

Comparison of severity index and plasma paraquat concentration for predicting survival after paraquat poisoning

A meta-analysis

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Abstract

Background: Severity index and plasma paraquat (PQ) concentration can predict the prognosis of patients with PQ poisoning. However, the better parameter is yet to be systematically investigated and determined. Thus, we conduct this systematic review and meta-analysis to investigate the prognostic value of severity index and plasma PQ concentration in patients with PQ poisoning.

Methods: We searched PubMed, Embase, Web of Science, ScienceDirect, and Cochrane Library to identify all relevant papers that were published up to March 2019. All diagnostic studies that compared severity index and plasma PQ concentration to predict mortality in patients with PQ poisoning were enrolled in this meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) for individual trials were pooled using a random-effect model. We also aggregated heterogeneity testing, sensitivity analysis, and publication bias analysis.

Results: Ultimately, seven studies involving 821 patients were included. The pooled OR with a 95% CI of severity index was 24.12 (95% CI: 9.34–62.34, $P < .001$), with an area under the curve of 0.88 (95% CI: 0.85–0.90), sensitivity of 0.84 (95% CI: 0.74–0.91), and specificity of 0.81 (95% CI: 0.75–0.87). Meanwhile, the pooled OR with 95% CI of plasma PQ concentration was 34.39 (95% CI: 14.69–80.56, $P < .001$), with an area under the curve of 0.94 (95% CI: 0.91–0.96), sensitivity of 0.86 (95% CI: 0.75–0.93), and specificity of 0.89 (95% CI: 0.76–0.95). Sensitivity analysis demonstrated the stability of the results of our meta-analysis. No significant publication bias was observed in this meta-analysis.

Conclusion: Overall, this study indicated that severity index and plasma PQ concentration have relatively high-prognostic value in patients with PQ poisoning, and that the sensitivity and specificity of plasma PQ concentration are superior to those of severity index.

Abbreviations: CI = confidence interval, OR = odds ratio, PQ = paraquat, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2 tool.

Keywords: meta-analysis, paraquat, prediction, severity index, survival

1. Introduction

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride; PQ) is a widely used nonselective herbicide that is commonly used in

agriculture. PQ ingestion occurs frequently in the agricultural countryside, either accidentally or as a suicide attempt. PQ is extremely toxic to humans and animals, and PQ poisoning results in multiple organ dysfunctions and rapid onset of death within days of ingestion due to excessive production of reactive oxygen species and the subsequent fulminant inflammatory response.^[1] Therapy has concentrated on reducing PQ absorption from the gastrointestinal tract, increasing its elimination, and minimizing its toxicity; approaches include gastric lavage, activated catharsis, fluid infusion, absorption, charcoal hemoperfusion, and immunosuppressive therapy.^[2–4] At present, no special antidote is available to inhibit toxicity, and the survival of PQ poisoning is 20% to 50%.^[5–7]

Establishing a quick, simple, and accurate assessment of the prognosis is critical. The early identification of inevitable deaths can help spare hopeless or minimally poisoned patients from needless aggressive treatment. Moreover, assessment of the clinical effect of any new therapy should be based on poisoned severity. Plasma PQ concentration and the severity index of PQ poisoning (SIPP), calculated by multiplying the time since the PQ ingestion (hour) by the plasma PQ concentration (milligram per liter), are recognized as the most potentially valuable prognostic indicators for patients with PQ poisoning.^[8–14] However, the better approach is yet to be systematically investigated and

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determined. Considering that meta-analyses benefit synthesized data from individual studies for a specified outcome, we systematically conducted a meta-analysis to clarify the predictive accuracy of SIPP for the prognosis of patients with PQ poisoning.

2. Materials and methods

2.1. Study design and registration

This study is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.^[15] Institutional review board approval was not required. The systematic review and meta-analysis were pre-registered at the International Prospective Register of Systematic Reviews in April 2019 with the registry number CRD42019131405.

