
30-Apr-2020
BMJ-2020-057265
Factors associated with hospitalization and critical illness among 4,594 patients with COVID-19 disease in New York City: A prospective cohort study

Dear Dr. Horwitz,

Thank you for sending us your paper, which we sent for external peer review and discussed at our manuscript committee meeting. I'm please to say that we would like to move forward with your manuscript, if you are able to amend it in the light of our comments and those of the reviewers.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

I look forward to receiving your revision as quickly as possible, hopefully within 1 week. If you anticipate any delay beyond that, please contact me.

Yours sincerely,

David Ludwig
Professor David Ludwig
Associate Research Editor
The BMJ
dludwig@bmj.com

To submit your resubmission: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=0409f212faff4d719fc05f7308a983e6

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (Chair), ,Julie Morris (Statistician), David Ludwig, Tiago Villanueva, Joseph Ross, Timothy Feeney, Elizabeth Loder, Shivali Fulchand, Helen Macdonald, Mark Richards

Decision: Put points
Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* Extend length of follow-up to at least 21 days (data that now should be available), to reduce risk of bias from right censoring.
* As Reviewer 2 and our staistical consultant (Reviewer 4) emphasize, your study includes 2 groups, those who test positive and those who were hospitalized. There is substantial risk for bias in the first. Can you provide any additional information about those who tested negative? In view of this issue (and other peer review comments), perhaps your paper would best be considered a case series rather than a prospective cohort?
* Conduct a survival analysis
* Omit the decision tree analysis
* Clarify patient flow (e.g., did patients first arrive at ambulatory clinics?)
* Clarify missing data
* Regarding the lipid findings: 1) How did you defined hyperlipidemia? 2) Can you separate high LDLc, statin treatment, and high triglyeride-to-HDLc ratio? The hypothesized protective effects involve LDLc (anti-viral or anti-inflammatory), whereas high trigs-to-HDLc ratio is a biomarker of metabolic syndrome, a potential major risk factor. Statin treatment might may be protective independly of LDLc, with anti-inflammatory effects reported for this drug. Ideally, run these 3 baseline covariates in a multivariate model of risk for bad outcome.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1
The manuscript "Factors associated with hospitalization and critical illness among 4,594 patients with COVID-19 disease in New York City: A prospective cohort study" presents a comparison of clinical observations and risk factors among confirmed COVID-19 cases who are or are not hospitalized and/or admitted to intensive care by time of writing. As the authors note this is the largest case series I have seen described and the first comparison of hospitalized versus non-hospitalized patients, which is valuable. In addition, many risk factors are assessed although there are some important limitations to the design and statistical analysis which may limit the value of these analyses in my view. Some of these can be corrected just by using survival analysis methods, which I believe is important to prevent misinterpretation of the observations regarding clinical outcomes.

Main comments:

1) My first of two key concerns is that observations are reported/analyzed only for patients with observed death/hospice/discharge outcome, resulting in right-censoring (and exclusion) of about 20% of all hospitalized patients; more troubling, we have right-censoring/exclusion of 40% of patients receiving mechanical ventilation. Since this censoring affects a unique class of patients (those requiring longer stay/longer ventilation than those with outcomes observed at time of writing, thus probably sicker patients than those with outcomes observed), interpretation of the clinical outcome data is greatly undermined. The unaddressed censoring issues do not support the authors' aim to "improve the reliability of future mortality rate estimation". This issue should be corrected with survival analysis methods rather than those used here as the reported CFR from this study will be extensively quoted by press, etc. and non-statistical audiences.

Related to the point above is that we also have a fundamental censoring problem of who, among all those diagnosed, will ultimately become a hospitalized case: since time elapses from initial presentation

at an outpatient visit to hospitalization (at least for cases whose first interaction is not an inpatient admission) the concerns above apply to this comparison. Same goes for critical care/no critical care among the hospitalized.

