PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of acute deterioration and care complexity individual factors associated with health outcomes in hospitalised patients with COVID-19: a multicenter cohort study.
AUTHORS	Adamuz, Jordi; González-Samartino, Maribel; Jiménez-Martínez, Emilio; Tapia-Pérez, Marta; López-Jiménez, María-Magdalena; Rodríguez-Fernández, Hugo; Castro-Navarro, Trinidad; Zuriguel-Pérez, Esperanza; Carratala, Jordi; Juvé-Udina, Maria-Eulàlia

VERSION 1 – REVIEW

REVIEWER	Dr Ewan Carr King's College London, UK
REVIEW RETURNED	17-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review this study. Drawing on retrospective data from seven hospital in Catalonia, Spain, the authors assessed associations between VIDA score (an early warning system) and adverse outcomes (mortality and AEs) among 1,176 hospitalised patients with COVID-19. They found that patients with high VIDA scores were more likely to experience adverse outcomes. While the study has merits, such as the large multi-site sample, I have a number of concerns as listed below. 1. **Lack of focus** The aims of the paper are unclear and the text is at times hard to follow. The stated aim (p. 4, line 11) was to determine associations of "acute deterioration risk" and "care complexity individual factors" with unfavourable outcomes. - I don't understand the utility of evaluating associations of VIDA with severe outcomes. If this early warning score is any use at all (which I'm sure it is) then surely it will be associated with poorer outcomes? What have we learnt by demonstrating this association? How would this influence clinical decision-making? - Instead, I would be much more interested in the utility of VIDA to predict severe outcomes in new patients. It seems discrimination was assessed (p. 11, line 3) but it is unclear what this AUC refers to -- all variables simultaneously? VIDA? Moreover, the authors report apparent discrimination and make no attempt to estimate optimism (e.g. through bootstrapping or cross-validation) or to validate the model in external samples. (Model

	calibration was not assessed, as mentioned below). - Overall, I am confused about the aims. Is the paper showing associations between risk factors and outcomes, or is the paper developing a prognostic model? The former is less interesting, because it is almost inconceivable that the chosen risk factors would not be associated with poorer outcomes. The latter was not done. - In addition, the manuscript considers many other risk factors, besides those stated in the aims (VIDA and CCIF), without clear justification or introduction. These include: chronic disease, mental impairment, length of hospital stay, high tech hospital admission, position impairment, communication disorders. 2. **Sample** I do not understand how the sample was constructed and analysed. - 1838 patients were hospitalised with COVID, but only 1176 had the required data. Or, put another way, 36% of patients were excluded due to missing data. This is a problem that needs to be addressed. - It seems that analyses involving VIDA were only conducted on 806 patients (presumably, those with a non-missing VIDA score). So for the primary analysis -- to assess associations of VIDA with adverse outcomes -- only 44% of participants were included. - The samples used for different analyses are unclear. Table 3 seems restrict the sample to 486 patients only; Table 4 uses a different sample size for each column, but doesn't provide these for the reader. - It's unclear whether included patients were admitted for COVID-19 or for another reason. Were nosocomial patients included? For example, if a patient was admitted to hospital on 1st March without COVID infection, but developed COVID a week later, they would be eligible for inclusion? - I don't understand why patients who remained hospitalised after the recruitment period were excluded. Severe COVID infection can last many weeks, and certainly, more than one month. These patients should have been included. - How many patients were admitted directly to ICU? Why weren't they included? Given that direct-to-ICU patients are likely to have more severe symptoms and have adverse outcomes, this information would be needed to interpret the results. 3. **Outcomes** - I'm no expert, but a composite outcome combining death and AEs seems like a bad idea. What was the justification here? - It would be clearer to present these separately (indeed, in many of the analyses these are presented separately). The line "the frequency of unfavourable outcomes reached near 80%" is therefore very hard to interpret. - The primary outcome ("unfavourable outcomes") is described as "in-hospital mortality AND AEs" but is defined as mortality OR adverse events. For example 43% patients