2.2. Search strategy

We searched PubMed, Embase, Web of Science, ScienceDirect, and Cochrane Library to identify all relevant papers that were published up to March 2019. Studies that compared severity index and plasma PQ concentration to predict mortality in patients with PQ poisoning were selected. The following terms were used in the databases: severity index and paraquat (Search strategy in Supplemental Table 1, <http://links.lww.com/MD/D765>). No restrictions were placed on language or year of publication.

2.3. Inclusion and exclusion criteria

Original studies were included if they met the following inclusion criteria: patients with definite PQ poisoning diagnosis; studies reporting associations of severity index, plasma PQ concentra-

tion, and prognosis after PQ ingestion; death was the end point of prognosis; prospective or retrospective diagnostic studies involving humans; and published articles without language restrictions. Clear observable data for sufficient data were provided to calculate the number of true-positive, false-positive, false-negative, and true negative cases. Exclusion criteria were as follows: animal experiments, duplicate studies, reviews, abstracts, case reports, and informal publication. Studies with incomplete data were also excluded.

2.4. Data extraction

Two investigators blinded and independently extracted data from the included studies using predesigned data-extraction forms and compared data to achieve maximum reliability. The following patient-specific characteristics were collected: first author's last name, years of publication, study region, study design, sample size, mortality, follow-up, language of publication, severity index, and plasma PQ concentration. Discrepancies among the investigators were resolved by consensus.

2.5. Risk of bias

Methodological quality and risk of bias were assessed independently by two investigators who followed the checklist of Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2).^[16] QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias, and the first three domains were also assessed for applicability. Each domain comprises a set of signaling questions that should be marked as "yes," "no," or

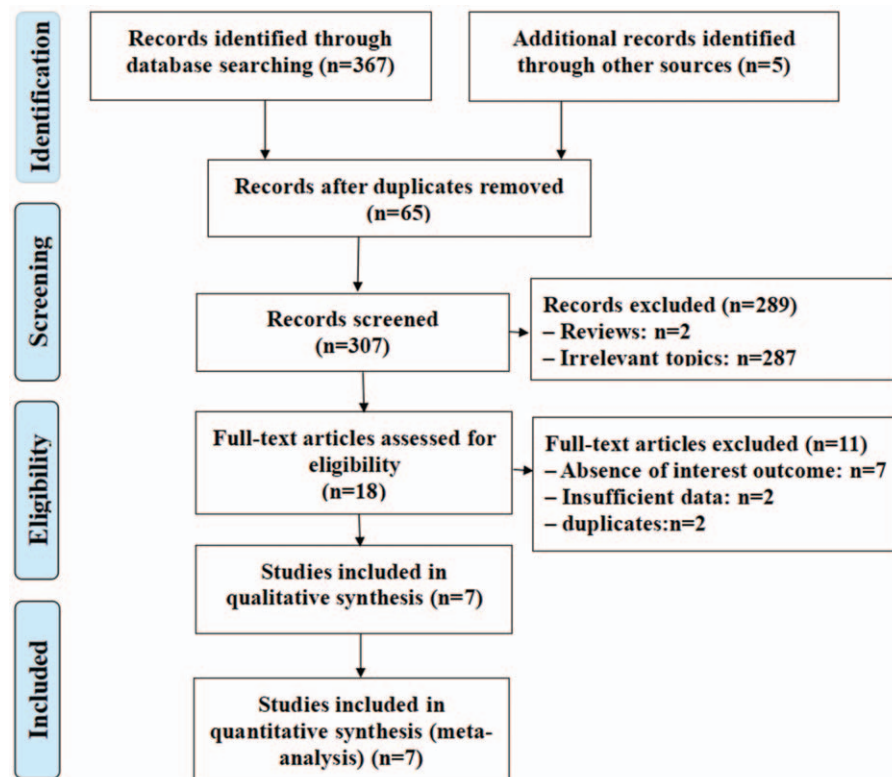


Figure 1. Flowchart for study selection.

