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The effect of diabetes on the risk and mortality of acute lung injury/acute respiratory distress syndrome
A meta-analysis

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Abstract
Background: The role of pre-existing diabetes in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is still controversial. This systematic review and meta-analysis of observational studies aimed to evaluate the effect of diabetes on the risk and mortality of ALI/ARDS.

Methods: A comprehensive literature search was performed in PubMed, Scopus, Cochrane Central Register of Controlled Trails and Web of Science for their inception to September 2018. Summary risk estimates were calculated with a DerSimonian and Laird random-effects model. Heterogeneity was evaluated using Cochran chi-square test and the I^2 statistic.

Results: Ultimately, 14 studies with a total of 6613 ALI/ARDS cases were included. The risk of ALI/ARDS was not significantly reduced in diabetes patients (OR 0.82, 95% CI 0.57–1.18, $P = .283$), with obvious heterogeneity across studies ($I^2 = 72.5\%$, $P < .001$). Further analyses in the meta-analysis also showed no statistically significant associations between pre-existing diabetes and in-hospital mortality (OR 0.79, 95% CI 0.51–1.21, $P = .282$) or 60-day mortality of ALI/ARDS (OR 0.91, 95% CI 0.75–1.11, $P = .352$).

Conclusion: This systematic review and meta-analysis of observational studies indicates that pre-existing diabetes have no effect on the risk and mortality of ALI/ARDS.

Abbreviations: CI = confidence interval, ICU = intensive care unit, RR = relative risk, SIRS = systemic inflammatory response syndrome.

Keywords: ALI, ARDS, diabetes, meta-analysis

1. Introduction

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, and inflammatory form of lung injury, characterized by increased pulmonary vascular permeability, and loss of aerated tissue, increased work of breathing and impaired gas exchange.[1] The hallmarks for ARDS are refractory hypoxemia

and bilateral radiographic opacities.[2] ARDS is associated with significantly increased morbidity, mortality and usage of critical care resources.[3] Although numerous interventions, including protective ventilation strategies, prone positioning, and neuromuscular blockade,[4] are proposed to be of potential benefit, mortality of ARDS still remains high. A 2017 systematic review assessing the mortality of ARDS over time indicated that since 2010, the overall rates of in-hospital, ICU, and 28/30-day and 60-day mortality were 45, 38, 30, and 32%, respectively.[5] Thus, risk factors for the development of ARDS and prognostic predictors of ARDS may exert a role in diagnosis, and therapeutic decision-making in patients with suspected ARDS.

Risk factors for the development of ARDS include advanced age and clinical factors such as sepsis, pancreatitis, trauma, pneumonia, and aspiration.[6] The influence of diabetes on the risk and outcomes of ARDS in the critically ill patients is uncertain. Some studies,[7,8] including a previous meta-analysis,[9] have reported that pre-existing diabetes was associated with a decreased risk of ARDS in critically ill adult patients, whereas one study[10] suggested that diabetes was associated with an increased risk of ARDS in postsurgical patients. However, several other studies[11,12] found that diabetes was not associated with development of ARDS in ICU population.

Overall, the evidence on the association of pre-existing diabetes with the risk and mortality of ARDS remains conflicting and inconsistent. Hence, we performed this systematic review and meta-analysis of all eligible observational studies of the association between diabetes and ARDS.

2. Methods

2.1. Search strategies

A comprehensive literature search was performed in PubMed, Scopus, Cochrane Central Register of Controlled Trails and Web of Science for their inception to September 2018 using the following keywords "diabetic" or "diabetes" and "ARDS" or "ALI" or "acute respiratory distress syndrome" or "acute lung injury", without restrictions on publication type or language. The cited references listed in relevant and reviews were also reviewed to identify any additional eligible studies and to minimize the potential publication bias. This is a systematic review and meta-analysis, which was based on previous published studies and did not have original data. Therefore, no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

Eligible studies were identified according to the following criteria:

1. the study population was critically ill adult patients with a high risk of ALI/ARDS;
2. the exposure was diabetes;
3. the outcome was risk or outcome of ALI/ARDS; and
4. enough data were provided for calculation of risk estimates.