	experienced unfavourable outcomes and 19% died. - What was the endpoint for these outcomes? If a patient was admitted on March 31st, how long were they followed up for? Did you ensure that all patients had reached their endpoint (e.g. 14 days post-admission)? 4. **Measures** - When were the included features measured? The text states that measures were extracted "whenever they were e-charted". What does that mean, and how was this reduced to a single time point or measure for analysis? - More detail regarding the definitions of these measures is needed. It would not be possible to replicate this study based on the provided information. 5. **Analysis** - Statistical significance in univariate analyses should not be used for feature selection (e.g. Steyerberg, 2019; p. 209). - In addition to assessing discrimination, model calibration must be considered (e.g. Steyerberg and Vergouwe, 2014). Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931. doi:10.1093/eurheartj/ehu207

REVIEWER	Carla Felice Department of Medicine, University of Padua Medicine 1^, Ospedale Ca' Foncello, Treviso, Italy
REVIEW RETURNED	24-Jul-2020

GENERAL COMMENTS	The manuscript entitled "Risk of acute deterioration and care complexity individual factors associated with health outcomes in hospitalised patients with COVID-19" describes the utility of nurse scoring systems in identifying COVID-19 inpatients at high risk for negative clinical outcomes (death and/or adverse events). Nurses have a central role in monitoring and in routine care of inpatients, in both non-intensive and intensive units. The management of COVID-19 emergency often required re-organization (even structural) of the hospitals, redirecting the resources to intensive-care or COVID-19 specific units. Such changes also affected the role of nurses in the management of this new critical ill. However, data on nurse protocols in COVID-19 pandemic are very scarce so far. In this context, the contribution given by this study could be precious. This is a retrospective multicentre analysis inclluding more than 1,000 COVID-19 hospitalised patients. The VIDA score was used to measure the risk of acute deterioration. Also care complexity individual factors were analysed from medical records. Interestingly, the VIDA score was found to be predictive of worse clinical outcomes. However, there are some important limitations which make this paper not suitable for publication as it is.

	1. First of all, the VIDA score in not a validated scoring system (no references are available) and it is locally used in Catalonia. At least, the items used in the VIDA score should been listed somewhere (even as supplementary material). Or is it just a subjective risk classification, as described in the methods? Also, time required to calculate the VIDA score (if several items are considered) should be described: is it time-consuming? 2. The analysis of care complexity individual factors (CCIF) is not properly described in this paper. Probably, there is enough material to be included in a separate paper. Otherwise supplementary material should be given to better specify all data and items considered. 3. It is not clear why a further classification of patients severity and risk of mortality is given (based in APR-DRG, as reported in "Data collection"). 4. Outcome measures: this section should be better structured. Please, specify all the outcomes considered (the combined "unfavourable", death and adverse events). 5. table 3: what "unadjusted" and "adjusted" mean? Which statistical test was performed? 6. What does "High-tech hospital" mean? Please, give a clear definition. 7. The title of the paper should be modified underlying the nurse setting of the study. Minor comments: - please, perform English editing of the "strenghts and limitations of this study" section. Some mistakes should be corrected also in the full text. - please remove the number "28" from the abstract (referred to CCIF), because in the manuscript it is not mentioned further.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr Ewan Carr
Institution and Country: King's College London, UK
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below. Thank you for the opportunity to review this study. Drawing on retrospective data from seven hospital in Catalonia, Spain, the authors assessed associations between VIDA score (an early warning system) and adverse outcomes (mortality and AEs) among 1,176 hospitalised patients with COVID-19. They found that patients with high VIDA scores were more likely to experience adverse outcomes.

While the study has merits, such as the large multi-site sample, I have a number of concerns as listed below.

1. **Lack of focus**

The aims of the paper are unclear and the text is at times hard to follow. The stated aim (p. 4, line 11) was to determine associations of "acute deterioration risk" and "care complexity individual factors" with unfavourable outcomes.

