Author's response to reviews

Title: Two distinct do-not-resuscitate protocols leaving less to the imagination: an observational study using propensity score matching

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Dear Dr. Sabina Alam,

The Editor of BMC Medicine

We are pleased to submit our revised manuscript entitled: “Two distinct do-not-resuscitate protocols leaving less to the imagination: an observational study using propensity score matching”, for consideration as a research article. We thank editors’ and reviewers’ for their comments and suggestions on the prior version of the manuscript.

In this version of the manuscript, we have done a lot of work to revise our manuscript following the two reviewers’ and the Editor’s comments and suggestions. We also provided a point-to-point response to each reviewer in the following pages.

This revised manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other journals. All authors listed in this revised manuscript have contributed substantially to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted. The authors have no competing interests.

To the best of our knowledge, no conflict of interest exists. This study was partly supported by a research grant from Taiwan National Science Council (NSC 101-2511-S-002-007). This study was approved by the Institutional Review Board in MetroHealth Medical Center (IRB07-01218).

Best Regards,

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Dear Editor,

Thank you again for your comments on our work. Our point-to-point responses to your comments are as follows:

1. This study was approved by the Institutional Research Committee at MetroHealth Medical Center. This information is shown at the end of the “Methods” section.

2. We have tried our best to follow the STROBE guidelines regarding the study design of retrospective cohort study in this revised manuscript. Please let us know if there is anything we need to follow.

3. “Authors’ Contributions” has been revised following the format you provided.

We would like to thank you again for your effort in review of our study. We hope that the current version of this revised manuscript is suitable for publication in this journal.
Dear Dr. Buiting,

Thank you again for your comments on our work. Our point-to-point responses to your comments are as follows:

<Minor Comments (essential)>

1. Thank you for pointing out issues in the “Abstract”. We defined the two different orders in the “Background” section. We explained the three medical costs in the “Methods” section. At the beginning of the “Background” section, we mentioned “DNR patients tend to receive less medical care after the order is written,” in order to be in line with the “Conclusion” section.

2. In response to “Paragraph ‘Medical Care’”: We reviewed the background of the medical care provided to traditional DNR patients, examined what we have in the dataset, and deliberated the appropriateness of each available intervention. Finally we came to the six interventions: pharmacological/electrical cardioversion, vasopressor,
intravenous antibiotics, renal replacement therapy, blood component transfusion, and central venous line placement. Furthermore, the hospital had hospice/palliative care available, but not all DNRCC patients were required to request a hospice/palliative care consultation.

3. In response to “Paragraph ‘Propensity Score Matching’”: We added a paragraph at the beginning of the “Propensity Score Matching” outlining why propensity score matching was used for statistical analysis in this study (highlighted by yellow).

4. In response to your comment, “40 confounding variables; that’s a lot, could the authors please explain this finding a little more?”: Thank you for pointing out this important issue. A confounding variable, being included in a statistical model, is defined as being associated with the dependent variable or the independent variable. When building up a regression model, confounding variables to be included in the model can be identified mainly based on the literature. Although several studies in the literature of DNR have reported many confounding variables when examining the issues associated with DNR, no studies in the literature have reported the issues associated with the two different protocols of DNR. Therefore, we did not have references regarding what confounding variables should be included in the model. We therefore decided to include as many confounding variables as possible in the two
propensity score models (logistic regression models).

5. In response to “Paragraph ‘Main Findings’”: Following your suggestion, in order to highlight the merit of this study at the end of the second paragraph in the “Background” section, we added, “The latter interpretation of medical care provided to DNR patients raised the ethical concern that healthcare professionals may blindly decrease medical care if patients have a DNR order.”

6. In response to “Strengths and Limitations”: We emphasized again that based on our findings, medical care provided to DNR patients is not decreased after an order is written; we also highlighted the difference between our study findings and the findings of other studies in the literature. We decided to delete, “It clearly demonstrated that medical care provided to DNR patients was not decreased after the order was written.” We hope that this omission will clear up any confusion for the reader.