Table 1

Characteristics of included studies.

Publication year	Study region	Sample size	Mortality (%)	Follow-up	Language	Study design	Plasma PQ concentration (mg L ⁻¹)		Severity index (h mg L ⁻¹)		Time from ingestion to arrival (h)	
							Survival	Non-survival	Survival	Non-survival	Survival	Non-survival
Chen et al 2015	China	65	64.6	30 days after ingestion	Chinese	Retrospective	3.0 ± 1.8	19.6 ± 8.7	11.7 ± 9.0	84.4 ± 69.6	5.9 ± 4.7	6.6 ± 6.2
Du et al 2013	China	73	56.2	7 days after discharge	Chinese	Retrospective	0.5 (0.05–5.48)	2.13 (0.23–7.44)	2.66 (0.345–12.87)	11.56 (4.56–22.9)	5 (2–48)	6 (2–50)
Huang et al 2006	Taiwan	64	71.9	in-hospital mortality	English	Retrospective	NA	NA	NA	NA	NA	NA
Min et al 2011	Korea	102	76.5	7 days after discharge	English	Retrospective	0.69 (0.06–4.60)	15.00 (0.20–3010.00)	1.28 (0.10–56.58)	40.95 (0.50–2107.00)	2.70 (0.5–19.2)	2.0 (0.3–19.0)
Niu et al 2018	China	126	59.5	7 days after discharge	Chinese	Prospective	0.48 ± 0.20	2.61 ± 0.32	2.71 ± 0.65	12.06 ± 0.63	5.22 ± 2.01	5.51 ± 2.47
Sun et al 2015	China	189	48.1	NA	Chinese	Retrospective	4.70 (2.80–6.40)	9.90 (6.20–14.70)	25.20 (12.80–44.80)	73.50 (45.60–124.80)	5 (4–8)	7 (4–10)
Zhou et al 2016	China	202	52.0	30 days after ingestion	English	Retrospective	0.28 (0.10–16.47)	5.17 (0.11–58.50)	3.52 (0.44–260.40)	34.37 (0.33–715.60)	8.00 (2.00–24.00)	5.00 (1.00–22.00)

NA=not available, PQ=paraquat. Continuous variables are presented as means ± SD or median (interquartile range) and categorical variable is presented as no. (%).

“unclear.” Any discrepancy was resolved by consensus or third-party adjudication if needed.

2.6. Statistical analysis

STATA 12.0 software (StataCorp LP, College Station, TX) was used to analyze data and data synthesis. Pooled odds ratio (OR) with 95% confidence intervals (CIs) represent the predictive value of severity index for survival in patients with PQ poisoning. Potential heterogeneity among included studies was addressed by the estimation of Cochrane Q statistics and I² statistics, with I² < 25%, 50% to 75%, or >75% considered as low, moderate, and high heterogeneity, respectively.^[17] Data were synthesized using a fixed-effect model; however, for a value of I² > 50%, a random-effect model was used. Meta-regression analysis will be conducted to investigate the source of heterogeneity if heterogeneity exists. Publication bias was assessed by Begg rank correlation and Egger linear regression methods.^[18,19] P-values < .05 were considered to indicate a statistically significant result.

3. Result

3.1. Literature search

Figure 1 is a detailed flow diagram of the literature search and screening process according to the inclusion/exclusion criteria. A total of 372 relevant records were initially identified from electronic databases based on the search strategy, of which 65 duplicates were excluded. After browsing the titles and abstracts, 289 records were excluded because of irrelevant records (n=287) or being reviews (n=2). Another 18 full-text records were excluded because of insufficient data (n=2), absence of interest outcome (n=7), or duplicates (n=2). Finally, seven studies^[8–14] with more detailed and sufficient evaluation meeting our entry criteria were retrieved for further analysis.

3.2. Characteristics of the included studies

Table 1 shows the characteristics of the seven included studies,^[8–14] all of which were retrospective and published from 2006 to 2018. In terms of the study location, five studies^[8,9,12–14] were conducted in China, one was in Taiwan,^[10] and one was in Korea.^[11] Sample sizes ranged from 64 to 202, and the mean sample size was 117.