- I don't understand the utility of evaluating associations of VIDA with severe outcomes. If this early warning score is any use at all (which I'm sure it is) then surely it will be associated with poorer outcomes? What have we learnt by demonstrating this association?

VIDA early warning system started in 2013 at eight Catalan public hospitals. This system was developed and used to early identify and act upon initial acute deterioration among hospitalized patients. According to recommendations of previous studies this system was adapted to each hospital context. Moreover, nowadays no studies have assessed care complexity individual factors (broader health conditions) associated with poor health outcomes in COVID-19 inpatients. Therefore, the aim of this study was determining the association between acute deterioration risk and care complexity individual factors with unfavourable outcomes in hospitalised patients with COVID-19, because we would demonstrate the health care factors associated with poor outcomes, not only VIDA score.
The results of this study had proved the significant association between unfavourable outcomes with high risk of acute deterioration and CCIF, although a validate the model is still needed. We have added this sentence in study limitations section.
The findings contribute to identify that systematic nursing surveillance of patients at risk of acute deterioration and the assessment of CCIF may contribute to reduce deleterious health outcomes in COVID-19 inpatients.

How would this influence clinical decision-making?

VIDA early warning system helps us to identify the risk of clinical deterioration and to improve clinical decision making. Three out of five VIDA score level's (moderate risk, high risk and manifested complication initial status) make an alert in the electronic health records with clinical recommendations. These recommendations were standardized for each context in line to intensify the measurement of vital signs and notify to medical team. The health team (nurse and specialist) had the final clinical decision-making. We have added this sentence in methods section.

- Instead, I would be much more interested in the utility of VIDA to predict severe outcomes in new patients. It seems discrimination was assessed (p. 11, line 3) but it is unclear what this AUC refers to -- all variables simultaneously? VIDA? Moreover, the authors report apparent discrimination and make no attempt to estimate optimism (e.g. through bootstrapping or cross-validation) or to validate the model in external samples. (Model calibration was not assessed, as mentioned below).

We have added a footnote in table 4 "Multivariate analysis included: high risk of acute deterioration (VIDA score 3-4), clinically relevant care complexity individual factors (old age, chronic disease, position impairment, communication disorders and mental status impairments) and potential confounders (sex, hospital level and LOS)."
Although the bootstrapping was not performed, table 3 shows an adjusted analysis of unfavourable outcomes in 486 patients with high risk of mortality (APR-DRG 3-4) was carried out (according to VIDA early warning system). We have added a limitation in the manuscript concerning that futures studies should validate the model in external samples.

- Overall, I am confused about the aims. Is the paper showing associations between risk factors and outcomes, or is the paper developing a prognostic model? The former is less interesting, because it is

almost inconceivable that the chosen risk factors would not be associated with poorer outcomes. The latter was not done.

The aim of this study was determining the association between acute deterioration risk and care complexity individual factors with unfavourable outcomes in hospitalised patients with COVID-19. Please, see the response to the first question.

- In addition, the manuscript considers many other risk factors, besides those stated in the aims (VIDA and CCIF), without clear justification or introduction. These include: chronic disease, mental impairment, length of hospital stay, high tech hospital admission, position impairment, communication disorders.

The multivariate analyses included the following variables: high risk of acute deterioration (VIDA score 3-4), clinically relevant care complexity individual factors (old age, chronic disease, position impairment, communication disorders and mental status impairments), and other potential confounders (sex, hospital level and LOS). We have added a footnote in table 4.

2. **Sample**

I do not understand how the sample was constructed and analysed.

- 1838 patients were hospitalised with COVID, but only 1176 had the required data. Or, put another way, 36% of patients were excluded due to missing data. This is a problem that needs to be addressed.

We included 1,176 patients due to exclusion criteria: patients' directly admitted and discharged from intensive care units (ICU), as well as those who remained hospitalized after the recruitment end date, were excluded. Following the reviewer suggestion, we have modified the first sentence in the results section.

