Author's response to reviews

Title: Association between Hospital Case Volume and Mortality in Non-elderly Pneumonia Patients Stratified by Severity: a Retrospective Cohort Study

Authors:

Hiraku Kumamaru (kumamaru-tky@umin.ac.jp)
Yusuke Tsugawa (ytsugawa@bidmc.harvard.edu)
Hiromasa Horiguchi (hiromasa-tky@umin.ac.jp)
Kanako K Kumamaru (kkumamaru@partners.org)
Hideki Hashimoto (hidehashimoto-circ@umin.ac.jp)
Hideo Yasunaga (yasunagah-tky@umin.ac.jp)

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Author's response to reviews: see over
Dear Editor,

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Association between Hospital Case Volume and Mortality in Non-elderly Pneumonia Patients Stratified by Severity: a Retrospective Cohort Study

We are pleased to resubmit our revised manuscript at your invitation. We thank you and the reviewers for the very pertinent and useful comments that we believe have helped us improve the quality of our manuscript. We are submitting a clean revised copy, and a tracked copy with all the corrections made in the original manuscript tracked.

Our responses to the comments and suggestions are outlined below. We hope the paper is now suitable for publication and we look forward to hearing from you again soon.

Yours sincerely

Hideo Yasunaga, MD, PhD
Department of Health Economics and Epidemiology Research
Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku
Tokyo 1138655, Japan
yasunagah-tky@umin.ac.jp
Tel.: +81-3-5800-9518, Fax: +81-3-5800-9164
Editor's comments:

Make sure that the scientific basis of your study becomes justified. Why hospital volume would affect the mortality of non-elderly pneumonia patients?

We appreciate this comment and have revised our Background section to emphasize the scientific basis and the context of our study. Specifically, the following statements have been added to the Background (2nd paragraph):

Many previous studies have reported that higher hospital case volume was associated with better outcomes in surgical procedures [7-10], non-surgical interventional procedures [11-14], medical treatments [15, 16], and in pneumonia in the elderly population [16-18]. Although the evidence is still scarce on the mechanism of the relationship, larger case volume hospitals are thought to be associated with better outcome for a number of reasons, such as better standardized care complying with recommended practice guidelines [17,19,20], increased use of peri-procedural testing, monitoring, or preventive processes [21], and care by physicians with greater clinical experience and skill. We hypothesized that in non-elderly pneumonia patients, there was also an inverse relationship between case volume and outcome, as providers with greater experience would likely be more aware of the risks associated with mismanagement of the treatment in these cases.
Can you consider non-elderly pneumonia patient population to be homogenous or should the clinically meaningful sub-groups be separated?

As described in the Background section, severe cases of non-elderly pneumonia occur in the presence of underlying chronic illnesses and the population is most probably heterogeneous with regard to their background health profiles. In the study, we partially adjusted for this heterogeneity using the patients’ comorbidity score. However, since the patients’ primary diagnosis was pneumonia, we believe that the most important factor which determined their in-hospital mortality is its severity. We adjusted for the severity using the indices and also stratified patients into subgroups by severity of pneumonia. No further clinically meaningful sub-groups based on background disease status could be formed since not all details are recorded in the DPC database.

Are patients “randomly” admitted to all hospitals or is there some (known) selection going on?

As with most previous studies investigating volume-outcome relationships, there was no randomness in patient admission to hospital and inclusion in our study. As shown in Table 1, a substantial proportion of the patients had been referred to the hospitals leaving the possibility of a selective referral pattern. We saw from the baseline characteristics of our patient population that, while no substantial differences in age or Charlson Comorbidity Index score were observed across the case volume levels, the differential distribution of severity indices showed that larger volume hospitals were on average treating less severe patients compared with smaller volume hospitals. The difference in the severity distribution suggests a differential admission threshold among the hospitals, and supports the need for strong case-mix adjustment in the analysis.
What your study adds that is interesting for an international reader?