3.3. Quality assessment

The quality assessment based on QUADAS-2 is presented in Figure 2. The patient-selection risk of bias domain in six studies was labeled as unknown because the authors did not report whether the subjects were consecutively enrolled, and the index test was labeled as high risk because the diagnostic threshold was not prespecified. These omissions may have introduced some bias.

3.4. Meta-analysis of survival

As shown in Figures 3 and 4, the pooled OR with 95% CI of severity index was 24.12 (95% CI: 9.34–62.34, P < .001), with area under the curve of 0.88 (95% CI: 0.85–0.90), sensitivity of 0.84 (95% CI: 0.74–0.91), and specificity of 0.81 (95% CI: 0.75–0.87). The pooled OR with 95% CI of plasma PQ concentration was 34.39 (95% CI: 14.69–80.56, P < .001), with

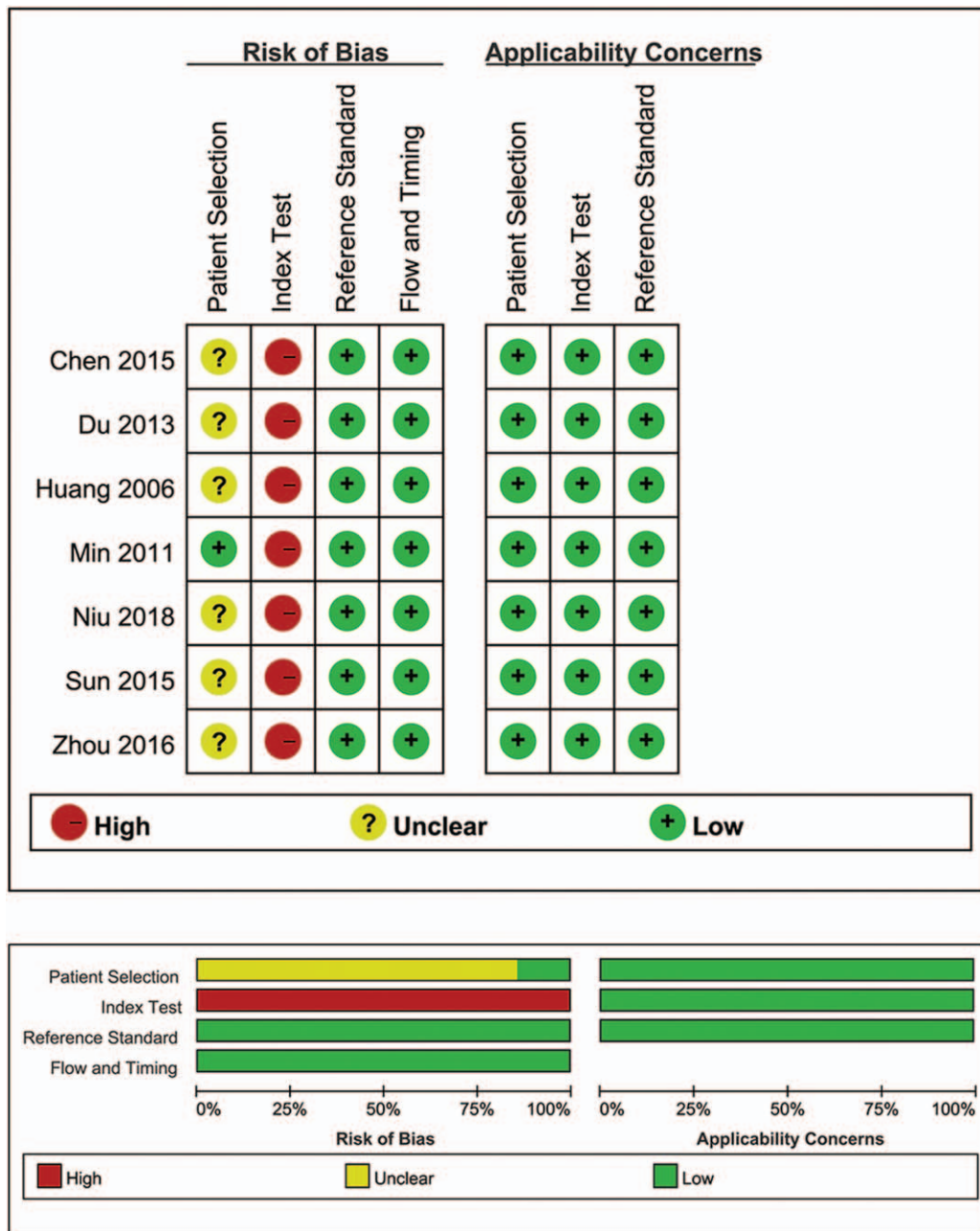


Figure 2. Risk of bias and applicability concerns.

an area under the curve of 0.94 (95% CI: 0.91–0.96), sensitivity of 0.86 (95% CI: 0.75–0.93), and specificity of 0.89 (95% CI: 0.76–0.95).

3.5. Heterogeneity, sensitivity analysis, and publication-bias assessment