- It seems that analyses involving VIDA were only conducted on 806 patients (presumably, those with a non-missing VIDA score). So for the primary analysis -- to assess associations of VIDA with adverse outcomes -- only 44% of participants were included.

During the study period, among 1,176 patients included, 806 patients were hospitalised with VIDA early warning system because in some wards this system was not implemented. We have added this information in the results section.

- The samples used for different analyses are unclear. Table 3 seems restrict the sample to 486 patients only; Table 4 uses a different sample size for each column, but doesn't provide these for the reader.

In table 3 the VIDA sample was n = 486 because an adjusted analysis has been carried out with high risk of mortality (APR-DRG 3-4). We have added this information in table title.
In table 4 the sample for the three outcomes was 806 hospitalised patients with VIDA early warning system. We have modified it in table 4.

- It's unclear whether included patients were admitted for COVID-19 or for another reason. Were nosocomial patients included? For example, if a patient was admitted to hospital on 1st March without COVID infection, but developed COVID a week later, they would be eligible for inclusion?

All patients admitted to the hospital from March 1, 2020 to March 31, with a medical diagnosis of COVID infection were included whether they were admitted for COVID or other causes. We have added it in the manuscript.

- I don't understand why patients who remained hospitalised after the recruitment period were excluded. Severe COVID infection can last many weeks, and certainly, more than one month. These patients should have been included.

During the study period, 1,838 patients were hospitalised with COVID-19. 662 patients were excluded because they were directly admitted and discharged from intensive care units (ICU), as well as those who remained hospitalized after the recruitment end date. The inclusion criteria included only patients with a completed hospital minimum data set report because research variables were extracted from those reports. This information was included in study design section.

- How many patients were admitted directly to ICU? Why weren't they included? Given that direct-to-ICU patients are likely to have more severe symptoms and have adverse outcomes, this information would be needed to interpret the results.

Patients' directly admitted and discharged from intensive care units (ICU), were excluded. In these wards there is no electronic health records and we do not have information on VIDA or CCIF variables. Too as well as those who remained hospitalized after the recruitment end date, were excluded because we didn't have a completed hospital minimal data set report. These reports are generated when the hospital episode finishes.

3. **Outcomes**

- I'm no expert, but a composite outcome combining death and AEs seems like a bad idea. What was the justification here?

Previous study which validate other deterioration index model among hospitalized COVID-19 patients had used the composite outcome that included: AEs and in-hospital mortality (Singh K, et al. medRxiv, 2020). Moreover, our multivariate analysis was performed to determine associated factors with unfavourable outcomes, deceased and AE independently.

- It would be clearer to present these separately (indeed, in many of the analyses these are presented separately). The line "the frequency of unfavourable outcomes reached near 80%" is therefore very hard to interpret.

According to the suggestion of the reviewer, these results have been presented separately in the discussion section.

- The primary outcome ("unfavourable outcomes") is described as "in-hospital mortality AND AEs" but is defined as mortality OR adverse events. For example 43% patients experienced unfavourable outcomes and 19% died.

We thank the reviewer for this comment. We have modified this sentence in the methods section.

- What was the endpoint for these outcomes? If a patient was admitted on March 31st, how long were they followed up for? Did you ensure that all patients had reached their endpoint (e.g. 14 days post-admission)?

As a described in the methods section, patients with a completed hospital minimum data set report

were recruited retrospectively and followed up during all the hospitalization until discharge or deceased. Therefore, we only included patients with a completed hospital minimum data set report that will be discharged or deceased during the study period. We have included a sentence to clarify this issue in study design.

4. **Measures**

- When were the included features measured? The text states that measures were extracted "whenever they were e-charted". What does that mean, and how was this reduced to a single time point or measure for analysis?

Patient progress data were extracted from anonymized clinical records as many times as they were registered. For the purpose of this study patients were classified in each group according the highest degree of VIDA score obtained during their hospitalization. We have modified this issue in data collection section.

- More detail regarding the definitions of these measures is needed. It would not be possible to replicate this study based on the provided information.

