PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predictors of clinical deterioration in patients with suspected COVID-19 managed in a 'virtual hospital' setting: a cohort study
AUTHORS	Francis, Nick; Stuart, Beth; Knight, Matthew; Vancheeswaran, Rama; Oliver, Charles; Willcox, Merlin; Barlow, Andrew; Moore, Michael

VERSION 1 – REVIEW

REVIEWER	Maralyssa Bann Harborview Medical Center, University of Washington- USA
REVIEW RETURNED	20-Oct-2020

GENERAL COMMENTS	This manuscript provides a review of patients monitored remotely after COVID-19-like illness and aims to identify prevalence of and risk factors for death or readmission. Overall, this is a useful question that adds to the growing body of literature surrounding programs that address COVID-19 clinical needs. In particular, the use of the "virtual hospital" monitoring program is an important element that has been used in many places - and it is important to analyze outcomes related to this type of innovation. My major concern about this manuscript is the heterogeneity of results being presented. Both community-referred and post-hospitalization patients are included in analysis, which while pragmatic in nature does lead to comparison of seemingly different groups of individuals. Adding to this concern, 20% of the community-referred group did not undergo SARS-CoV testing. It is also unclear if the "low-risk" and "high-risk" patients were both included in analysis. In the Data Collection section towards the bottom of page 5, there are 2 different followup techniques described based on risk assessment. If both of these are included in analysis, this presents yet another distinction between groups that could impact the comparison and conclusions drawn. (It is unclear, however, because in Figure 1 only the "high risk" group is labeled as "virtual hospital" but I cannot find description that "low risk" was excluded so presume all entrants are reported). Finally, the combined outcome of death and readmissions leads to less conclusive results; while both are important outcomes, they do not necessarily always have the same contributors so seeking associations with this multifaceted end-point creates murkiness. Altogether, the multiple referral sources (and underlying populations), multiple care processes, and multiple/combined end-point makes it challenging to parse results in a meaningful way. I would strongly suggest the authors consider limiting the research question to a specific focus in order to more thoroughly address the aim and solidify the findings.

	Additional comments are below: Abstract: Main outcome measure indicates risk of death or (re)-hospitalization within 28 days. Please clarify this timeframe and align with timeframes for outcome elsewhere in the main text (for example p 7 line 15 says two weeks after discharge) Background: P 3 line 40-41 says "Factors associated with prognosis are likely to be different in VH patients because they are at a different stage of the disease and/or have less severe symptoms." Please provide citations to support your claim. If this is a hypothesis of the study, please restate as such. Would appreciate additional discussion and support for the reasoning behind a combined outcome of both death and re-admissions as described in opening paragraph of my review above. I can appreciate if the goal of this manuscript is to help identify appropriate candidates for this type of monitoring program, though if this were to be an approach used to offload overwhelmed inpatient units an outcome such as readmission may not necessarily be viewed as a failure. The secondary analysis provided in Table 4 of predictors for each outcome by referral source is not convincing that these are similar enough groups. Methods: Page 5 line 5 labels this a "prospective observational study". However, study data was not collected in a prospective fashion. Page 4 line 57-58 reads "Data for this study were subsequently extracted from participants' medical records. Therefore, data were not collected in a protocolised way but reflect the recording of healthcare data in a busy clinical setting." It sounds like patients were enrolled into the virtual hospital in a prospective, clinically-relevant manner, but the study itself is a retrospective analysis of information from the medical chart. Please clarify. Better define the medications data. What criteria were used to identify a relevant medication? Presence on the medication list at time of referral into the virtual hospital? Time course of prescription? Etc. Clarify the timing of "baseline" data. This would have occurred at the time of entry to virtual hospital program? For patients referred from community this is at time of presentation, but for hospitalized patients this would have been at discharge from the hospital? Provide additional detail about patient selection in the inpatient setting. Were all patients who met criteria referred for virtual hospital at discharge? Page 5 line 9-11 reads "The aim was to reduce pressure on in-patient capacity by providing remote clinical assessment to patients at home in place of hospital admission, or to facilitate early discharge from hospital." How was this operationalized in practice? Additional detail about the hospitalized population is necessary. What was their length of stay? Percentage with ICU admissions, percentage on oxygen or intubated at any time during hospitalization, percentage treated with therapies (note this has changed over time – likely, hydroxychloroquine for ex), etc? Outcome is not sufficiently described. What constituted (re)admission? Did this include observation status? Was reason