Studies performed in animals or cells, reviews or case reports were removed. The primary outcome was the risk of ALI/ARDS. Secondary outcomes were in-hospital and 60-day mortality of ALI/ARDS.

2.3. Data extraction

Two independent reviewers (MJ and MC) extracted the desired data from each included study with a pre-defined standard form,

which included information on first author, publication year, study design, geographical region, participants and population, sample size, assessments of disease, outcome measures, and effect size estimates. Discrepancies between the 2 reviewers were resolved by consulting a third reviewer.

2.4. Assessment of study quality

The quality of the studies was independently assessed by two reviewers (MJ and MC) with the Newcastle-Ottawa Scale (NOS). High quality was defined as a grade of ≥7. Discrepancies were resolved through discussion and consensus.

2.5. Statistical analysis

Effect size estimates were extracted as adjusted risk estimates, crude risk estimates, or estimates using raw data. We used the most fully-adjusted estimates in preference. Heterogeneity was evaluated using Cochran chi-square test and the I^2 statistic.[13] A DerSimonian and Laird random-effects model was used for summary analysis.[14] Sensitivity analysis was performed for the primary outcome by omitting each study in turn to assess the robustness of the pooled results. Publication bias was assessed by Begg test[15] and Egger test.[16] A P value $< .05$ was considered statistically significant. All statistical analyses were performed with STATA, version 10.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Study search and characteristics

Details of the study selection procedure are shown in Figure 1. Ultimately, a total of 14 studies[7,8,10–12,17–25] were included in
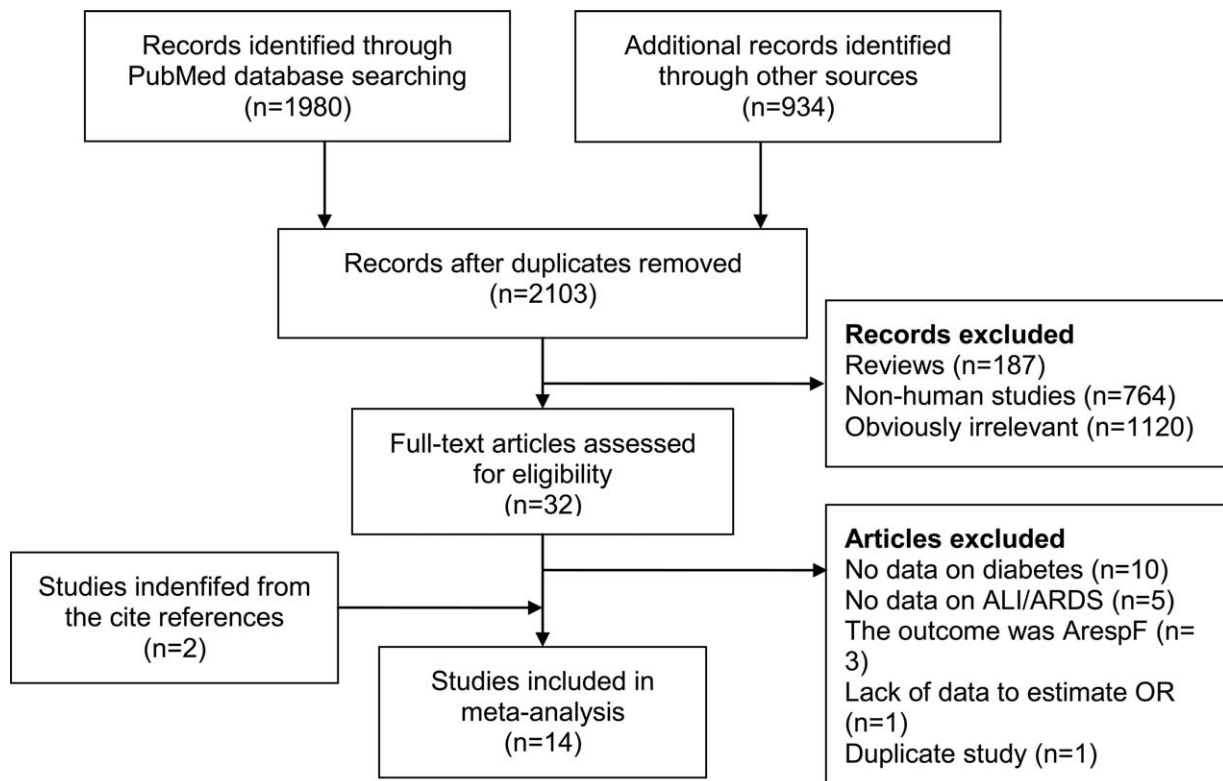

Figure 1. Flow of literature search and selection.