Thank you for this comment. The volume-outcome relationship has previously been established for many diseases and procedures, but almost no evidence exists in non-elderly pneumonia patients. Also, our result suggests an effect modification of the relationship by disease severity. This concept of the relationship between quality of care and outcome being modified by disease severity is clinically intuitive, but there is little evidence in the literature owing to the lack of such clinical information in the large administrative databases commonly used for such studies.

Name of ethics committee: Please update your ethics statement to include the name of the ethics committee that approved your study.

As stated in the Methods section of the manuscript, study approval was obtained from the Institutional Review Board of University of Tokyo (Tokyo, Japan).

Copyediting: After reading through your manuscript, we feel that quality of written English needs to be improved before the manuscript can be considered further.

The manuscript has been edited by Edanz as recommended.
Reviewer #1:

(R1C1) Research hypothesis unknown; In Background, author mentioned research hypothesis if hospital volume which is nearly equal to “the number of patients” affects health outcome of interest in all patients. However, in method section, author defined the number of pneumonia patients, number of patients with specific disease. Is the number of pneumonia patients who discharged from hospital the proxy measure of the number of patients? Now I do not know hospital volume the author defined.

Thank you for your comment. We understand that our definition of “volume” was not clear, due in part to the interchangeable use of the terms “case volume” and “hospital volume”. We have clarified the definition in the methods section, and unified the term as “hospital case volume” throughout the text. Please see below for the revised definition of the factor in the Methods section (page 11 ln4-8):

Hospital case volume was defined as the number of pneumonia patients discharged from each hospital during the 6-month period of the study. We examined the distribution of the hospitals with different case volumes, and categorized the hospitals into four groups (very low-, low-, medium-, and high-volume) based on the total case volume quartiles.

(R1C2) Is the model statistically valid where study outcome is in-hospital death and main exposure variable is hospital volume (number of patients who discharged from hospital). Does the author try to investigate how much the number of patients with pneumonia contributes to mortality in hospital? Is what the author investigated in this
study compatible with research hypothesis?

We believe that our clarification of the case volume definition has resolved the reviewer’s concern about the model’s validity. The variable of interest was the hospital case volume of non-elderly pneumonia patients admitted to the hospital in the 6-month study period, and the outcome was the patients’ discharge status (alive/dead). We evaluated the association between the two using a logistic model with generalized estimating equations to account for hospital level clustering.

(R1C3) Definition of Hospital volume may not be clear.

We believe that this comment is resolved in our response to Comment 1.

(R1C4) In Background, the research hypothesis is not clearly mentioned. The author should describe what is already known in this field and what is expected to be elucidated. The author just mentioned “a small UK....” in background. This is not enough for reader to be convinced why this study needs to be conducted.

We appreciate this comment. To improve the clarity of the scientific basis of our study, we have revised the Background section to address this issue. Specifically, the following paragraph has been added (2nd paragraph):

Many previous studies have reported that higher hospital case volume was associated with better outcomes in surgical procedures [7-10], non-surgical interventional procedures [11-14], medical treatments [15,16], and in pneumonia in the elderly population [16-18]. Although the evidence is still scarce on the mechanism of the relationship, larger case volume hospitals are thought to be associated with better outcome for a number of reasons, such as better
standardized care complying with recommended practice guidelines [17,19,20],

increased use of peri-procedural testing, monitoring, or preventive processes [21],

and care by physicians with greater clinical experience and skill. We hypothesized that in non-elderly pneumonia patients, there was also an inverse relationship between case volume and outcome, as providers with greater experience would likely be more aware of the risks associated with mismanagement of the treatment in these cases.
Reviewer #2:

(R2C1) Improve the completeness of the table and figure labels so that the content is understandable without reading the text.

Thank you very much for this suggestion. We have altered the headings of the tables in accordance to the suggestion to make them more independently comprehensible.