	for (re)admission captured? Were planned hospitalizations excluded? Were patients on hospice or palliative care excluded? Provide additional details about the study setting including characteristics of the hospital involved: # of patient beds, # of emergency visits/year, referral or catchment area served, etc. It is important to understand the local COVID-19 context during this time period, as well. If the healthcare system was extensively overstretched, this knowledge would help interpretation of the findings. Please include local numbers of COVID cases and a general description of processes (were crisis standards met? what % of beds were occupied? what % of beds were occupied by COVID-19 patients?) during the study time period. It is interesting that the first 900 patients enrolled in this program were almost perfectly divided in referrals from community and hospital discharge sources. How was this accomplished? Does this represent consecutive cases seen and diagnosed at your site? Did patients consent to the virtual hospital intervention or were they able to decline to be part of the intervention? Presumably patients who failed the clinical criteria would be admitted to the hospital but what about the criteria that they had to be able to use the telephone or videoconference and that they had to be able to isolate and self care? How many were disqualified from inclusion based on these criteria? Results: Clarify what is meant by "patients were followed for a median of 21 days" (p 8, line 19). The study protocol itself is 14 days. Is this time after enrollment that the study team reviewed notes? If so, this does not match time frame noted in abstract. Revise Table 1 and Table 2 to either compare patients with adverse events vs those without or compare patients who were referred from community vs those referred from hospital discharge. What statistical comparison test is being used? Include results of statistical comparison tests when identifying differences in groups. Any distinctions reported in the text should represent statistically significant differences and should be denoted in Tables 1 and 2 (can use bolding, asterisks, additional column to include p-values, etc). Why is negative SARS Co-V swab a reference value in Table 3? Why would patients be included in this study with a negative test? Discussion: P 18 lines 31-37 read “It is reasonably safe to assume that the population included in this study includes the vast majority of those that required monitoring in the community during this period as there were no other services providing remote monitoring of patients that had required a face-to-face assessment in the area at that time.” Additional data is necessary to justify this claim. Just because this is the only monitoring program in the community does not mean that all who required monitoring received this intervention. I would hesitate to draw strong conclusions from the currently presented findings especially without knowing the reason for return

	hospitalization. The findings here that patients with comorbidity are readmitted may be confounded by the fact that they are chronically ill. Without knowing the reason for (re)hospitalization, it is plausible that patients might return for planned or semi-planned encounters or for a reason entirely unrelated to COVID-19. For example, patients with poor kidney function might return for dialysis or for vascular access placement; patients with cancer may return for chemotherapy or radiation treatments or for vascular access placement; patients with mental health disorder may return for mental health crisis. Likewise, there may be entirely extraneous issues that are not accounted for. Nearly 20% of the patients discharged to skilled nursing facility had an adverse event. Could it be that nursing facilities experienced overstretch during this time period and if they had infection control issues returned patients to the hospital because of their own lack of capabilities? Etc. As noted above, I think this manuscript could be made much stronger with a more cohesive message. I find it compelling that this program seemed to safely provide an alternative to hospitalization from the emergency presentation. I also think there is a unique story to be told about how this program can serve as an additional layer of support at discharge – with enough additional detail this could help refine the program and its selection/monitoring process. But, in my opinion, combining the two points detracts from each.

REVIEWER	Min Xie Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
REVIEW RETURNED	25-Oct-2020

GENERAL COMMENTS	The authors made an analysis of 900 patients enrolled in virtual hospital setting for COVID-19 and tried to identify the predictors of adverse outcomes including death or re-admission. While it is critical to manage patients outside the hospital with advanced virtual hospital mode, the analysis and results in this article arouse concerns as follows: Major concerns: 1. The post-hospital patients and community patients are basically quite different in clinical characteristic and disease severity, also in the requirement of virtual hospital management. It's not suitable to put them together to analyze the risk factors for adverse outcomes. 2. How the COVID-19 were identified as suspected or confirmed? In the community cohort, only 31.4% were positive COVID-19 and 48.9% were abnormal CXR. It's better to clarify it or choose the confirmed COVID-19 patients as study subjects. Minor concerns; 1. Please state the timepoint of laboratory index, especially for the post-hospital patients. Do they indicate the first or last or pre-discharge of lab test? 2. How were the patients treated or managed in the virtual hospital setting? Did the therapy associate with the adverse outcomes? 3. How the adverse outcomes associated with COVID-19? Did they directly due to COVID-19 or indirectly or not related at all?