Following the reviewer suggestion, we have added two supplementary files (VIDA score algorithm and detail of care complexity individual factors.)

5. **Analysis**

- Statistical significance in univariate analyses should not be used for feature selection (e.g. Steyerberg, 2019; p. 209).

According to reviewer suggestion we deleted the sentence “only covariates with p values less than 0.05 in the univariate analysis were entered in the multivariate model”. For the purpose of this study we included in the logistic-regression model: VIDA score, clinically relevant CCIF and other potential confounders.

- In addition to assessing discrimination, model calibration must be considered (e.g. Steyerberg and Vergouwe, 2014).
Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.doi:10.1093/eurheartj/ehu207

Although the aim of this study was determine the association between acute deterioration risk (as measured with VIDA early warning system) and care complexity individual factors with unfavourable outcomes, we performed the first step in evaluating discrimination of the model with the ROC curve, but an external validation of the model is needed. We also performed an adjusted analysis to compare unfavourable outcomes in patients admitted in wards with VIDA system and without this system. In this regard we have added a limitation in the manuscript concerning that futures studies should validate the model in external samples.

Reviewer: 2
Reviewer Name: Carla Felice
Institution and Country: Department of Medicine, University of Padua
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The manuscript entitled "Risk of acute deterioration and care complexity individual factors associated

with health outcomes in hospitalised patients with COVID-19" describes the utility of nurse scoring systems in identifying COVID-19 inpatients at high risk for negative clinical outcomes (death and/or adverse events).

Nurses have a central role in monitoring and in routine care of inpatients, in both non-intensive and intensive units. The management of COVID-19 emergency often required re-organization (even structural) of the hospitals, redirecting the resources to intensive-care or COVID-19 specific units. Such changes also affected the role of nurses in the management of this new critical ill. However, data on nurse protocols in COVID-19 pandemic are very scarce so far.

In this context, the contribution given by this study could be precious.
This is a retrospective multicentre analysis inclluding more than 1,000 COVID-19 hospitalised patients. The VIDA score was used to measure the risk of acute deterioration. Also care complexity individual factors were analysed from medical records.
Interestingly, the VIDA score was found to be predictive of worse clinical outcomes.

However, there are some important limitations which make this paper not suitable for publication as it is.

1. First of all, the VIDA score in not a validated scoring system (no references are available) and it is locally used in Catalonia. At least, the items used in the VIDA score should been listed somewhere (even as supplementary material). Or is it just a subjective risk classification, as described in the methods?

Following the reviewer recommendation, we have included a supplementary material with VIDA score algorithm).

Also, time required to calculate the VIDA score (if several items are considered) should be described: is it time-consuming?

The calculation of the VIDA scale is automatic when the nurse records the required variables. We have added this information in data collection section.

2. The analysis of care complexity individual factors (CCIF) is not properly described in this paper. Probably, there is enough material to be included in a separate paper. Otherwise supplementary material should be given to better specify all data and items considered.

In the statistical analysis section, we described only the clinically relevant CCIF included in the logistic-regression model. According to the reviewer comment, we have added a supplementary file with the detail of care complexity individual factors. Also, the variables included in the multivariate analysis are described in table 4.

3. It is not clear why a further classification of patients severity and risk of mortality is given (based in APR-DRG, as reported in "Data collection").

Patient severity and mortality risk (according to APR-DRG) were collected with the hospital minimum data set report. We used this classification to perform an adjusted analysis of patient’s outcomes with and without VIDA early warning system. Table 3 shows this analysis only with 486 patients with high risk of mortality (APR-DRG 3-4) and it were described in the results section. We have modified the sentence in the statistical analysis section to clarify this analysis.

4. Outcome measures: this section should be better structured. Please, specify all the outcomes

considered (the combined "unfavourable", death and adverse events).

Following the reviewer recommendation, we have modified the outcomes measures section.

5. table 3: what "unadjusted" and "adjusted" mean? Which statistical test was performed?

According to the reviewer comment, we have added this information in footnotes of table 3.