This meta-analysis revealed high heterogeneity in the relationship between severity index, plasma PQ concentration, and survival ($I^2=81.7\%$, $P<.001$; $I^2=67.6.7\%$, $P=.005$, respectively). Meta-regression analyses were conducted based on mortality percentage ($\geq 58.2\%$ vs $<58.2\%$), published year (before 2015 vs after 2015), sample size (≥ 117 vs <117), and study region (China

vs other regions), but they did not account for the source of heterogeneity (Table 2).

Sensitivity analysis demonstrated the conclusion was not affected by the exclusion of any single study (Fig. 5). No evidence of significant publication bias was observed for severity index (Begg test $P=.548$, Fig. 5A; Egger test $P=.125$, Fig. 5B) and plasma PQ concentration (Begg test $P=.230$, Fig. 6C; Egger test $P=.142$, Fig. 6D).

4. Discussion

To the best of our knowledge, this review is the first comprehensive, systematic meta-analysis to investigate the

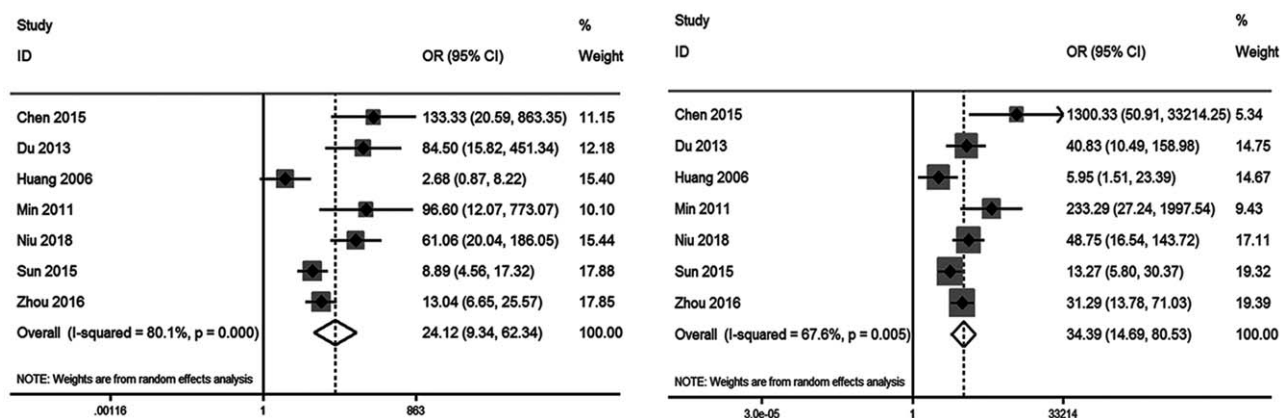


Figure 3. Forest plot of severity index (A) and plasma PQ concentration (B) for mortality. PQ=paraquat.

predictive value of severity index and plasma PQ concentration for the prognosis of PQ poisoning patients. Our results indicated that severity index and plasma PQ concentration have relatively high-prognostic value in patients with PQ poisoning, and that the prognostic value of plasma PQ concentration is superior to that of severity index.