Table 1

Main characteristics of the included studies.

Author	Year	Region	Design	Study population	Sample size	ALI/ARDS cases No.	Outcome NOS
Moss	2000	USA	P	ICU patients with septic shock	113 patients in 4 centers	46	ALI/ARDS risk
Gong	2005	USA	P	ICU patients with > 1 predisposing ARDS condition	1795 patients in 2 centers	221	ALI/ARDS risk/mortality
Iscimen	2008	USA	P	ICU patients with septic shock	160 patients in 1 center	71	ALI/ARDS risk
Trillo-Alvarez	2011	USA	R	ICU patients with > 2 predisposing ARDS condition	409 patients in 1 center	68	ALI/ARDS risk
Gajic	2011	USA	P	ICU patients with > 3 predisposing ARDS condition	5584 patients in 22 centers	377	ALI/ARDS risk
Kor	2012	USA	R	Patients mechanically ventilated during elective surgery	4366 patients in 1 center	113	ALI/ARDS risk
Deng	2012	China	R	ICU patients with military tuberculosis	466 patients in 4 centers	85	ALI/ARDS risk
Koh	2012	Netherlands	R	ICU patients	2013 patients in 1 center	720	ALI/ARDS risk
Yu	2013	USA	P	ICU patients with > 1 predisposing ARDS condition	3860 patients in 2 centers	954	ALI/ARDS risk/mortality
Singla	2014	USA	R	ICU patients	249 ARDS patients	249	ALI/ARDS mortality
Soubani	2015	USA	R	ARDS Network	2914 ARDS patients	2,914	ALI/ARDS mortality
Luo	2017	USA	P	ICU patients	2952 patients in 1 center	707	ALI/ARDS mortality
Luo	2017	China	R	ICU patients with severe pneumonia	157 patients in 1 center	43	ALI/ARDS risk
Yang	2018	USA	R	ICU patients with cirrhosis	559 patients in 1 center	45	ALI/ARDS risk

ALI = acute lung injury, ARDS = acute respiratory distress syndrome, No. = number, NOS = Newcastle-Ottawa Scale, P = prospective, R = retrospective.
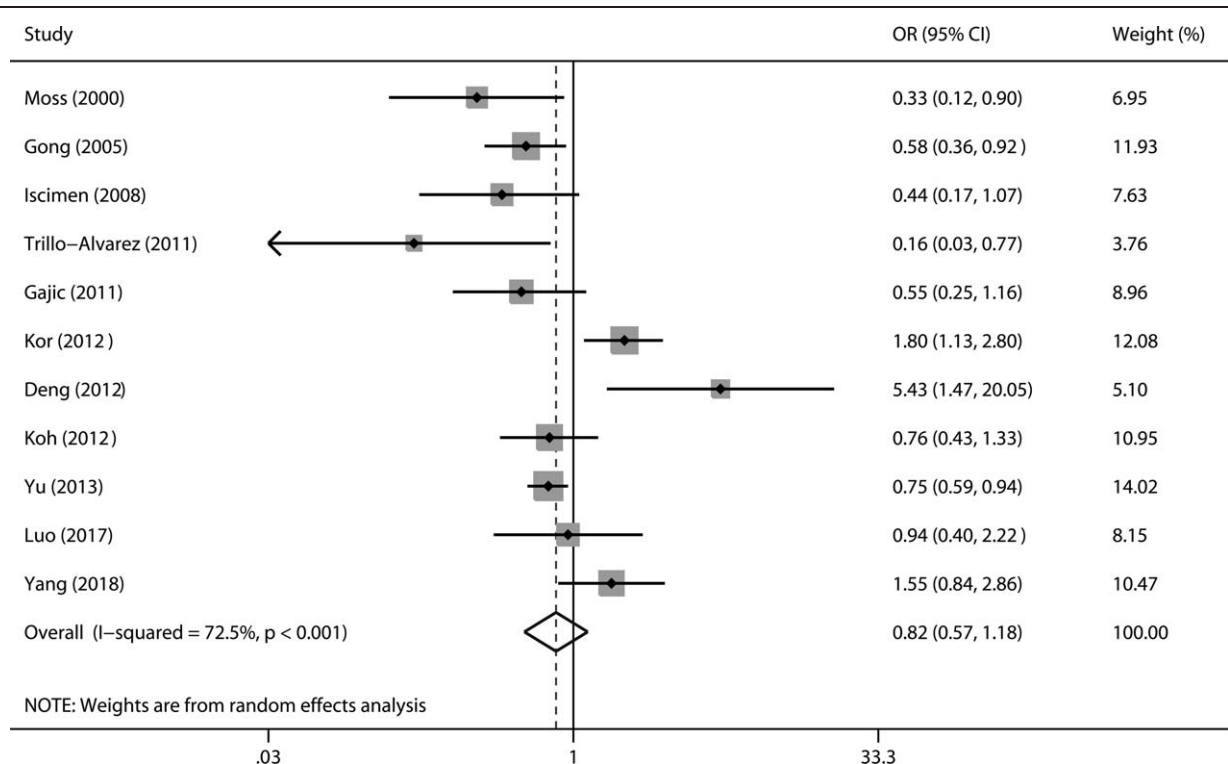
this meta-analysis. All of the included studies were published as peer-reviewed articles and were in English. A total of 6613 ALI/ARDS patients were included in these studies. All included studies defined ALI/ARDS in accordance with the American-European Consensus Conference definition. The quality of each included study was summarized in Supplementary Table S1, http://links.lww.com/MD/C907 with an average score of 7.86. Eleven studies reported ALI/ARDS risk, 2 reported in-hospital mortality, and 3 reported 60-day mortality as outcome of interest. Main study characteristics are presented in Table 1.

