

MATTERS ARISING

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# Association between arterial oxygen partial pressure and mortality in sepsis

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To the editor,

The appropriate arterial oxygen partial pressure (PaO<sub>2</sub>) in sepsis patients has been investigated in dozens of studies. However, no consensus has been reached. In a recent study [1], Dr. Hyun et al. investigated the association between PaO<sub>2</sub> and mortality in critically ill sepsis patients. Data on PaO<sub>2</sub> of 4147 sepsis patients from the Korea Sepsis Alliance Registry (KSA) during the first three days was extracted, and patients were divided into conservative PaO<sub>2</sub> group (<80mmHg) and liberal PaO<sub>2</sub> group (≥80mmHg). Statistical methods, including propensity score matching, mixed linear model, and competitive risk models, were used to explore potential causal relationships. The results showed higher PaO<sub>2</sub> (≥80 mmHg) during the first three ICU days was associated with a lower 28-day mortality than conservative PaO<sub>2</sub>. Several issues should be noted when interpreting these findings.

First, dividing the entire cohort into groups based on the cut-off value of one continuous variable is a common strategy in observational studies. In the current research, a cut-off value of 80 mmHg of PaO<sub>2</sub> was used. However, the results may be biased when the correlation between PaO<sub>2</sub> and mortality is non-linear. For instance, previous studies [2, 3] have pointed out that there may be a U-shaped correlation between PaO<sub>2</sub> and death, which means either extremely high or low PaO<sub>2</sub> may be

associated with increased mortality compared to normal PaO<sub>2</sub>. In this case, whether there is a difference between the conservative and liberal PaO<sub>2</sub> groups can be significantly affected by the cut-off value. For instance, in the current study, the restrictive cubic spline between PaO<sub>2</sub> and mortality showed that the PaO<sub>2</sub> with the lowest mortality possibility was around 100mmHg. Thus, when using 80mmHg as the cut-off value, the comparison between conservative (PaO<sub>2min</sub><80mmHg) and liberal (PaO<sub>2min</sub>≥80mmHg) PaO<sub>2</sub> groups was actually comparing the low PaO<sub>2</sub> group with the normal PaO<sub>2</sub> group combined with the high PaO<sub>2</sub> group (<80mmHg vs. (80 – 110mmHg + >110mmHg)), which thus lead to a potentially biased result that liberal PaO<sub>2</sub> was associated with low mortality rate. Similarly, the difference in mortality rate between the two groups may also be affected by the proportion of patients with high PaO<sub>2</sub>. In the current study, we noted that the PaO<sub>2</sub> was relatively low even in the liberal PaO<sub>2</sub> group (median values were 107, 110, and 106 during three days). In the case of a low proportion of patients with high PaO<sub>2</sub>, using 80mmHg as the cut-off value may actually be the comparison between the low PaO<sub>2</sub> group and the normal PaO<sub>2</sub> group, which may also be one factor for the inconsistent results of previous studies.

Second, there may be some statistical issues that also need to be noted. For instance, we note that a total of 4147 patients were included. However, in the multivariable COX regression analysis, only patients (n=2422) matched in the propensity score matching (PSM) were included. Theoretically, implementing regression analysis only in the matched cohorts may reduce the variability of the cohort, which may result in a biased result. For instance, the PaO<sub>2</sub> in the matched cohorts was

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relatively low (median values were 107, 110, and 106 during three days). Thus, whether higher PaO<sub>2</sub> (such as PaO<sub>2</sub>>180mmHg) was associated with poor prognosis cannot be inferred. Another minor issue is that the author used the 5th percentiles of PaO<sub>2</sub> as the reference point in restricted cubic spline analysis. This seems a little inappropriate as the selected cut-off point of PaO<sub>2</sub> was around 100 mmHg.

Finally, we thank Dr. Hyun et al. for their great work, and we hope our opinions will help interpret these findings.

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#### Author contributions

Dr. Xinyuan Ding raised the clinical issue and Dr. Shangzhong Chen wrote the letter. All authors have reviewed and approved the letter. Dr. Xinyuan Ding raised the clinical issue and Dr. Shangzhong Chen wrote the letter. All authors have reviewed and approved the letter.

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#### Declarations

##### Ethics approval and consent to participate

Not applicable.

##### Consent for publication

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##### Competing interests

The authors declare no competing interests.

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