The clinical prognosis of acute PQ poisoning is usually determined by the degree of PQ exposure, and plasma PQ concentration has been regarded as the best prognostic indicator.^[20,21] However, this assessment method has been questioned because some studies indicate that plasma PQ concentration is not as reliable as reported.^[22-24] Gil et al^[22] reported that plasma PQ concentration is not a good predictor of non-survivors in the low-plasma PQ level because some patients with low-PQ concentration still die. The phenomenon may be explained by the pharmacokinetics of PQ. Plasma concentration initially peaks within the first few hours after PQ exposure and then decreases with a steep gradient, with a distribution half-life

of 5 hours.^[24] During this short period, plasma PQ concentration has obvious variations even with slight changes in time interval from PQ exposure to plasma PQ measurements. The prognosis in acute PQ poisoning largely depends on the time from ingestion to plasma PQ measurements.

In theory, the severity index calculated by multiplying the time from ingestion to plasma PQ measurements by the plasma PQ concentration may be more reliable to evaluate the prognosis of acute PQ poisoning. Contrary to our expectations, the prognostic value of plasma PQ concentration is superior to that of severity index. We speculate that estimates of time from ingestion to plasma PQ measurements are often unobtainable or unreliable in many intoxicated patients. Patients may not remember the exact time of ingestion and thus provide general descriptions such as “after breakfast” or “approximately two hours ago.”

Although our results and conclusions seem to be relatively consistent and robust, they should be interpreted in light of a number of limitations. First, despite an exhaustive search of

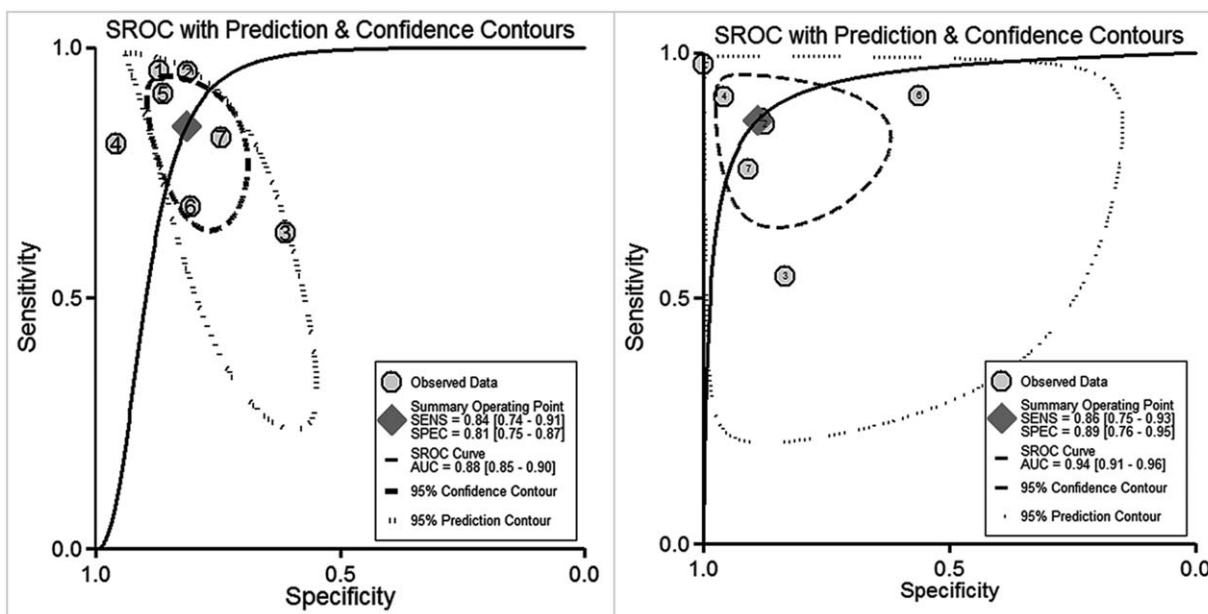


Figure 4. Summary receiver-operating-characteristic curves for estimating the testing accuracy of severity index (A) and plasma PQ concentration (B) for mortality. PQ=paraquat.

