Author's response to reviews

Title: The impact of ventilator-associated pneumonia on medical utilization of acute stroke and traumatic brain injured patients in a long term: a case-control study

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We appreciated two reviewers’ precious comments on this study. The following are our responses to their comments.

Responses

1. The major issue with this study is that it is unlikely that all of the case patients actually had VAP. The authors use a clinical definition of VAP, which is known to overestimate the frequency of true pneumonia. The addition of microbiological data, although not perfect, would at least strengthen the assumption that pneumonia was likely present. Additionally, VAP is defined as pneumonia that develops AFTER at least 48 hours on the ventilator or within 48 hours AFTER extubation. While the dates of ventilator resources are probably available in the database, the date that pneumonia was first identified is unlikely to be there (only an ICD-9 code indicating that it occurred sometime during admission). As such, it is very possible that many of the ‘cases’ developed pneumonia before ventilation or well after 48 hours and thus were not VAP. This is a large limitation to using billing databases to identify such cases. One potential way around this would be to change the title and corresponding discussion to hospital acquired pneumonia, not VAP.

Reply: Although the Bureau of National Health Insurance (BNHI) of Taiwan did not require health care institutions to record VAP in special method, most health care institutions used ICD-9-CM codes 481, 482, 483 and 486 to record VAP when necessary. For this reason, we used the following steps to define patient who suffered from VAP. First we selected first traumatic brain injury (ICD-9-CM codes 852, 853), acute hemorrhagic stroke (ICD-9-CM codes 430-432), or acute ischemic stroke (ICD-9-CM codes 433-436) patients had ICD-9-CM codes 481, 482, 483 and 486 (define whether had pneumonia or not) during their hospitalization. Second, we selected those patients who admitted to ICUs and used mechanical ventilators
for 48 hours or more among patients selected in previous step. Finally we selected those patients who received endotracheal tube at the emergency room on the day of admission or on the previous day of admission (meaning that the patient directly admitted to ICUs for treatment without staying at ward) from patients selected from previous step. Although the definition is not perfect, it could significantly minimize the likelihood of including patients who suffered hospital acquire pneumonia (HAP) in our study. In addition, previous study indicated that trauma was a risk factor for development of VAP [1], once these patients were admitted to hospitals, the immediate treatment would be intubation, placement of endotracheal tube and sent to ICUs directly for observation. And due to this, we selected patients with acute stroke and traumatic brain injury as research subjects for case cohort. We added the reasons of enrolling study subjects and modified VAP’s definition in page 5; line 17-20; page 6, line 1-9 and page7, line 15-17.

2. Another limitation as denoted by the authors is the lack of mortality data after the index hospitalization. This independent variable will greatly affect resources utilized. The authors speculate that the cases probably had greater mortality, and thus the findings of increased resource utilization may be a conservative estimate. I disagree, as the true attributable mortality of developing VAP is still quite debated.

Reply: The purpose of this study was to understand the subsequent medical utilization of VAP after discharging from index hospitalization. To avoid over-estimation or under-estimation of subsequent medical expenses of deceased patients after acquiring VAP in observation period, this study only analyzed patients who survived for more than two years after their discharge from index hospitalization. And as for the lack of mortality information written on page 15, we removed this sentence to avoid misunderstanding by the readers and reviewers.

3. This is a cost of illness study and should be reported as such in the methodology. Additionally, the study’s perspective should be outlined, as required in all economic analyses.
Reply: The purpose of this study was to show that direct medical expenses caused by VAP were significant even after discharging from index hospitalization. Therefore, all medical expenses discussed in this study were charges (from the BNHI’s perspective which were expenses) of all NHI services, including outpatient department, emergency room and inpatient department, provided by health care institutions. In Taiwan, all health care institutions charged their patients according to a uniform fee schedule published by the BNHI annually. During 2003-2006, there were no significant changes in this fee schedule. In other words, this study is not a cost of illness study. We apologized for the confusing terms of cost, charges, or reimbursement used in previous draft of this manuscript. We corrected all of these terms to expense.

4. This study was conducted over a 4 year period (2003-2006). The value of the dollar may have changed over that time period and early cost estimates should be indexed or normalized to the 2006 dollar.

Reply: We discounted all the expenses into 2006 value by the prime rates published in the 2007 Bulletin of the Central Bank of Taiwan before statistical analyses.

5. It should be made clearer in the title that this was a population of patients admitted for head/brain trauma. This is a very distinct population relative to patients admitted to medical intensive care units or surgical intensive care units for other types of trauma/elective surgery, etc.

Reply: We revised the title according to the reviewer’s opinions. The new title is “The impact of ventilator-associated pneumonia on medical utilization of acute stroke and traumatic brain injured patients in a long term: a case-control study”.

6. I strongly feel the authors should have also considered matching by index hospital. This would remove the observation of different types of hospitals among the groups of patients. Additionally, each hospital has their own ‘methods’ of treating such patients and thus it would not be surprising to see
resource utilization, as well as outcomes differ between institutions. The authors should consider re-matching the population before analysis.

Reply: We followed the reviewers’ opinions and re-matched the studied subjects by age (± 2 years), gender, diagnosis, date of admission (± 1 month), and hospital size. Since most RCWs in Taiwan were operated by regional and district hospitals, a re-matching of studied subjects increased the proportion of subjects treated by medical centers than our first draft of this manuscript. This may result in an underestimate of results of RCW days. Therefore, we excluded the discussion of VAP on RCW days in this version of manuscript.

7. I am confused. If data are de-identified, how can the patients outpatient resources be tracked and linked back to the index hospitalization? Do you mean that PHI is not available, but each patient does have a ‘trackable’ number in the database?