(R2C2) Create an additional descriptive table that provides more information on the variability of volume, deaths, and mortality rates across all hospitals. I am not asking for individual hospital rates to be published but summary measures of the variability in volume deaths and mortality rate (which should be moved from Table 1 to the new table) across hospitals.

Thank you for this suggestion. Please see the histogram in the Figure depicting the distribution of case volume across all hospitals. We also added “Table 2” to describe the range of mortality rates at the hospital level, and across hospital case volume levels.

(R2C3) Why were the cut points chosen for the hospital volume categories?

We used quartiles as cut points to categorize the case volume into four groups. Quartiles and quintiles are commonly used as cut points for categorizing continuous variables when clinically relevant pre-specified cut points are unavailable. In our case, lack of previous evidence precluded us from using pre-specified cut-off points. We decided to present the odds ratios from comparisons of volume categories rather than using it as a continuous variable in a complex model, as interpretations are more straightforward and understandable to many readers.

(R2C4) Are there limitations due to the 6 months period of data capture? Provide
supporting citations for whether community acquired pneumonia in this age group varies by season or not and how that might influence findings.

Thank you very much for this important suggestion. Lin and colleagues have previously reported a seasonal trend of pneumonia admissions beginning in November and peaking through March in all age groups in Taiwan (reference below). Seasonality is most likely present in Japan as well, and our data captures only a part of that season. Misclassification could occur if the peak seasons were delayed in some hospitals compared with others. This discussion is added into the limitation section as follows (Page 21, In 12–17):

Also, since the DPC database captures hospitalization that occurred only between July and December, we are not fully capturing the yearly occurrence of pneumonia. Lin and colleagues previously reported a seasonal trend of pneumonia admissions that starts in November and peaked through March in all adult age groups [34]. If the seasonality of pneumonia occurs differentially among the hospitals, misclassification of the case volume level may bias our results.


(R2C5) Are there limitations to inference associated with the small number of discharges per hospital and small number of deaths? Should future research pool multiple years to improve estimation? What if any are the analytic issues when using GEE when so many hospitals have a small number of discharges and zero or only a few deaths. For example, are ten discharges adequate to create an appropriate correlation structure?
The small number of samples per hospital was certainly an issue in selecting meaningful cut-off points for the exposure. The results of the main analyses have rather narrow confidence intervals and the strong trend in the point estimates does not suggest that these findings are a result of instability in the estimates because of small sample size. Future research would certainly benefit from larger sample sizes to verify the results, especially in the sub-group analysis where small sample sizes restricted the number of covariates going into the model. As for the analytic model, we do not think that there is a problem specific to the use of GEE. Use of a prespecified exchangeable correlation matrix assumes the same correlation among all observations within the cluster, across clusters (i.e., only a single within-cluster correlation coefficient is estimated, rather than estimating correlations for each cluster); therefore, a small sample size within each cluster should not cause instability in the estimated correlation matrix.

(R2C6) What are the limitations associated with only capturing 45% of discharges nationally? What is known about hospitals that do not report to DPC? To what degree can it be said that the reporting hospitals are representative or not representative of all hospitals?

We appreciate this comment on the representativeness of the population. As we briefly mention in the Discussion section, adoption of the DPC system is voluntary for non-academic hospitals. It is known that very small hospitals have a low participation rate in the DPC system, therefore, we may have underestimated the true overall mortality in our analysis. We have added this last point to our limitation as follows (P 21, Ln 8–12)

Finally, because participation of community hospitals in the DPC database was voluntary, the population identified might not be completely
representative of the whole population in Japan. Very small hospitals are
known to have a low participation rate in the DPC system, and thus the
overall mortality may be underestimated by this.