Table 2
Meta-regression analysis of potential sources of heterogeneity.

Heterogeneity factors	Coefficient	SE	Z	P-Value	95% CI (lower limit, upper limit)
Sample size	-0.781	2.503	-0.31	.785	-11.552, 9.990
Mortality percentage	1.736	2.022	0.86	.481	-0.693, 10.435
Publication year	1.280	3.289	0.39	.735	-12.870, 15.430
Study region	-3.642	2.992	-1.22	.348	-16.514, 9.229

CI = confidence interval.

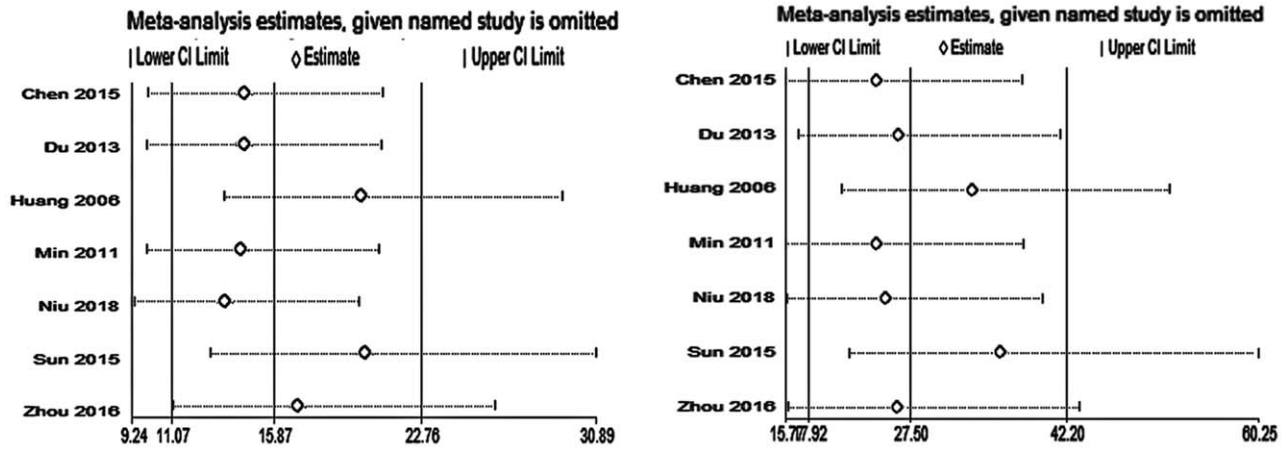


Figure 5. Sensitivity analysis of severity index (A) and plasma PQ concentration (B) for mortality. PQ = paraquat.