VERSION 1 – AUTHOR RESPONSE

Reviewer comment	Author's response
Reviewer 1 This manuscript provides a review of patients monitored remotely after COVID-19-like illness and aims to identify prevalence of and risk factors for death or readmission. Overall, this is a useful question that adds to the growing body of literature surrounding programs that address COVID-19 clinical needs. In particular, the use of the "virtual hospital" monitoring program is an important element that has been used in many places - and it is important to analyze outcomes related to this type of innovation.	Thank you for this recognition of the importance of identifying predictors of clinical deterioration in patients admitted to a virtual hospital (VH) setting during the early phase of the COVID-19 pandemic.
My major concern about this manuscript is the heterogeneity of results being presented. Both community-referred and post-hospitalization patients are included in analysis, which while pragmatic in nature does lead to comparison of seemingly different groups of individuals. Adding to this concern, 20% of the community-referred group did not undergo SARS-CoV testing.	We agree with the reviewer that by including patients entering the virtual hospital from both direct community referrals and post-hospitalisation, we have introduced some heterogeneity to our study population. Our study aims to provide data that is relevant to real-world settings, and therefore we deliberately chose to include all patients admitted to the virtual hospital. As hospital in-patient services become overwhelmed, as they did during the first wave of the pandemic in the UK and as is currently happening in the second wave in many countries, virtual hospital services can help relieve pressure by monitoring patients from both of these groups – those that have been referred from the community and those that are being discharged early with remote monitoring. Clinicians managing these services therefore need to understand whether there are predictors of clinical deterioration that are common to all VH patients, or if the predictors are different for these two groups. By using a real-life cohort of all patients admitted to the virtual hospital during the recruitment period, we have produced data that are representative and generalisable to the real world. Instead of limiting our study to one group or the other (community-referred or post-hospitalisation) we have presented data for each group separately and combined. As such, our study allows the reader to identify predictors that are relevant to each of the sub-populations making up the VH population, as well as the overall VH population. We believe that this is

	the most useful data for clinicians operating services like this. Regarding SARS-CoV2 testing, we believe that it is essential that patients who were not tested are included in the cohort. In the UK, very few people with suspected COVID-19 were tested in the community during the first wave of the pandemic, and those that were tested were often tested late, leading to false negatives. We agree that it is important to control for SARS-CoV2 testing status, which we have done, but excluding participants who had not had testing (or who had negative or inconclusive test results) would lead to selection bias and biased estimates.
It is also unclear if the "low-risk" and "high-risk" patients were both included in analysis. In the Data Collection section towards the bottom of page 5, there are 2 different followup techniques described based on risk assessment. If both of these are included in analysis, this presents yet another distinction between groups that could impact the comparison and conclusions drawn. (It is unclear, however, because in Figure 1 only the "high risk" group is labeled as "virtual hospital" but I cannot find description that "low risk" was excluded so presume all entrants are reported).	We apologise that this was not made clearer. We have now clarified that patients assessed as being at both 'low-risk' and 'high-risk' were included in the study. We have now made this clearer and have added risk status as a co-variable to the models, although it was not included in the final models as was not significantly associated with clinical deterioration.
Finally, the combined outcome of death and readmissions leads to less conclusive results; while both are important outcomes, they do not necessarily always have the same contributors so seeking associations with this multifaceted end-point creates murkiness. Altogether, the multiple referral sources (and underlying populations), multiple care processes, and multiple/combined end-point makes it challenging to parse results in a meaningful way. I would strongly suggest the authors consider limiting the research question to a specific focus in order to more thoroughly address the aim and solidify the findings.	We agree that the predictors of death and hospital admission may differ, but they both follow from clinical deterioration and so it is not unreasonable to assume that there will be common predictors. To improve clarity, we have renamed our outcome 'clinical deterioration'. Death was a relatively uncommon outcome in this population (18/900 = 2%) and we would have needed a much larger study to power on deaths alone. We have added sensitivity analyses excluding death as an outcome. The majority of patients that died were admitted before they died and excluding only the 3 patients that died without having a hospital admission did not result in any changes in which predictors were significantly associated with outcome. However, if all 18 patients that died are excluded then age is no longer significant, but all other predictors remain the same.