6. What does "High-tech hospital" mean? Please, give a clear definition.

We have included the definition of high-tech hospital (referral centre that provides tertiary care for either open-heart surgery or major organ transplants or both, or other centre).

7. The title of the paper should be modified underlying the nurse setting of the study.

The title has been modified according the reviewers and editor suggestions.

Minor comments:
- please, perform English editing of the "strenghts and limitations of this study" section. Some mistakes should be corrected also in the full text.

According the reviewer comments we have modified "Strengths and limitations of this study" section.

- please remove the number "28" from the abstract (referred to CCIF), because in the manuscript it is not mentioned further.

This mistake has been corrected.

VERSION 2 – REVIEW

REVIEWER	Dr Ewan Carr King's College London United Kingdom
REVIEW RETURNED	27-Nov-2020

GENERAL COMMENTS	I would like to thank the authors for their detailed response to my comments on the previous version of the manuscript, and for the helpful supplementary files. The changes in this revision have improved the manuscript. However, the manuscript is still relatively light on detail and the limitations of the analysis are not adequately addressed in the text. *** In many ways, the author's response letter is a better summary of the paper's aims and limitations, and much of this material could usefully be included in the main text. For example, some of my biggest concerns were around the definition of the sample, exclusions of various groups, and missing data. These issues remain in the revised manuscript. In response, the authors have restated information already

	presented in the manuscript. I don't think this is enough. The fact that of 1838 hospitalised with COVID only 806 were analysed (and in some cases, 486 or fewer) is a serious limitation. Yet the 'limitations' section makes no mention of this. Similarly, it would be helpful to expand on "patients directly admitted and discharged [...] were excluded". What impact is this likely to have on the results? Do you expect many patients to be excluded this way? Again, there is no mention of this in the limitations. From the lack of changes made to the analysis or sample definition, I presume that it is not possible or feasible to make these changes. That is fine, but the issues raised last time remain and should be made clear to readers in an expanded limitations section. I recommend including a flow chart showing the sample definition and exclusions. *** Some issues have been only partially addressed. I asked last time for clarification about when the included variables were measured. This information has been provided for VIDA ("the highest degree of VIDA score obtained during their hospitalization") but not for other measures. It is unclear when variables such as age, sex, hospital level, LOS, or mental status impairments were measured. *** Some minor points: "Multivariable" not "multivariate". The definition of "high-tech hospital" is all-encompassing: "referral centre that provides tertiary care for either open-heart surgery or major organ transplants or both, or other centre". So, any referral centre? In the abstract it's still unclear what the AUROC is referring to. *** Overall, the revised manuscript is improved but I was hoping it would go further in addressing or outlining the limitations of the analysis.

REVIEWER	Carla Felice Department of Medicine, University of Padua Medicine 1^, Ospedale Ca' Foncello, Treviso, Italy
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Thanks for all changes done. Now the paper is more clear, even for healthworkers who have no confidence with such scores. Please, reconsider tables 2 and 3: is the number of all patients correct? or is there an extra number? I have no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Carla Felice
Institution and Country: Department of Medicine, University of Padua, Medicine 1^, Ospedale Ca' Foncello, Treviso, Italy
Please state any competing interests or state ‘None declared’: None declared.

Comments to the Author
Thanks for all changes done. Now the paper is more clear, even for healthworkers who have no confidence with such scores.
Please, reconsider tables 2 and 3: is the number of all patients correct? or is there an extra number? I have no further comments.
This mistake has been corrected according to the suggestion of the reviewer.

Reviewer: 1
Reviewer Name: Dr Ewan Carr
Institution and Country: King's College London, United Kingdom
Please state any competing interests or state ‘None declared’: None declared.

Comments to the Author
I would like to thank the authors for their detailed response to my comments on the previous version of the manuscript, and for the helpful supplementary files.

The changes in this revision have improved the manuscript. However, the manuscript is still relatively light on detail and the limitations of the analysis are not adequately addressed in the text.

