the study, only 13.8% of the population of New York State received at least one dose and 7.4% received two doses39. Given the heterogeneous distribution of vaccination within the state (and the city of New York), it is impossible to meaningfully account for these parameters." - It is better to have a more clear representation (ex in the begining of the last analysed month, vaccine coverage of those above 75 yo was xx%) and in those aged 60-75 "Inpatient mortality from COVID-19 decreased to a degree disproportionate to advances in disease specific therapeutics and was associated with bed occupationoccupancy. " -Rephrase? Increaase Bed occupancy was associated with higher mortality after adjustement. Advances in therapeutics were associated with decresased mortality but did not account for all of the reduction. Non pharmacological and other seasonal variations may have an impact on mortality.

REVIEWER	Andrew Udy Monash University Faculty of Medicine Nursing and Health Sciences, ANZIC-RC
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	Thank-you for the detailed changes to the manuscript. I have no further questions or comments. Congratulations on this work.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2

Comment #1: Thank-you for the detailed changes to the manuscript. I have no further questions or comments. Congratulations on this work.

Response: We thank Dr. Udy for his positive comments.

Reviewer #1

Abstract -Conclusions
Make it clearer "Higher hospital occupancy was associated with higher mortality after adjustment." However the use of new therapeutics has contributed to lower mortality after the first wave."

Response: Results and Conclusion of the abstract have been changed to "*Results: Inpatient mortality decreased from 25.0% in spring to 10.8% over the course of the year. During this time, the use of Remdesivir, steroids, and anticoagulants increased; the use of hydroxychloroquine and other antibiotics decreased. Daily bed occupancy ranged from 62% to 118% occupancy. In a multivariate model with all year's data controlling for demographics, comorbidities, and acuity of illness, percentage of bed occupancy was associated with increased 30-day in-hospital mortality of COVID-19 patients (HR 1.007, CI: 1.001, 1.013, p=0.004)*

Conclusion: Inpatient mortality from COVID-19 was associated with bed occupancy. Early reduction in epicenter hospital bed occupancy to accommodate acutely ill and resource-intensive patients should be a critical component in the strategic planning for future pandemics"

Comment #1A: "Second, we describe - for the first time - hospital bed occupationoccupancy as an independent risk factor for inpatient mortality from COVID-19." Second ? or is this the main findings?

Response: as indicated in lines (205-208) "*First, we observed a substantial reduction of in-hospital mortality coinciding with multiple pandemic related public health measures focusing on hospital resources on COVID-19 – and preceding comprehensive changes in pharmacotherapy - towards the end of the first surge"* our initial finding was a reduction of in-hospital mortality. As consequent logical process, we evaluated the possible reasons behind this reduction and discovered that "*[Second], hospital bed occupancy as an independent risk factor for inpatient mortality from COVID-19".* The current order is to improve readability.

Comment #1B: How did public health measures may have contributed to reduction in hospital case fatality rate beyond new therapuetic approaches?

Response: As stated on lines 222-226 "*Specifically relevant to hospital operations, executive order no. 202.5 (March 16, 2020)27 allowed healthcare providers not licensed or registered in New York State to temporarily work in the State, and executive order no. 202.10 (March 22, 2020)27 suspended elective operations.* ***These executive orders were associated with a dramatic drop in non-COVID-19 admissions at our institution beginning March 16, 2020***". The effect of these public health measurement allowed a better allocation of hospital resources and decreased the level of stress on the hospital system. This is the main point of our paper and elaborated in the discussion.

Comment #1C: Non pharmacological measure for COVID prevention may reduced inicial viral load into the respiratory tree, allowing more time for the immune system to react before wide spread infection of the respiratory mucosa and lungs?

Response: Although we recognize the importance of a better understanding of the interaction between immune system and SARS-CoV-2 virus, our report focuses only on the outcome of patents requiring hospitalization; speculation on the correlation between viral load and severity of illness is beyond the scope of our manuscript.

Comment #2 "Although randomized controlled trials have shown morbidity benefits with the use of remdesevir7 and mortality reduction with steroids8, the magnitude of these effects cannot explain the more than 50% reduction in mortality we observed."
- What else could explain it?

Response: We postulate that part of this reduction may be attributed to reduced stress on the hospital system and better allocation of resource, thanks to the reduced census

Comment #3 "Change in Hospital Stress Load "
-It should be clear that after multivarible analysis considering all other relevant factors associated with mortality and after PSM you found an associtation between occupancy and mortality. This is in my opinionthe most relevant findings of the study.
However, did you adjust for Pandemic periods : 1st ; 2nd wave? This can be a proxy for other things

that changed... . It must be present in the discussion that more widespread use of masks and social distancing adoption may have contribute to reduction in severity due to lower initial viral inoculates

Response Although we recognize the importance of effects of public health measures (such as use of social distancing and mask use), our report focuses only on the outcome of patients admitted to the hospital, not on the diffusion of the disease; speculation on the correlation between viral load and severity of illness is beyond the scope of our manuscript.

Comment #4
"it is conceivable that an uptrend in mortality observed late in the pandemic with established treatment paradigms could be due to new viral strains or a sicker patient population"
- Winter effect in the frail?

Response: We focused on examining the difference in in-hospital death between patients admitted in the spring and in the winter, after adjustment of patients' demographics, comorbidities, and acuity of illness, bed occupancy. A significant lower mortality rate during the second surge compared to the initial surge (HR 0.520, CI 0.448-0.604, p<0.001) was observed, which was likely contributed by public health polices, specific therapeutic approaches and hospital management changes in the second surge. This result was further confirmed by the propensity score analysis when patients from two seasons were matched on demographics, comorbidity and acute of illness.

Comment #5 "Lastly, single-patient data on vaccination status were not available. At the conclusion of the study, only 13.8% of the population of New York State received at least one dose and 7.4% received two doses39. Given the heterogeneous distribution of vaccination within the state (and the city of New York), it is impossible to meaningfully account for these parameters."
- It is better to have a more clear representation (ex in the begining of the last analysed month, vaccine coverage of those above 75 yo was xx%) and in those aged 60-75

Response: Unfortunately, single-patient vaccination status was not available and we cannot provide further granularity.

Comment #6: "Inpatient mortality from COVID-19 decreased to a degree disproportionate to advances in disease specific therapeutics and was associated with bed occupationoccupancy. "
-Rephrase? Increaase Bed occupancy was associated with higher mortality after adjustement. Advances in therapeutics were associated with decresased mortality but did not account for all of the reduction. Non pharmacological and other seasonal variations may have an impact on mortality.

Response: Conclusion has been rephrases as following: "*Inpatient mortality from COVID-19 decreased to a degree disproportionate to advances in disease specific therapeutics. Increased bed occupancy was associated to a higher in-hospital mortality. Implementation of non-pharmacological approaches and other seasonal variations might also had a role in the mortality reduction. Early reduction in epicenter hospital bed occupancy to accommodate acutely ill and resource-intensive patients should be a critical component in the strategic planning for future pandemics.*"