	We agree that there is significant heterogeneity in terms of our patient population. However, we have taken the view that it is better to control for this variation and present results that are applicable for the different groups within the study, rather than exclude and restrict our analyses.
Abstract: Main outcome measure indicates risk of death or (re)-hospitalization within 28 days. Please clarify this timeframe and align with timeframes for outcome elsewhere in the main text (for example p 7 line 15 says two weeks after discharge)	Thank you for highlighting this mistake. Participants were followed for the period that they were under the care of the VH (median 21 days, range 15 to 43 days) and through a medical record review for the two-weeks post discharge from the VH. This has now been made clear.
Background: P 3 line 40-41 says "Factors associated with prognosis are likely to be different in VH patients because they are at a different stage of the disease and/or have less severe symptoms." Please provide citations to support your claim. If this is a hypothesis of the study, please restate as such.	We have removed this sentence.
Would appreciate additional discussion and support for the reasoning behind a combined outcome of both death and re-admissions as described in opening paragraph of my review above. I can appreciate if the goal of this manuscript is to help identify appropriate candidates for this type of monitoring program, though if this were to be an approach used to offload overwhelmed inpatient units an outcome such as readmission may not necessarily be viewed as a failure. The secondary analysis provided in Table 4 of predictors for each outcome by referral source is not convincing that these are similar enough groups.	We have added more rationale to the introduction and discussion sections.
Methods: Page 5 line 5 labels this a "prospective observational study". However, study data was not collected in a prospective fashion. Page 4 line 57-58 reads "Data for this study were subsequently extracted from participants' medical records. Therefore, data were not collected in a protocolised way but reflect the recording of healthcare data in a busy clinical setting." It sounds like patients were enrolled into the virtual hospital in a prospective, clinically-relevant manner, but the study itself is	We have changed this sentence to indicate that the analysis was conducted on retrospective data.

a retrospective analysis of information from the medical chart. Please clarify.	
Better define the medications data. What criteria were used to identify a relevant medication? Presence on the medication list at time of referral into the virtual hospital? Time course of prescription? Etc.	Medication documented were those that were assessed as being potentially relevant to COVID-19 prognosis at the time the virtual hospital was set up. This has now been made clear in the manuscript.
Clarify the timing of "baseline" data. This would have occurred at the time of entry to virtual hospital program? For patients referred from community this is at time of presentation, but for hospitalized patients this would have been at discharge from the hospital?	Baseline data is taken from the day that the patient was admitted to the VH, which for the post-inpatient cohort was the day of discharge from inpatient care. This has now been made clear in the manuscript.
Provide additional detail about patient selection in the inpatient setting. Were all patients who met criteria referred for virtual hospital at discharge? Page 5 line 9-11 reads "The aim was to reduce pressure on in-patient capacity by providing remote clinical assessment to patients at home in place of hospital admission, or to facilitate early discharge from hospital." How was this operationalized in practice? Additional detail about the hospitalized population is necessary. What was their length of stay? Percentage with ICU admissions, percentage on oxygen or intubated at any time during hospitalization, percentage treated with therapies (note this has changed over time – likely, hydroxychloroquine for ex), etc?	All patients meeting the eligibility criteria provided in the manuscript were eligible for admission to the VH post-hospital admission. Decisions regarding whether to refer patients to the VH or not were made by the medical team responsible for the care of the patient, and as this study was conducted in the middle of a pandemic, the reasons for referral or not were not recorded. We have added detail about length of stay and admissions to ITU, but do not have more detailed data on therapies received during hospitalisation. We have added this to the limitations section.
Outcome is not sufficiently described. What constituted (re)admission? Did this include observation status? Was reason for (re)admission captured? Were planned hospitalizations excluded? Were patients on hospice or palliative care excluded?	We apologise for not making this clearer. All hospital admissions were for COVID-19 or complications resulting from COVID-19. Planned palliative admissions and other routine and emergency admissions were not included in the outcome.
Provide additional details about the study setting including characteristics of the hospital involved: # of patient beds, # of emergency visits/year, referral or catchment area served, etc. It is important to understand the local COVID-19 context during this time period, as well. If the healthcare system was extensively overstretched, this knowledge would help interpretation of the findings. Please include local numbers of COVID cases and a general description of processes (were crisis standards met? what % of beds were occupied? what % of	We have added additional information to the methods and discussion sections to provide greater context.