### 3.2. Diabetes and the risk of ALI/ARDS

Eleven studies were eligible for the ALI/ARDS risk analysis. The incidence of newly developed ALI/ARDS (OR 0.82, 95% CI 0.57–1.18, $P = .283$) (Fig. 2) was not significantly reduced in diabetes patients, with obvious heterogeneity across studies ($I^2 = 72.5\%$, $P < .001$).

3.3. Diabetes and 60-day mortality of ALI/ARDS

Three studies reported data on 60-day mortality. The pooled OR in a random model (OR 0.91, 95% CI 0.75–1.11, $P = .352$)

Study		OR (95% CI)	Weight (%)
Moss (2000)		0.33 (0.12, 0.90)	6.95
Gong (2005)		0.58 (0.36, 0.92)	11.93
Iscimen (2008)		0.44 (0.17, 1.07)	7.63
Trillo–Alvarez (2011)		0.16 (0.03, 0.77)	3.76
Gajic (2011)		0.55 (0.25, 1.16)	8.96
Kor (2012)		1.80 (1.13, 2.80)	12.08
Deng (2012)		5.43 (1.47, 20.05)	5.10
Koh (2012)		0.76 (0.43, 1.33)	10.95
Yu (2013)		0.75 (0.59, 0.94)	14.02
Luo (2017)		0.94 (0.40, 2.22)	8.15
Yang (2018)		1.55 (0.84, 2.86)	10.47
Overall (I–squared = 72.5%, p < 0.001)		0.82 (0.57, 1.18)	100.00