2) My second concern is the changing definition of the non-severe case group over time due to changes in testing practices (assays, conducted by NYC DOHMH vs. Langone, recommendation to restrict testing of patients with mild/moderate illness after March 26). However, not much can be done about this and there is still a value of comparing hospitalized/non-hospitalized patients.

In light of these considerations it is probably optimistic to call the study a prospective cohort rather than a case series. In my view a proper prospective cohort of COVID-19 cases would catch all patients meeting a given clinical threshold and assess how many go on to hospitalization, critical illness, ventilation, death, etc. Here patients are being ascertained at differing thresholds over the course of the study.

3) The patient EHR data used for analyses of risk factors like tobacco use, BMI, and comorbidities come from previous interactions with the health system. However it is not clear if all the patients routinely receive care from this system. For instance, 140 patients have only age and sex data and are excluded from the analysis—presumably they do not. Is further information available on this issue? The concern is that the absence of an indication of a comorbidity/risk factor could arise if the comorbidity/risk factor is truly absent, or patient is not routinely receiving care from the Langone system such that this is simply not recorded in the medical record. This becomes a problem of confounding when we consider that those who interact with the health system often (either because they are very sick or the worried well) probably differ from those who do not. This concern is well illustrated in the smoking analyses, for instance. The fact that smoking appears protective could suggest that simply having EHR risk factor data available suggests individuals are better linked to care/in better health.

4) Are too many covariates being included if hyperlipidemia is associated with lower hospitalization risk/critical illness when all the other findings are opposing this? Is there a scientific reason to assess the association with hyperlipidemia after controlling for BMI, overweight, etc.? The findings are hard to interpret given multiple forms of censoring and a time-varying spectrum of patients who would be ascertained as COVID-19 cases without meeting the hospitalization threshold. Another explanation is offered in the discussion but I do not know the merits/significance.

5) What is the interpretation/value of the decision tree? It doesn't inform who benefits most from hospitalization (deaths averted etc.) and therefore should be hospitalized; moreover, the information presented in the tables already addresses risk factors—the "use case" of this analysis is not clear to me. The issues around censoring are masked even further in this analysis and ultimately I don't think it adds much to the paper, unless I am missing something.

Minor/specific comments

6) The endpoint of the paragraph beginning "After adding admission vitals…" is not clear. Is this still critical illness? Presumably the finding that children ages 0-18 had high risk is hard to interpret given only very susceptible children would experience such illness to begin with. Age probably isn't the risk factor so much as a basis for selection.

7) I remain concerned that the discussion puts undue weight on the interim results among patients with observed definitive outcomes, i.e. more than 20% are likely to die here once outcomes are observed for those with very long hospitalizations and/or readmissions.

8) The authors claim that the findings can help epidemiologists improve projections around hospital beds, staffing, etc. although I think these claims may be unsupported as the paper does not address key aspects like incidence and trends in incidence/transmission intensity (nor can it since there is no population-at-risk denominator to work from), and does not address duration of hospital stay.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Joseph Lewnard

Job Title: Assistant Professor

Institution: University of California, Berkeley

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2
This is an important paper representing the largest COVID-19 clinical case series from the U.S. with 4,734 cases identified in an NYC private health system identified between March 1 through April 5th , including 2,390 who were hospitalized. For reference, this is more total cases than over 25 U.S. states. The goal of this study was to describe the characteristics of patients that tested positive for COVID-19 within a health system and the association between those characteristics and adverse outcomes. The rapid reporting and analysis of these data is impressive and commendable, providing useful clinical and

public health evidence as areas around the world are currently grappling with how to manage this disease. However, there are number of concerns and limitations. The majority of these concerns are addressable. If these concerns are addressed, this paper will make a high impact contribution to the literature particularly with the understanding of obesity and inflammatory parkers as being associated with adverse outcomes among COVID19 patients requiring hospitalization, as well as understanding the overall rates of critical illness in a large US cohort of hospitalized COVID19 patients.

