### PEER REVIEW HISTORY

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### ARTICLE DETAILS

| TITLE (PROVISIONAL) | Prognostic Nomogram for the Severity of Acute Organophosphate Insecticide Self-Poisoning: A Retrospective Observational Cohort Study |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Dong, Ning; Wang, Shaokun; Li, Xingliang; Li, Wei; Gao, Nan; Pang, Li; Xing, Jihong                                                  |

### VERSION 1 – REVIEW

| REVIEWER                   | Walline, Joseph |
|----------------------------|-----------------|
|                            | The Chinese University of Hong Kong Accident and Emergency Medicine Academic Unit |
| REVIEW RETURNED            | 31-Aug-2020     |
| GENERAL COMMENTS           | Very good study that is well-written. I have just a few questions and edits which I have written on the review proof on the attached PDF. Key questions: 1) Abstract mentions primary and secondary outcome measures, but really only the primary outcome measure is described - either discuss secondary measures or delete reference to secondary measures. 2) I'd recommend adding mention of the well-known Rumack-Matthew acute paracetamol poisoning nomogram (probably the most famous nomogram in emergency medicine) to your introduction 3) Last paragraph of the introduction needs to be re-written to express the goal of the study not what the study actually achieved. 4) Serum amylase and Lactic acid are significantly different between cohorts. Please explain and add this to limitations and/or discussion section. 5) As a side-note, the gender balance seems quite even between men and women in both cohorts - this may or may not be worth commenting on depending on prior studies' gender balance. Overall, this is a great paper that reads well on an important topic. Acute OP poisoning cases are relatively common in China, so using the large number of cases to derive this nomogram should be quite helpful around the world. |

| REVIEWER                   | Eddleston, Michael |
|----------------------------|---------------------|
|                            | University of Edinburgh, Pharmacology, Toxicology and Therapeutics |
| REVIEW RETURNED            | 16-Sep-2020         |
| GENERAL COMMENTS           | I have already reviewed this paper for Human Exp Toxicology. None of the comments I presented in my review at that time have been addressed in this revised version. I have pasted below my comments from the previous version (the only difference I can see is |
in the reference numbers). Many of the comments need to be addressed in the limitations section and discussion.

This paper aims to produce a ‘nomogram’ that will allow prediction on initial assessment of which patients with acute OP insecticide self-poisoning will have severe poisoning or a poor outcome.

It is retrospective and so lacks a number of important variables. It is of moderate size and includes objective variables in the model. The selection of markers of severity is good, as is the AUC measured.

The modelling appears comprehensive but needs assessing by an epidemiologist.

Main points

1. Pls revise the title to be explicit about the subject matter, mentioning both insecticides and self-poisoning (the authors usefully excluded patients who did not ingest the insecticides from the analysis). The title could be:

   “Prognostic Nomogram for the Severity of Acute Organophosphate Insecticide Self-Poisoning”

   Many OP insecticides are not organophosphates - so the term organophosphorus insecticides is more accurate.

2. Nomograms have been used widely for 40 years in toxicology, a fact that appears to have been missed by the authors who state

   “The nomogram has been predominantly used in other [non-toxicology) clinical areas… This encouraged the use of a nomogram in the field of toxicological diseases.”

   The authors need to recognise work on paracetamol (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4500323/) and paraquat (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2659600/) nomograms in the introduction of their paper. I am unsure why these are missed.

3. The authors confuse variables with parameters (which are the boundaries for variables). Pls revise parameters to variables as appropriate in the paper

4. Other prognostic modelling for acute OP self-poisoning is not acknowledged or reviewed in the paper, other than the statements:

   “These variables were established to be linked with poor prognosis of AOPP patients in certain earlier studies.9, 20-24”

   (Of note, reference 24 is an in vitro paper and does not provide any evidence on prognosis. Seems to be an error)

   and

   “First, due to the retrospective design of this study, some valuable parameters such as symptoms and certain clinical risk scores...
(Glasgow coma scale, Peradeniya Organophosphorus Poisoning Scale, etc.) were inaccessible. Thus, the discrimination of this nomogram and other risk scoring systems was not compared."

Just because the weak retrospective design of the study prevented collection of these data and therefore direct comparison, does not mean that they should be ignored.

The AUC for GCS less than or equal to 13 is 0.84, similar to the AUC for this nomogram which is more expensive to collect. Similarly there are data on Peradeniya Organophosphorus Poisoning which should be included in this paper. See https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2493062/

There should be discussion of the other studies and their weaknesses/strengths/AUCs rather than presenting these data in isolation.

5.
Two other key variables that need discussing and ideally including into the analysis are time to presentation and OP insecticide (or class) ingested

Including all patients who present within 24 hours incorporates a great deal of variability - since patients presenting late will often have a poorer prognosis. The authors point out the importance of starting treatment early.

“Quick assessment of patients’ severity and prognosis, as well as instantaneous and suitable therapy are vital.”

This variable should be collected from dataset and included in the analysis.

The prognosis paper above (in #4) and ref 14 in the manuscript report the key importance of the particular OP ingested in determining the outcome (and therefore prognosis). Were these data collected in the medical records? Again this should be incorporated into the analysis and discussed in the paper.