NOTE: Weights are from random effects analysis

.03   1   33.3

Figure 2. Forest plot showing risk estimates from included studies estimating the association between diabetes and ALI/ARDS risk. ALI/ARDS = acute lung injury/acute respiratory distress syndrome.
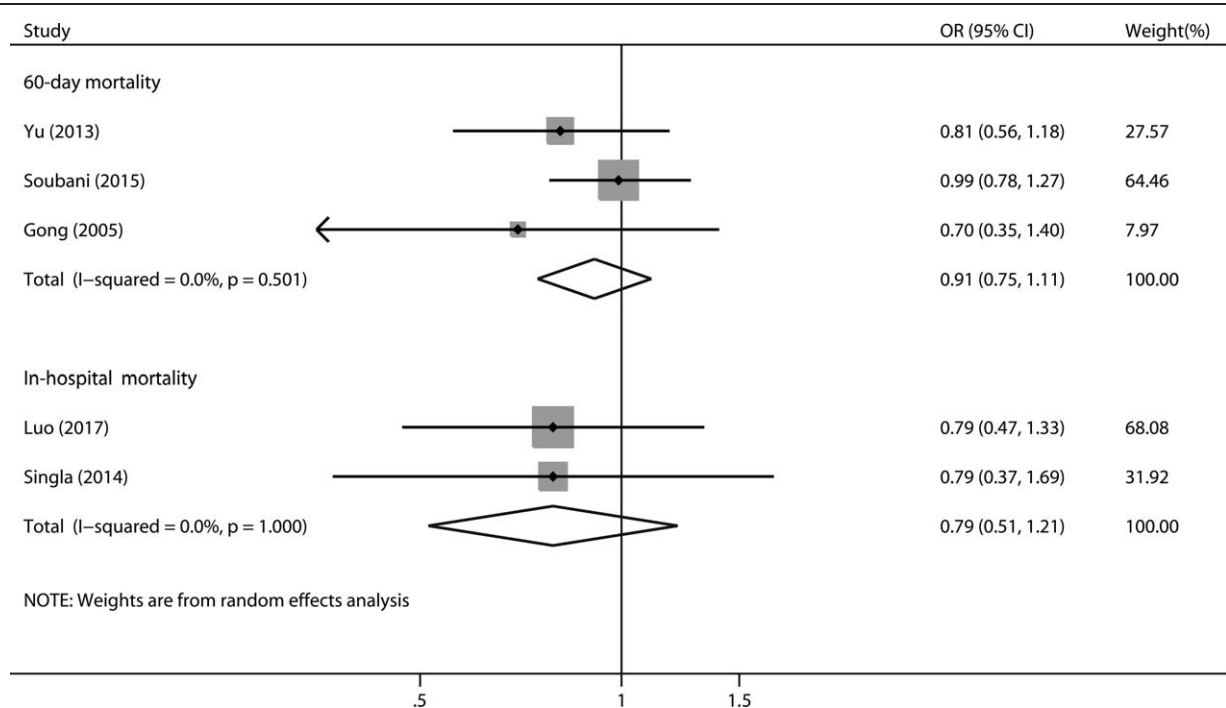
Figure 3. Forest plot showing risk estimates from included studies estimating the association between diabetes and 60-day or in-hospital mortality in ALI/ARDS patients. ALI/ARDS = acute lung injury/acute respiratory distress syndrome.

indicated no association between pre-existing diabetes and 60-day mortality of ALI/ARDS, with low heterogeneity among the results ($I^2 = 0.0\%$, $P = .501$) (Fig. 3).

### 3.4. Diabetes and in-hospital mortality of ALI/ARDS

Further analyses in the meta-analysis based on 2 eligible studies showed no statistically significant association between pre-existing diabetes and in-hospital mortality of ALI/ARDS (OR 0.79, 95% CI 0.51–1.21, $P = .282$), without obvious heterogeneity across the studies ($I^2 = 0.0\%$, $P = 1.000$) (Fig. 3).

### 3.5. Sensitivity analysis and publication bias analysis

Sensitivity analysis was performed for the risk of ALI/ARDS by excluding each study in turn and the ORs (95% CIs) ranged from to 0.74 (0.52–1.04) to 0.88 (0.61–1.27) (Fig. 4). No significant publication bias was detected by Egger test ($P = .624$) or Begg test (Fig. 5, $P = .350$).