Reply: The NHIRD is an administrative database which is prepared and released to the public annually for research purposes by the National Health Research Institute (NHRI) of Taiwan. Before release, the NHRI used a computer program to de-identify every patient’s ID into another unique code for protecting personal privacy. Since this code is unique and constant, it allows researchers to aggregate all the utilization of an enrollee into a patient profile. Therefore, this study does not need to obtain permission from an Institutional Review Board (IRB). This is why we could aggregate all the subsequent medical utilization of a subject in both cohorts in this study. For more NHIRD details, please refer to http://w3.nhri.org.tw/nhird/index.php.

8. How did you handle patients who developed a second pneumonia on readmission? I am guessing you matched by only the first pneumonia, but did you conduct a double check on these subject (especially those in the earlier part of 2003) to confirm that this was indeed the first pneumonia?

Reply: To avoid the possibility of a subject acquiring pneumonia before admitted to
a hospital caused by acute stroke / traumatic brain injury, we excluded all the patients who had pneumonia one year before admission to assure that no patient developed pneumonia after admission was caused by community acquired pneumonia.

9. For the cost analysis, it appears that expenses for the entire primary hospitalization were counted. This overestimates expenses since none of the patients were admitted with pneumonia. The cost analysis should start on the day of pneumonia identification/diagnosis. Unfortunately, again, that is likely not possible. The authors might consider starting the clock on first date of antibiotics while ventilated.

Reply: The NHIRD does not have data such as the first date of injecting antibiotics when a patient used a ventilator or suffered from pneumonia. To reduce the possibility of including patients with hospital acquired pneumonia in the case cohort, we only selected those patients who were directly sent to ICUs from the emergency department. Besides, such selection of subjects could minimize the possibility of a patient’s medical utilization due to previous poor health condition. (please also see response to comment 1)

10. Along these same lines, the primary purpose of the study is to outline resources AFTER discharge from the index hospital. This gets lost with all of the different expense outcomes that are reported. How is total medical expenses defined?

Reply: In our study, we followed each patient’s medical expenses after they discharge from the index hospitalization by two years. To assist our analyses of the total medical expense, we also included expenses of utilization in the index hospitalization for comparison purpose. In this study, total medical expense of a patient included all the medical expenses in outpatient department, inpatient department and emergency room service which were recorded in the NHIRD.

11. For statistical purposes, it is not clear how the cost data were ‘normalized’. Typically, these data are log-transformed before inclusion in the regression
models.

Reply: In our study, we understood that all variables of medical expenses violated the assumption of normal distribution for regression analysis. So we used robust regression to diminish the impact of outliers during the modeling of the effect of VAP on medical expenses. Therefore, results of this study were presented after log-transformation.

12. What criteria were utilized to add independent variables to the model? Was a univariate analysis performed first to look at differences in expenses (or other resource utilization) among different variables (i.e., gender, type of hospital, etc)?

Reply: The objective of this study was to investigate VAP’s impact on the medical utilization post index hospitalization. Therefore, besides VAP, we also included those variables, which were found by previous studies to have effects on medical utilization as control variables in regression models [1-5]. The main reason of including control variables in regression analyses was to avoid VAP’s effects on utilization were confounded by other variables.

13. I am not familiar with the approach the authors utilize to report the results (the exponent of beta minus 1)? To get a value that resembles the odds ratio of a logistic regression, one would simply log transform beta. This value is often reported as the ‘multiplicative effect’ and can be interpreted similarly to an odds ratio. As such, I am unable to interpret the reported values in Tables 2 and 3.

Reply: Our study used Poisson regression models to analyze medical utilization variables which were discrete and followed Poisson distribution. This study described the results of Poisson regressions by exp (β). The original sentence regarding the results of Poisson regressions by exponent of beta minus 1 was an inappropriate description, we revised these sentences in page 10, lines 16.
Minor Comments

1. Describe why patients were excluded from the analysis.

   Reply: In addition to discussing the medical expenses in index hospitalization caused by VAP, this study also explored the medical utilization within two years after discharging from hospitals. Therefore, any patient who died during hospitalization was excluded from this study. Furthermore, to ensure that pneumonia was developed after admission rather than that admission was caused by recurrent pneumonia, patients who had pneumonia record in the previous year before admission date were also excluded.

2. Define all variables (medical center vs regional hospital vs district hospital).

   Reply: In our study, the variable “hospital level” represents hospital size. It is a term used in Taiwan for hospital accreditation purpose. The term “medical center” is a major teaching hospital with over 500 acute beds, “regional hospital” is a major/minor teaching hospital with over 250 but fewer than 500 acute beds, and “district hospital” is a hospital with less than 250 acute beds. We revised the definition of hospital level to hospital size according to reviewer’s comment in page 9, line17-19.

3. During your results section, you repeat a lot of detail that is already included in the tables. If in the table, no need to list in text.

   Reply: We have revised results section in page 11-12.

4. Were the $$ data costs, charges, or reimbursement? This is never made clear and all three are very different.

   Reply: The term ‘expense’ in this article was defined based on the view of the BNHI since all payments paid to hospitals by the BNHI were charges of hospital as well as expenses of the NHI. Therefore, costs, charges and reimbursement in this article were all modified to ‘expenses’ in uniform to avoid the misunderstanding of the readers.
5. During the last paragraph of conclusion, your first significant finding regarding high VAP incidence among old male patient should be removed. This study was not appropriately designed to identify the prevalence of VAP among patients with certain characteristics, and this is the first time the authors really stress this observation.

Reply: We have removed the sentence.

6. Table 1 is missing footnotes.

Reply: We have added footnotes for Table 1 in page 25.

7. Provide the $R^2$ values for all regression models so the reader can determine the applicability of the model.

Reply: We have added the $R^2$ values of regression models in table 2-3(page 26-27).

References