Major concerns

1. Design of the study cohort(s)

The study has two study cohorts, one nested within the other:

Cohort #1 All patients who tested positive for COVID-19 via ambulatory or ED testing in the NYU Lagone system. Outcome = hospitalization in NYU Lagone system.

Cohort #2: All patients who were hospitalized in the NYU Lagone system and were not still hospitalized on an inpatient ward at the time of followup. Outcome = critical illness (ICU, mechanical ventilation, discharge to hospice or death)

Problems with Cohort #1: There are multiple potential sources of bias in the construction of this cohort for answering the question which demographic and clinical factors are most associated with need for hospitalization.
- Heterogeneity in site of test/hospitalization decision resides in the emergency department (ED). The cohort includes patients tested in ambulatory settings, concerned employees, and those presenting to the emergency department. However, no data are provided on proportion of the sample by location of testing and whether there are demographic and clinical differences according to location of testing. Therefore, imbalances in demographics and severity of illness by location of testing could account for associations between these factors and hospitalization. For example, if Hispanic patients are overrepresented in the population of patients tested in the ED, the higher hospitalization rates could simply represent higher unobserved severity of illness in this population. Furthermore, the decision to hospitalize is made exclusively in the ED Therefore, those who were tested as outpatients but never presented to or were referred to the emergency department could never experience the outcome of hospitalization. To make these data useful and generalizable for clinicians practicing in the ED, a cohort could just be limited to those who presented to the ED. Likewise, to assist outpatient clinician determine which patients should be referred to the ED for evaluation and consideration of hospitalization, a separate cohort could be created addressing that decision.

- Potential biases in who gets tested. We do not know from the data what the total denominator of patients who were eligible to be tested based on influenza or COVID-19 like illness - https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/04172020/covid-like-illness.html. (Obviously, it takes a lot more work to define that cohort). Therefore, it cannot be ruled out that there were biases in who was tested all else equal even though there are number of other reports indicating that blacks and Hispanics have been tested at lower rates. So even if just limiting to the patients presenting to the emergency department, there could be unobserved differences in severity of illness according to demographic groups. Finally, for patients presenting the ED, the decision to admit is based on assessment of clinical presentation/severity. If the decision is made to admit, a COVID-19 test is sent. If the decision is made that the patient is well and can be discharged, these patients often do not get tested for COVID-19 at all or do not receive any other tests (see assessment of well patients: https://emupdates.com/cv3w/). The authors could make the case this is not a major deal if a high proportion of those presenting to the ED with COVID-19 like illness and were discharge did receive testing.

- Substantial missing physiologic data between hospitalized and non-hospitalized patients. Table 1 indicates that Temperature was missing for 74% of non-hospitalized patients and that there substantially higher proportions of oxygen saturation measurements were made while supplemental oxygen was

being administered among hospitalized patients (99% vs. 23%). These major observable imbalances are problematic and there are likely major unobservable imbalances as well for the reasons above.

- Patients testing positive in outpatient settings may have been hospitalized in non NYU EDs

Cohort #2: This is a much cleaner and more generalizable population. The methodological problems with Cohort #1, detract from the important information that can be gleaned from Cohort #2.

2. Statistical Analysis and Modeling
- Given the goal of this paper is to "describe the clinical and laboratory characteristics associated with severity of illness" and not the distribution of clinical and laboratory characteristics among those with severe illness, it seems that Tables 1 and 2 would provide more clarity to clinicians if reporting row percentages instead of column percentages. (eg https://www.annalsthoracicsurgery.org/article/S0003-4975(15)01520-9/pdf).

-The model presented in Table 1 includes a common outcome (2,390/4,594 = 52% experienced event of hospitalization). The "risk of hospitalization" is presented as an odds ratio, but this overinflates relative "risk" given this is a common outcome (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348192/). Hence an odds ratio of 48.53 for patients 75 and older. As a clinician, a really high odds ratio loses meaning. Could consider presenting as predicted probabilities, relative risks, or average marginal effects to make the data more meaningful and useful for clinicians.