4. Discussion

This article reports a large meta-analysis of observational studies aimed to evaluate the association between diabetes and the risk and mortality of ALI/ARDS among adults. We found that pre-existing diabetes was not associated with development and mortality of ALI/ARDS in the critically ill patients.
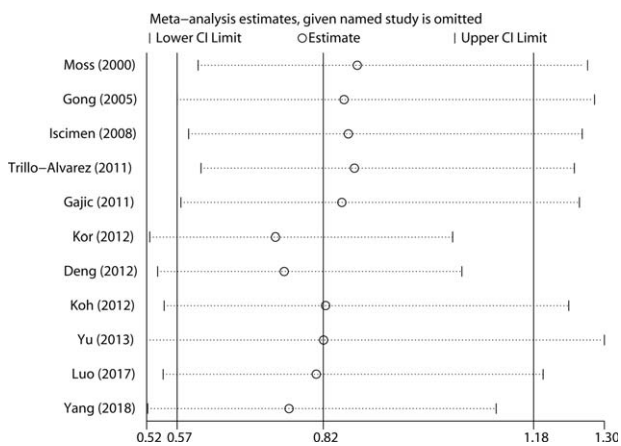
Figure 4. Sensitivity analysis was performed by excluding each study in turn and then recalculating the pooled estimate to determine the influence of each study.
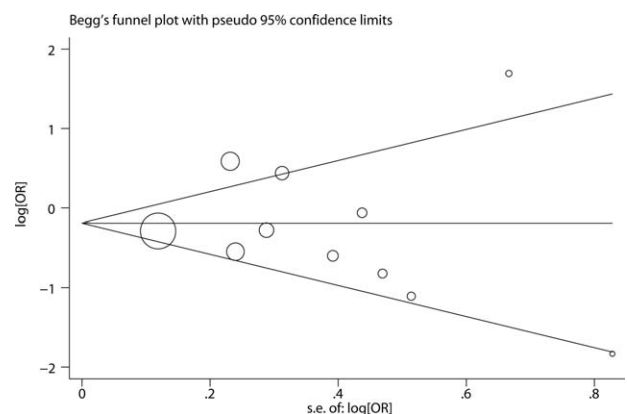
Figure 5. Funnel plot for the risk of ALI/ARDS. ALI/ARDS = acute lung injury/ acute respiratory distress syndrome.

A previous systematic review and meta-analysis published in 2014[9] has drawn attention to the potential association of diabetes with the risk of ALI/ARDS in ICU patients. It included seven studies and found a decreased risk of ALI/ARDS in critically ill adult patients with pre-existing diabetes. By contrast, our study included the more recent published studies and thereby increased the overall sample size; potentially improved statistical power. Furthermore, we also evaluated the impact of pre-existing diabetes on the mortality of ALI/ARDS patients, which was firstly assessed by a comprehensive meta-analysis.

Diabetes may play an important role in the immune system and inflammatory response.[26] It was reported that patients with diabetes had reduced inflammatory response, which was associated with attenuation of cytokine release and reduction of neutrophil migration.[27] As a consequence, a blunted inflammatory response might help reduce rate of ALI/ARDS in the critically ill patients. However, up to now, combined with our study, there is no clear evidence on the association between diabetes and ALI/ARDS in clinical studies.

Our study has several limitations that need to be discussed. First, there was significant heterogeneity in risk estimate for development of ALI/ARDS and a lack of risk adjustment for many important variables. Second, although no significant publication bias was detected by Egger or Begg tests, unpublished studies or conference abstracts were not included, which might lead to some bias. Third, the critically ill patients were really a heterogeneous population. Most included studies defined it as ICU patients with various ALI/ARDS predisposing conditions, such as sepsis, pneumonia, pancreatitis, aspiration, trauma, or high-risk surgery. This might introduce heterogeneity and limited the general application of our findings. Fourth, as the enrolled studies of our manuscript were observational study, the evidence of level in this meta-analysis was relatively low. Finally, regarding mortality analysis, only 3 and 2 studies reported the 60-day and in-hospital mortality, respectively. In addition, we were not able to evaluate the effect of the ALI/ARDS severity on mortality outcomes.

This study also has some strengthens. We performed a comprehensive search of the potential relevant studies in main medical databases with a reasonable search strategy. In addition, we also checked the reference lists from the related articles and reviews. It is, therefore, likely that our findings are representative and generalizable. In addition, we only included cohort studies and conducted various analyses, such as sensitivity analysis and publication bias analysis.

5. Conclusion

The present meta-analysis based on eligible observational studies indicated that pre-existing diabetes was not associated with the risk and mortality of ALI/ARDS in the critically ill patients.

Author contributions

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Supervision: Ning Zhang.
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Visualization: Mingxia Ji, Mengyan Chen, Ning Zhang.
Writing – original draft: Mingxia Ji, Mengyan Chen.
Writing – review & editing: Ning Zhang.

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