<Minor Comments (discretionary)>

1. In response to “Paragraph ‘Results and discussion’”: We followed your suggestion to further divided the “Results and discussion” section into a “Results” and a
“Discussion” section.

2. In response to your suggestion regarding “Aggressive care”: Thank you for this suggestion. “Aggressive intervention” is a commonly used term in clinical practice. It may be similar to “life-sustaining treatment” or “life-supporting treatment”, but “life-sustaining treatment” and “life-supporting treatment” are not exactly the same as “aggressive intervention”. Therefore, we decided not to use another term in replace of “aggressive intervention.” We hope that you can accept our decision. Or if you would like to suggest any term, we will adopt the term, suggested by you, in place of “aggressive intervention.”

We would like to thank you again for your effort in review of our study. In summary, we are grateful for how your feedback has benefited and advanced our approach to the study. We hope that the current version of this revised manuscript is suitable for publication in this journal.
Dear Dr. Onwuteaka-Philipsen,

Thank you again for your comments on our work. Our point-to-point responses to your comments are as follows:

<Major Compulsory Revisions>

1. Thank you for reminding us of the aim and hypothesis. Accordingly, we re-wrote the aim and hypothesis (please see the end of the last paragraph of the “Background” section). In addition, we also briefly provided the rationale at the beginning of the second paragraph in the “Medical Care” sub-section. We hope that the revisions are in agreement with your suggestion.

2. In the second paragraph of the “Data Collection” sub-section (highlighted by yellow), we added “during their ICU stay” to clearly indicate that the DNRCC and DNRCC-Arrest orders were written during the patients’ ICU stay. Thank you for pointing out this discrepancy.

3. Thank you for your feedback as well as the opportunity for us to further clarify the
confusion. Regarding your concern about using propensity score model rather than using multivariate logistic regression model: Propensity score model is a very good method for group matching and simulating the design of randomized controlled trial in observational study. Even if the model is not ideal (i.e. not good as indicated by the area under ROC curve, and the \( p \) value of Hosmer-Lameshow Goodness-of-fit Test), it can be recognized as “good” if all the confounding variables in the propensity score model are perfectly matched. After the perfect matching by the propensity score model, the association between the independent variable of interest and the dependent variable can be directly examined. This is our case.

Multivariate logistic regression analysis is a good method for examining the association between the independent variable of interest and the dependent variable. However, if we compare 88 DNRCC patients (188 DNRCC-Arrest patients) with 2,051 Non-DNR patients, the multivariate logistic regression model will be undesirable due the huge difference in the sample sizes. This is why we chose propensity score matching rather than multivariate logistic regression analysis. We also presented the merits of using propensity score matching in this manuscript. Please see the first paragraph of the “Propensity Score Matching” sub-section (highlighted by yellow).

If we only used one group before and after study to examine the six aggressive
interventions and three comfort care measures, we would only know the change of medical care associated with the initiation of DNRCC/DNRCC-Arrest, and we would never know whether DNRCC/DNRCC-Arrest patients received similar level of medical care as compared to Non-DNR patients. We believe that this issue is also very important, and must be examined in this study. We hope that you accept our explanation.

Please do not hesitate to let us know if you still have any concern regarding the study design.

<Minor Essential Revision>

1. Thank you for inquiring about the clinical practice for DNRCC patients. If a patient has a DNRCC order written during the ICU stay, he/she may receive the following: (1) life-extending aggressive interventions will be gradually withdrawn; (2) comfort care measures, such as hospice/palliative care consultation, the use of morphine and so on, will be gradually added on based on the discussion between health care professionals and patients/family members; (3) the patient will be transferred to another non-ICU bed for further care.
<Discretionary Revision>

1. At the end of the first paragraph of the “Results” section, we added, “A total of 104 patients, who changed their order either from DNRCC to DNRCC-Arrest, or from DNRCC-Arrest to DNRCC, were excluded from this study.”

We would like to thank you again for your effort in review of our study. In summary, we are grateful for how your feedback has benefited and advanced our approach to the study. We hope that the current version of this revised manuscript is suitable for publication in this journal.