- Given the data on critical illness come from 4 hospitals, which are in different neighborhoods, may have different surge/ICU capacity and practice patterns, seems like the multivariable models should consider adjusting for hospital effects. Seems especially important given that one of the hospitals is a children's hospital.

- Table 3 – because of all the potential sources of bias with Cohort # 1 (all patients), the model looking at risk of critical illness among all patients tested in the health system is going to have all the same limitations and biases. I think this detracts from the more useful and more robust results of critical illness among hospitalized patients.

- It appears that the laboratory data in the multivariate regression model in Table 3 are not missing at random.

- Give the dynamics of the surge, and changes in practice over time and adjustment to available hospital capacity, consideration should be given to adjusting for study week in the multivariate models

- Given that critical illness could occur upon admission or much later during hospitalization, may consider using a survival model approach instead

Other issues to address:
1. Introduction: Page 4, last paragraph and Page 5, 1st paragraph. This important paper suffers a little from trying to accomplish too much for too many audiences (epidemiologists/policy makers, outpatient docs, ED docs, inpatient docs). The focus on critical illness among those who are hospitalized is the strongest contribution.

2. Methods: Study setting. It would be helpful to list the hospital names (so people whether NYU Bellevue or the Children's Hospital are included).

3. Methods, p 6, Lines 24-33. Were emergency department testing results available on the same day (e.g under 3 hours?). In many EDs, same day tests are only sent if the patient is going admitted to the hospital. If patients are going to be discharged, patients may or may not be tested, and is often the

case in many EDs, if tests are going to be sent, they will be send out tests that don't result for several days. This should be clarified. It may be helpful to include an author from the emergency medicine as the decision to hospitalize a patient is made by clinicians working in the ED practices may have change dramatically in the surge.

4. Discussion. Page 14, Lines 3-5. "we found comorbidities to be less strongly associated with critical illness once patients were hospitalized." Would consider rewording since the outcome of critical illness includes those who were critically ill upon admission and those who became critically ill after a few days of being hospitalized.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: M. Kit Delgado, MD, MS

Job Title: Assistant Professor of Emergency Medicine & Epidemiology

Institution: University of Pennsylvania, Perelman School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 3
My comments here are in line with my other review of manuscript BMJ-2020-057242

I would publish this article rather than the above mentioned manuscript as it involves more patients and also include etnicity.

I have read the article with great interest but as a non-clinician it is difficult to estimate how useful this article would be for the medical world. I would recommend the BMJ to publish from the most interesting articles on COVID-19 only the abstract with a link to the whole article. And ask one or two very experiences COVID-19 scientists to comment on the particular 'added value' of this article for their colleagues. More or less like the way Mike Makris is doing this on Twitter. As a patient expert, I find that most helpful to get a feeling of the most important developments, lack in research etc.

Overall, this type of overview of patients can be very helpful and certainly from my own experience is very labour-intensive.

This article is helpful in understanding underlying comorbidities for patients and carers. But as etnicity is not mentioned, it doesn't say much about possible lack in access for certain groups as The Lancet recently described in their World Report of April 18, 2020 page 1243-4

The large use of hydroxychloroquine is remarkable and maybe lower as elsewhere in the world. But as I mentioned above something I cann't judge exactly.

Personally, I believe that public or patient involvement in these type of research could not be very helpful. However, there are certainly lessons to be learnt for the after COVID-19 period in the sense that patient groups should focus much more on the importance of comorbidities and the need for lifestyle coaching for especially those underlying conditions where lifestyle advice can be of assistance to decrease the number with diseases like diabetes, kidney failure, large BMI etc.

And we have to take in account that COVID-19 outcomes in the US may greatly differ from the outcomes in other parts of the world as the US lacks a good health care infrastructure and Insurance as well as another social security system or none at all.

Cees Smit

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Dr. h.c. Cees Smit

Job Title: Patient Reviewer

Institution: VSOP/EGAN

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 4
This cohort study of COVID-19 subjects aims to assess the relationship between patient characteristics and hospitalization, and between patient characteristics and 'critical illness'.