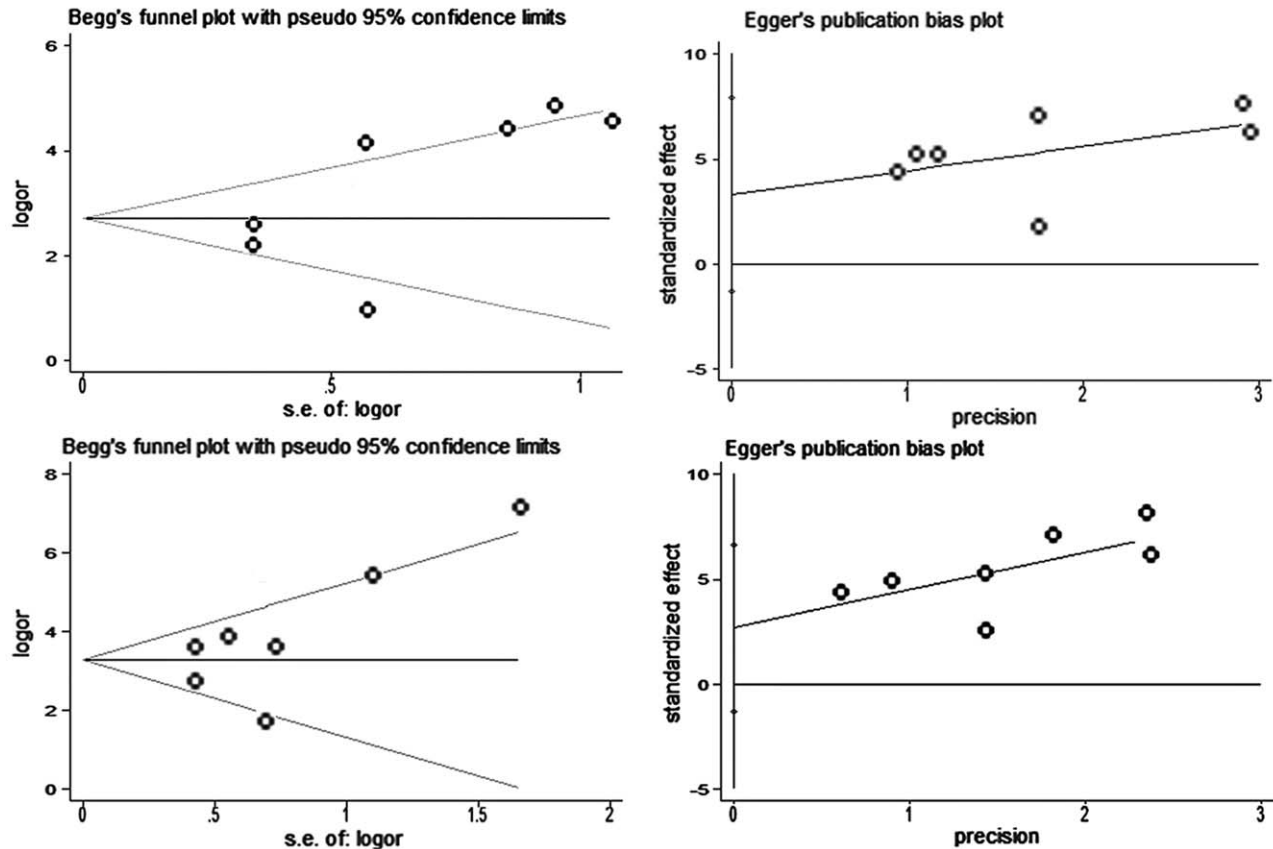


Figure 6. Funnel plot of the publication bias test for severity index ((A) Begg test and (B) Egger test) and plasma PQ concentration ((C) Begg test and (D) Egger test).

literature, the number of eligible studies was low. Second, we believe that potential language and publication biases may have been present in this meta-analysis because we sought published studies written only in English and Chinese. Third, significant heterogeneity was observed in pooled-analysis in retrospective studies. Fourth, detailed information, including the time from ingestion to blood sample measurement of plasma PQ concentration and blood sample collection before hemoperfusion therapy, should be included in the original article.

In conclusion, this study indicated that severity index and plasma PQ concentration have relatively high prognostic value in patients with PQ poisoning, and that the sensitivity and specificity of plasma PQ concentration are superior to those of severity index. Considering the limitations of this meta-analysis, this conclusion should be interpreted with caution. Additional clinical studies with larger sample sizes should be conducted to reduce the study heterogeneity and further verify this conclusion.

Author contributions

Conceptualization: Zong Xun Cao, Shun Yi Feng.

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Writing – review & editing: Shun Yi Feng.

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