beds were occupied by COVID-19 patients?) during the study time period.	
It is interesting that the first 900 patients enrolled in this program were almost perfectly divided in referrals from community and hospital discharge sources. How was this accomplished? Does this represent consecutive cases seen and diagnosed at your site? Did patients consent to the virtual hospital intervention or were they able to decline to be part of the intervention? Presumably patients who failed the clinical criteria would be admitted to the hospital but what about the criteria that they had to be able to use the telephone or videoconference and that they had to be able to isolate and self care? How many were disqualified from inclusion based on these criteria?	We included consecutive patients admitted to the VH between 17th March and 17th May 2020. Eligible patients were offered the virtual hospital as part of their standard care. As with any other aspect of standard care, they could have declined, but we are not aware of any patients that have declined admission to the virtual hospital so far. A patient without access to a telephone would not be eligible, but we are not aware of any patients who have not been eligible for this reason. Patients did not need to have access to videoconference facilities.
Results: Clarify what is meant by "patients were followed for a median of 21 days" (p 8, line 19). The study protocol itself is 14 days. Is this time after enrollment that the study team reviewed notes? If so, this does not match time frame noted in abstract.	Participants were followed for 14 days post discharge from the VH. We have amended the abstract to reflect this.
Revise Table 1 and Table 2 to either compare patients with adverse events vs those without or compare patients who were referred from community vs those referred from hospital discharge.	We have removed the final column (experienced adverse outcome) from Tables 1 and 2 so that these tables now focus on describing the study population(s).
What statistical comparison test is being used? Include results of statistical comparison tests when identifying differences in groups. Any distinctions reported in the text should represent statistically significant differences and should be denoted in Tables 1 and 2 (can use bolding, asterisks, additional column to include p-values, etc).	Tables 1 and 2 describe participant characteristics but the study was not set up to test hypotheses about differences between those recruited from the community and those who were post-inpatients. Therefore, we have not conducted hypothesis tests for differences between these groups.
Why is negative SARS Co-V swab a reference value in Table 3? Why would patients be included in this study with a negative test?	Most patients with suspected COVID-19 did not have a SARS-CoV2 test in the community, and those that were tested were often tested late, leading to a significant risk of false negatives. We chose to include all patients admitted to the VH with suspected COVID-19, regardless of testing status.

Discussion: P 18 lines 31-37 read “It is reasonably safe to assume that the population included in this study includes the vast majority of those that required monitoring in the community during this period as there were no other services providing remote monitoring of patients that had required a face-to-face assessment in the area at that time.” Additional data is necessary to justify this claim. Just because this is the only monitoring program in the community does not mean that all who required monitoring received this intervention.	As we explain in the discussion section, there were no other services for monitoring patients in the community at that time, so therefore it seems reasonable to assume that most patients who required monitoring were monitored through this service.
I would hesitate to draw strong conclusions from the currently presented findings especially without knowing the reason for return hospitalization. The findings here that patients with comorbidity are readmitted may be confounded by the fact that they are chronically ill. Without knowing the reason for (re)hospitalization, it is plausible that patients might return for planned or semi-planned encounters or for a reason entirely unrelated to COVID-19. For example, patients with poor kidney function might return for dialysis or for vascular access placement; patients with cancer may return for chemotherapy or radiation treatments or for vascular access placement; patients with mental health disorder may return for mental health crisis. Likewise, there may be entirely extraneous issues that are not accounted for. Nearly 20% of the patients discharged to skilled nursing facility had an adverse event. Could it be that nursing facilities experienced overstretch during this time period and if they had infection control issues returned patients to the hospital because of their own lack of capabilities? Etc.	We apologise for not making it clear that we only included admissions related to COVID-19 (or complications such as pneumonia or dehydration). Therefore, patients attending for routine treatments such as dialysis, vascular access, chemotherapy or radiotherapy were not included in the outcome. Nevertheless, we agree that it is not possible to draw ‘strong conclusions’ from our study, which is why we have indicated that these findings *may help* direct intensity of monitoring, and recommend further research to confirm our findings.
As noted above, I think this manuscript could be made much stronger with a more cohesive message. I find it compelling that this program seemed to safely provide an alternative to hospitalization from the emergency presentation. I also think there is a unique story to be told about how this program can serve as an additional layer of support at discharge – with enough additional detail this could help refine the program and its selection/monitoring process. But, in my opinion, combining the two points detracts from each.	Thank you, we agree that this study provides compelling evidence of the value of this service, both for providing an alternative to hospital admissions and for safely supporting early discharge. We have expanded our conclusions around your suggestions.