***

In many ways, the author's response letter is a better summary of the paper's aims and limitations, and much of this material could usefully be included in the main text.

For example, some of my biggest concerns were around the definition of the sample, exclusions of various groups, and missing data. These issues remain in the revised manuscript.
In response, the authors have restated information already presented in the manuscript. I don't think this is enough. The fact that of 1838 hospitalised with COVID only 806 were analysed (and in some cases, 486 or fewer) is a serious limitation. Yet the 'limitations' section makes no mention of this. Similarly, it would be helpful to expand on "patients directly admitted and discharged [...] were excluded". What impact is this likely to have on the results? Do you expect many patients to be excluded this way? Again, there is no mention of this in the limitations.
We have modified limitations section. “This study is not exempt of some limitations. First, VIDA score and CCIF data were comprehensively collected from clinical data warehouse of the Catalan Institute of Health and all patients included had a completed nurse charting in the patient electronic health record but we relied a proper compliance of electronic health records and administrative data. This is acknowledged as a significant limitation since voluntary completion of patient electronic documentation during the initial weeks of COVID-19 first wave in our country, might have been negatively influenced by the peak rising hospital system burden, the need for patient direct care activity prioritization, as well as the physical and emotional stress experienced by bedside healthcare professionals. Second, regarding the study selection criteria, patients directly admitted and discharged from intensive care unit were excluded, since no early warning system was use at the critical care setting at the outset of the pandemics in our context. In this sense, the results of this study only apply to adult ward and intermediate care inpatients. Third, it should be noted that

unpublished face validity studies have demonstrated the effectiveness VIDA early warning system. A full evaluation of its psychometric properties, in general medical-surgical inpatients, is pending and this must be acknowledged as a significant limitation. To minimize the potential effect of this limitation, this inquiry considered an adjusted analysis performed with patients in higher risk mortality (APR-DRG 3-4) comparing the ones admitted in wards with VIDA fully implemented and those being treated in units with no VIDA early warning system. The results proved a significant association of VIDA score and CCIF with unfavourable outcomes. Finally, we acknowledge as a potential limitation that other clinical measures such as the age adjusted Charlson comorbidity index or patient lab values were not assessed. Selected lab values such as lactate, ferritin or calciferol have been studied as indicators of COVID-19 prognosis and severity. Combining point of care lab data with clinical data from nurses' observations and judgments on patient complexity factors, status and progress would probably result in a improved system for early detection and prevention of critical complications and other unfavourable outcomes in COVID-19 inpatients."

Also, we have expanded the inclusion and exclusion criteria in the methods section "Patients' directly admitted and discharged from intensive care units (ICU) were excluded because VIDA early warning system was not implemented on ICU. Also, patients who remained hospitalized after the recruitment end date were excluded due the data of hospital minimum data set was not available".

From the lack of changes made to the analysis or sample definition, I presume that it is not possible or feasible to make these changes. That is fine, but the issues raised last time remain and should be made clear to readers in an expanded limitations section. I recommend including a flow chart showing the sample definition and exclusions.
According to reviewer suggestion a flow chart of patient selection process has been added.

***

Some issues have been only partially addressed. I asked last time for clarification about when the included variables were measured. This information has been provided for VIDA ("the highest degree of VIDA score obtained during their hospitalization") but not for other measures. It is unclear when variables such as age, sex, hospital level, LOS, or mental status impairments were measured.
To clarify when the variables were measured, an explanation was included in data collection section.

***

Some minor points:

"Multivariable" not "multivariate".
Thank you. The term has been modified.

The definition of "high-tech hospital" is all-encompassing: "referral centre that provides tertiary care for either open-heart surgery or major organ transplants or both, or other centre". So, any referral centre?
According to reviewer suggestion, high-tech hospital definition was modified.

In the abstract it's still unclear what the AUROC is referring to.
Following the reviewer suggestion, we have removed the AUROC from abstract.

***

Overall, the revised manuscript is improved but I was hoping it would go further in addressing or outlining the limitations of the analysis.