(R2C7) Discretionary Revisions:

a) Logistic regression is the usual approach but I wonder if a count model like Poisson
or negative binomial might provide some additional insight. Volume is the principal
interest but a count model with volume as an indicator versus a count model with
volume as the offset or exposure might provide additional information and would allow
use of a zero inflation approach to account for so many hospitals with no deaths. The
later would be a good way to characterize differences in the population with volume held
constant as a starting point. This would also be a convenient way to descriptively
characterize unadjusted variation across hospitals as noted in 2b.

Thank you very much for this suggestion, and we certainly agree that using count
models would be more intuitive especially when we are interested in looking at the
association between hospital level factors and hospital specific mortality rates (in which
case we would be aggregating the observations at the hospital level). For this study,
we decided to adhere to the current “usual” analytic method at the patient level to
maximize the use of patient level covariates including the pneumonia severity indices.
Reviewer #3:

(R3C1) I believe that the description in the Methods and Discussion is too vague for readers outside Japan to comprehend adequately. For example, owing to the reimbursement regulation in Japan, most health insurance claims include more than one diagnosis. Authors should explain the principal diagnosis of the patients indexed in the Japanese Diagnosis Procedure Combination database, and discuss patients with an additional diagnosis of pneumonia. The authors should additionally discuss the hospital characteristics, infection control doctor, and infection control team, among others, which have not been detailed in this study.

Thank you very much for pointing out the difficulty for overseas readers. We have added further information on selection of patients from the DPC database and our definition of the hospitalization diagnosis in the Methods section, as follows (P 9, ln 3-10):

There are three types of hospitalization diagnoses recorded in the DPC database; “admission diagnosis”, “main diagnosis” and “the diagnosis for which the largest resource was used for treatment during that hospitalization”. We used the last diagnosis as our principal diagnosis to select the patients from the database, following the common practice in studies conducted using DPC data. This seemed most appropriate because having the diagnoses codes for pneumonia in this diagnosis category was what triggered the pneumonia severity to be recorded into the database.

Unfortunately, no validation study has been conducted for pneumonia in the DPC database, and while the requirement for recording the pneumonia severity index for patients with the above principal diagnosis would ensure that these patients did have pneumonia, this is not yet supported by published evidence. We have added this discussion in the limitation section as follows (P 20, ln 4–10):
First, the study was based on administrative data which are less well validated compared with well-designed prospective cohorts or registries. Unfortunately, no validation study of pneumonia diagnoses has been conducted in the DPC database, which may cause potential misclassification. We defined the diagnosis such that all included patients had information on the pneumonia severity index, minimizing the possibility of non-pneumonia cases being included in the cohort.

We appreciate your suggestion to discuss other hospital factors that may affect the outcome of the non-elderly pneumonia patients. Unfortunately, there were no data available for this study to account for other hospital level characteristics, including the presence of infection specialists or infection control team. We have added this to our limitation section as follows (P 21, ln 2–8):

Fifth, no information on hospital characteristics, other than academic status, was available for this study. It is possible that factors such as provider care ratios (bed-physician or bed-nurse ratio), tertiary care-center status, urban/rural locale or the presence of infection specialists or infection teams at the hospitals may explain or enhance some of the differences observed between the lower volume hospitals and larger volume hospitals.

(R3C2) The vertical lines in the tables should be removed.

The lines have been removed.

(R3C3) Table 1: 1) The number of hospitals should be presented with respect to case volume (number of patients per 6 months). 2) The number of patients in each case
category should be presented. Table 2: “Reference” is used only in hospital case volume.

Thank you for the suggestion. We have added Table 2 that reports the number of hospitals in each volume level. As for the second suggestion for Table 1, the number of patients in each category was provided in Table 1. We changed the heading for that row from N to “Number of Patients” to make this clear. For the suggestion for Table 2: We have removed the term “references” and added “vs. High” in the category headings of Tables 2 and 4.

(R3C4) Discretionary revisions: P8L18: “mgdL-1” should be changed to “mg/dL”.
P13L16: “mgdL-1” should be changed to “mg/dL”.

The units have been changed to mg/dL in the text and also in the tables.