There are a number of issues (methodological, analysis, interpretation and presentation of results) which need to be addressed:

1. The 'tested' cohort is a very heterogenous group of subjects: those presenting to ED with symptoms or clinician concern, ambulatory testing with clinician's referral, outpatient testing of symptomatic/concerned employees, and repeat testing of negative specimens at clinician discretion. This results in a very biased group of COVID-19 positive subjects, the structure of which also varies with time (since testing was restricted further during the study period). It would be useful to see information on patient characteristics by reason for testing. The reason for hospitalisation may also vary according to the reason for presenting -see below.

2. How subjective is the decision to admit? Does this vary by reason for presenting? Does it vary over the study period? Could this not bias the comparisons between those who were and who were not hospitalised? If so, then it is difficult to interpret the 'hospitalised' vs 'non-hospitalised' comparisons. Should 'reason' and 'time' not be included in the statistical model? Or, perhaps the formal statistical analysis here (Table 1) should be omitted? In addition, what was the extent of missing data on comorbidities/health characteristics for those subjects not hospitalised?

3. What proportion of those COVID-19 subjects who were not hospitalised might have been subsequently hospitalised/died (after the study period)?

4. For the cohort who were hospitalised, an endpoint (critical illness/discharged well) was unavailable for 5% (n=115). These cases (although a small number) are omitted from the logistic regression analyses which assess factors predictive for critical illness, and hence may introduce bias. It would be preferable to use this censored information (and time to critical illness) in a 'survival-type' analysis, rather than logistic regression. Also, 'hospital' and 'time' would seem to be appropriate additional factors to include in the model.

5. Furthermore, the large proportion of missing endpoints (ie those still hospitalised/ventilated/extubated but still hospitalised) for those with 'critical illness' (see Figure 1), means that 'final outcomes' for this subgroup are difficult to judge. At the very least a simple sensitivity-type analysis could be carried out with 'good' and 'bad' outcomes substituted for the 'missing' endpoints, to show the possible range in rates.

6. Predictors of hospitalisation/critical illness. Some of the 'significant' multivariable-adjusted factors need to be interpreted carefully. For example, in Table 1 the multivariable logistic regression odds ratio for hyperlipidemia of 0.63 (0.50-0.80), is interpreted by the study authors as showing a 'protective' effect of hyperlipidemia for hospitalization. However, from Table 1, the % of those with hyperlipidemia for the hospitalised cohort is higher than that for the non-hospitalised cohort. In fact, the observed (unadjusted) hospitalization rates (Table 1) are 625/866 = 72% for those with hyperlipidemia and (approximately, assuming no missing values) 1765/3728 = 47% for those without hyperlipidemia, ie a higher risk (not a lower one) for those with hyperlipidemia. The 'change' from a higher to a lower risk with statistical adjustment indicates a high degree of intercorrelation between patient characteristics, and can lead to misleading results. This introduces problems in the interpretation of any multivariable result. Tobacco use data seems also to be affected by intercorrelation (and the observed data show 'former' smokers, with perhaps underlying health conditions, have a greater risk of hospitalisation/critical illness)

7. The maximum information gain decision tree classification analysis does not really add to the results, hence could be omitted from the paper.

8. Table 1. Temperature results should be omitted here as they were missing for most of the non-hospitalised cohort. Should oxygen saturation also be omitted as these values were obtained from differing proportions of patients on supplemental oxygen?

9. Tables 1 and 2. The hospitalization/critical illness data might be easier to understand if hospitalization/critical illness rates were shown by characteristic category (ie row percentages rather than column percentages were shown).

10. Table 3. The critical illness risk analysis for 'all patients' (ie those hospitalised plus those not hospitalised) is inappropriate surely as risk is dominated by decision to hospitalise? [None of the subjects not hospitalised had critical illness?]

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Julie Morris

Job Title: Honorary Reader in Medical Statistics

Institution: University of Manchester

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: