PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of do-not-resuscitate orders on patients with sepsis in the medical intensive care unit: A retrospective, observational and propensity score-matched study in a tertiary referral hospital
AUTHORS	Chang, Ya-Chun; Fang, Ying-Tang; Chen, Hung-Cheng; Lin, Chiung-Yu; Chang, Yu-Ping; Chen, Yu-Mu; Huang, Chi-Han; Huang, Kuo-Tung; Chang, Huang-Chih; Su, Mao-Chang; Wang, Yi-Hsi; Wang, Chin-Chou; Lin, Meng-Chih; Fang, Wen-Feng

VERSION 1 - REVIEW

REVIEWER	zhongheng zhang China
REVIEW RETURNED	18-Jan-2019

GENERAL COMMENTS	The authors addressed an interesting clinical question related to DNR in the ICU, since this is common in ICU ward. I have several concerns with this study. 1. In the introduction, the authors stated there are few studies in sepsis; however, to our knowledge there is such studies recently published (Intensive Care Med. 2017 May;43(5):715-717. doi: 10.1007/s00134-017-4690-7.). Thus, the authors need to clarify how can the preseng study add to the existing literature. the goal and hypothesis of the study should be stated in the INTRODUCTION. 2. what is the definition for sepsis as there are several versions of such definitions. 3. suggest to add a reference (Ann Transl Med. 2016 Mar;4(5):91. doi: 10.21037/atm.2016.02.11.) after the sentence " Univariate analysis was used to identify significant risk factors associated with DNR in this study. " to clarify how univariate analysis was performed. how did you hand non-normal data and missing values? 4. in the method section, the authors need to clarify how balance diagnostics were performed after propensity score matching (Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med 2019;7(1):16. doi: 10.21037/atm.2018.12.10). sometimes the caliper should be used if the two groups have little in common support. furthermore, assessing balance after PSM can be misleading by only using bivariate variable (see above reference).

REVIEWER	Anish K. Agarwal University of Pennsylvania Department of Emergency Medicine, Philadelphia, PA, USA
REVIEW RETURNED	24-Feb-2019

GENERAL COMMENTS	Thank you to the authors for putting together an interesting study design and question. I have a few questions for the group that should be addressed. 1) Did patients come from ED to MICU or from floor to MICU, or transfer. Please describe the breakdown of where patient came from, if any came to ICU with a DNR already etc 2) Did DNR include intubation, blood transfusion, or was it confined to CPR? 3) The mortality rate seems high in general – is this consistent with the hospital or local environment? 4) I would like to see a breakdown of cause of sepsis (i.e. pulmonary, skin, intra-abdominal, etc). 5) Also, would like to see Interventions completed? Central line, pressors, emergent HD, surgery for all groups. Did DNR groups get les ancillary care? 6) I'm not sure you can say that a DNR predicts outcomes for patients with sepsis (Line 40-43 ,page 8) but rather that patients with a DNR may have a different course overall within the hospital. 7) How does palliative care affect care in this hospital? Is there palliative care available? 8) Would like to hear/see more about discussion around DNR and who was making the DNR decision in this study (patient vs. family vs. proxy)

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: zhongheng zhang

Institution and Country: China

Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
The authors addressed an interesting clinical question related to DNR in the ICU, since this is common in ICU ward. I have several concerns with this study.
1. In the introduction, the authors stated there are few studies in sepsis; however, to our knowledge there is such studies recently published (Intensive Care Med. 2017 May;43(5):715-717. doi: 10.1007/s00134-017-4690-7.). Thus, the authors need to clarify how can the present study add to the existing literature. the goal and hypothesis of the study should be stated in the INTRODUCTION.

➔ We thank the reviewer. We revised this in the Introduction section as follows: "Few studies mentioned the influence of DNR orders in patients with sepsis, a life-threatening condition with critically rapid progression. (14) We chose to investigate the impact of DNR orders in patients with sepsis admitted to intensive care units. We thought to provide more objective data to help patient or their family make the DNR decision."

2. what is the definition for sepsis as there are several versions of such definitions.

➔ We thank the reviewer. We revised this in the Definitions section as follows: “According to “The Third International Consensus Definitions for Sepsis and Septic Shock”, sepsis was defined as life-threatening organ dysfunction due to a disproportionate host response to infection.(16-18).”

3. suggest to add a reference (Ann Transl Med. 2016 Mar;4(5):91. doi: 10.21037/atm.2016.02.11.) after the sentence " Univariate analysis was used to identify significant risk factors associated with DNR in this study. " to clarify how univariate analysis was performed. how did you hand non-normal data and missing values?

➔ We thank the reviewer. We revised this in the Statistical calculations section as follows: “…Univariate analysis was used to identify significant risk factors associated with DNR in this study. (25)…”

➔ We also revised in Table 1 as follows: “*We used Mann-Whitney U test for non-normal data before matching, and we used Wilcoxon signed-rank test for hand non-normal data after matching.”

4. in the method section, the authors need to clarify how balance diagnostics were performed after propensity score matching (Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med 2019;7(1):16. doi: 10.21037/atm.2018.12.10). sometimes the caliper should be used if the two groups have little in common support. furthermore, assessing balance after PSM can be misleading by only using bivariate variable (see above reference).

➔ We thank the reviewer. We revised this in the Statistical calculations section under the method section as follows: “ …We used Greedy methods with a 0.25×SD caliper width via using NCSS 12 software. The standardized mean difference (SMD) of propensity score was -0.09%. (26)…After propensity scoring matching, we used Wilcoxon signed-rank test for further evaluation. All p-value were > 0.05. (26)…”

Reviewer: 2
Reviewer Name: Anish K. Agarwal

Institution and Country: University of Pennsylvania Department of Emergency Medicine, Philadelphia, PA, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you to the authors for putting together an interesting study design and question. I have a few questions for the group that should be addressed.
1) Did patients come from ED to MICU or from floor to MICU, or transfer. Please describe the breakdown of where patient came from, if any came to ICU with a DNR already etc

➔ We thank the reviewer. We revised the sentences in the Patient characteristics and findings section as follows: “Most of patients came from emergent department without a signed DNR in place. Most DNR orders were signed in medical ICUs. The mortality rate seems high in general, which is consistent with the hospital environment, a 2,700-bed tertiary referral hospital. Sites of suspected infection were listed in Table 2.”

2) Did DNR include intubation, blood transfusion, or was it confined to CPR?

➔ We thank the reviewer. We revised this in the Definitions section as follows: “DNR means "Do Not Resuscitate." A DNR does not affect any treatment other than cardiopulmonary resuscitation and endotracheal tube intubation. If signed after endotracheal tube intubation and cardiopulmonary resuscitation, we keep the patient on ventilator support if withdrawing necessary support is not requested. DNR orders are written instructions from a physician telling health care providers not to perform further cardiopulmonary resuscitation. The doctor writes the order only after talking about it with the patient (if possible), the proxy, or the patient's family.(15) DNR in our study allowed for blood transfusion, vasopressors use, and emergent haemodialysis.”

3) The mortality rate seems high in general – is this consistent with the hospital or local environment?

➔ We thank the reviewer. We revised it in the Patient characteristics and findings section as follows: “…Most of patients came from emergent department without a signed DNR in place. Most DNR orders were signed in medical ICUs. The mortality rate seems high in general, which is consistent with the hospital environment, a 2,700-bed tertiary referral hospital. Sites of suspected infection were listed in Table 2.”

4) I would like to see a breakdown of cause of sepsis (i.e. pulmonary, skin, intra-abdominal, etc).

➔ We thank the reviewer. We revised this as “Table 2”

Site of suspected infection (n = 717)	n (%)
Pneumonia	464 (64.7)
Intra-abdominal infection	54 (7.5)
Urinary tract infection	153 (21.3)
Bacteraemia	53 (7.4)
Skin or soft tissue infection	37 (5.2)
Meningitis	4 (0.6)
Dengue	15 (2.1)
Influenza	4 (0.6)
Infective endocarditis	2 (0.3)
Unidentified	64 (8.9)

5) Also, would like to see Interventions completed? Central line, pressors, emergent HD, surgery for all groups. Did DNR groups get less ancillary care?

➔ We thank the reviewer. We revised it in the Discussion section as follows: “DNR groups did not get less ancillary cares, such as central line, vasopressors, blood transfusion, emergent haemodialysis or surgery.…”

6) I’m not sure you can say that a DNR predicts outcomes for patients with sepsis (Line 40-43 ,page 8) but rather that patients with a DNR may have a different course overall within the hospital.

➔ We thank the reviewer. We revised it in the Discussion section as follows: “This finding suggests that patients with a DNR may have a different course overall within the hospital.”

7) How does palliative care affect care in this hospital? Is there palliative care available?

➔ We thank the reviewer. We revised it in the Discussion section as follows: “….In our hospital, palliative care was available. If patient, the proxy or the patient’s family requested palliative care, we would consult palliative team for further evaluation. If patient’s condition was suitable for palliative care and patient, the proxy or the patient’s family agreed, we would start palliative care for the patient.”

8) Would like to hear/see more about discussion around DNR and who was making the DNR decision in this study (patient vs. family vs. proxy)

➔ We thank the reviewer. We revised it in the Discussion section as follows: “…DNR orders are written instructions from a physician telling health care providers not to perform further cardiopulmonary resuscitation. The doctor writes the order only after talking about it with the patient (if possible), the proxy, or the patient's family….”

VERSION 2 – REVIEW

REVIEWER	Z zhang zhejiang university
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	previous comments have been well addressed in this round of revision.

REVIEWER	Anish K. Agarwal University of Pennsylvania, Department of Emergency Medicine, Philadelphia PA USA
REVIEW RETURNED	18-Apr-2019

GENERAL COMMENTS	This revision adequately addresses my concerns.