Reviewer: 2 The authors made an analysis of 900 patients enrolled in virtual hospital setting for COVID-19 and tried to identify the predictors of adverse outcomes including death or re-admission. While it is critical to manage patients outside the hospital with advanced virtual hospital mode, the analysis and results in this article arouse concerns as follows: Major concerns: 1. The post-hospital patients and community patients are basically quite different in clinical characteristic and disease severity, also in the requirement of virtual hospital management. It's not suitable to put them together to analyze the risk factors for adverse outcomes.	As we have indicated in our response to reviewer 1, by including the whole population of patients admitted to the VH, and including analyses of the whole population controlling for route of admission (community-referred or post-inpatient) as well as providing subgroup analyses (for community-referred and post-inpatient), we are able to identify predictors for the combined population and both sub-groups, and therefore provide data that is most useful for clinicians. Excluding half of the participants would only result in one of these sub-group analyses.
2. How the COVID-19 were identified as suspected or confirmed? In the community cohort, only 31.4% were positive COVID-19 and 48.9% were abnormal CXR. It's better to clarify it or choose the confirmed COVID-19 patients as study subjects.	During the first wave of the pandemic, when this study was conducted, it was almost impossible to get a SARS-CoV2 test in the community. Most people in the community were therefore either not tested or were tested late (and therefore at greater risk of having false negative results). Patients in the community with a clinical syndrome suggestive of COVID-19 had to be managed as if they had COVID-19. Given this, it is important to include all patients who were admitted to the VH with clinically-suspected COVID-19, as excluding those who did not have a positive SARS-CoV2 test would lead to selection bias. Furthermore, we have controlled for testing status in our models, so our estimates are corrected for differences related to testing status.
Minor concerns; 1. Please state the timepoint of laboratory index, especially for the post-hospital patients. Do they indicate the first or last or pre-discharge of lab test?	We have now clarified that, for ease of data collection during a pandemic, we used laboratory results from the initial assessment. These were not necessarily the most contemporaneous results for the post-inpatient cohort, and we have added this to the limitations in the discussion section.
2. How were the patients treated or managed in the virtual hospital setting? Did the therapy associate with the adverse outcomes?	None of the patients admitted to the VH were given treatments aimed at treating COVID-19 (there were no treatments with evidence of efficacy at the time). Therefore, patients only

	received ongoing regular medications, and medications for symptoms or complications as assessed by their clinician.
3. How the adverse outcomes associated with COVID-19? Did they directly due to COVID-19 or indirectly or not related at all?	Only adverse outcomes related to the suspected COVID-19 illness were included.

VERSION 2 – REVIEW

REVIEWER	Maralyssa Bann, MD University of Washington, USA
REVIEW RETURNED	19-Jan-2021

GENERAL COMMENTS	This revised manuscript addresses the suggestions from previous round of peer review appropriately. Rationale and methodologic points have been clarified. The use of the term "clinical deterioration" as opposed to "adverse events" is a useful change. The authors present a comprehensive and compelling report on the use of this virtual hospital innovation in the midst of the COVID-19 pandemic.