6.
Further missing variables are a history of alcohol dependence, level of alcohol intoxication on arrival at hospital, and obesity, since these will affect outcome:

obesity: https://pubmed.ncbi.nlm.nih.gov/24856742/

alcohol: https://pubmed.ncbi.nlm.nih.gov/20002086/

7.
The authors state in the discussion:
“The outcomes of this study established the benefits of the nomogram used as a support tool for decision making by emergency physicians in AOPP patients.”

The paper does not provide any data that this nomogram benefits patients. This needs to be tested, so this statement is incorrect.

The abstract is more accurate in its conclusion:
“A convenient severity evaluation nomogram for AOPP patients was
developed, which could be used by physicians in making clinical
decisions and predicting patients’ prognosis."

Benefit from its use, versus other variables, has not been shown.

Clinical management of these patients requires careful resuscitation,
use of antidotes, and monitoring. It is not clear yet that prediction of
prognosis can be turned into improve management that results in
better outcome.

8.
The authors state that the nomogram uses:
“objective data, immediately available on presentation”

This is probably not true since it will take some time (hours) to
provide accurate albumin concentrations even if the white cell count
and cholinesterase activity can be measured at the bedside. Pls
revise.

This is important since GCS can be assessed immediately on
presentation, while I do not think this score can be done on
admission.

9.
“The treatment of AOPP patients was not standardized owing to the
retrospective design of this study.”

Although the treatment was not standardised, it still needs
describing. How was atropine given? What other drugs were given?

Management needs to be carefully described in the methods section.

10.
The analysis reports that a raised serum creatinine was initially
included in the analysis and albumin was included. However, table 1
shows that many of the patients with severe poisoning had normal
creatinine and albumin concentrations since the upper quartiles
were within the normal range (although these are not provided - it
would be useful to see these)

Why do the authors think that a small reduction in albumin is linked
with poor outcome? I understand raised lactate and low pH = poor
perfusion. Less sure about raised WCC

Can the results be discussed in terms of mechanism of the
poisoning and poor outcome. What was high pCO2 on admission
(=hypoventilation) not associated with poor outcome?

Was the blood gas taken on air or on oxygen?

11.
In section:
“Independent prognostic factors in the primary cohort”

what increase/decrease in WCC, Hb, albumin, etc, was associated
with the Odds ratios? eg what incremental increase in creatinine was
associated with an OR of 1.26?

Minor
In the definition of hypotension in the markers of severity, the authors state:
“Patients with a blood pressure of <90/60 mmHg and requiring vasopressor administration, BESIDES dopamine and norepinephrine were considered as hypotension.”

Does this mean that patients with low blood pressure requiring dopamine and norepinephrine were not considered hypotensive? This does not seem correct - possible typo?

2. “The patients included in this study comprised those who were severely poisoned”
I think this is a typo since the patients included those who were severe (~25%) and those who were not severely poisoned.

3. Table 1 - sex is usual term. Which sex is presented in the table? Male or female?

4. “An estimated 200,000 people are killed every year”
This statement needs a citation but is probably out of date. This was true in the late 1990s, but is now more likely to be around 100,000 - see Mew et al (https://pubmed.ncbi.nlm.nih.gov/28535450/)

5. “Limited studies exist on the management of AOPP patients.15, 16”
I am not sure this accurately summarises the situation. There have been many studies. Including just one on penetraycidine (ref 16), plus a recent review is superficial. Pls provide a comprehensive review of studies, that might include Bajracharya et al, but there are many others

6. “A five-variable risk-prediction nomogram”
It is a six variable model

7. figure 1 - combined is spelt incorrectly on both sides

REVIEWER
Zang, Yong
Indiana University School of Medicine, Biostatistics

REVIEW RETURNED 25-Dec-2020

GENERAL COMMENTS
This is an interesting work for the derivation of nomograms for AOPP severity, as it is known that nomograms are among the simplest, easiest and cheapest approaches for doctors to communicate with patients. The statistical models are clearly laid out and shown to be highly effective. I have a few minor comments as listed below that may require further clarifications.

1. In Table 1 and 2, the gender variable, it was not mentioned whether Female or Male was used as baseline.
2. It is not clear what is the point of Figure 3. What do the three
curves stand for? It is challenging to differentiate the curves “apparent” with the “Ideal”. More details is needed for Figure 3.

3. From Table 1, it seems that the outcome is a categorial variable with four different levels (severely poisoned, in-hospital deaths, hypotension, ventilator support). This table is a little confusing, as it almost made me think that the response is a multi-level categorical variable. I realized the table listed only the different scenarios for the “severe” patients, but not the “non-severe” patients. And the response is in fact a binary variable of “severe” or “non-severe”. The authors are suggested to make this point more clear in Table 1, and avoid any confusions that may cause.

4. What is the p-value for in Table 1?

VERSION 1 – AUTHOR RESPONSE

Replies to Reviewer 1
1. Very good study that is well-written. I have just a few questions and edits which I have written on the review proof on the attached PDF.
Response: Thank you for your feedback. It’s very encouraging. We have modified the manuscript as per your suggestions.
2. Abstract mentions primary and secondary outcome measures, but really only the primary outcome measure is described - either discuss secondary measures or delete reference to secondary measures.
Response: We are so sorry for our oversight; the “secondary outcome” has been deleted in the abstract. Please see page 3 line 40.
3. I’d recommend adding mention of the well-known Rumack-Matthew acute paracetamol poisoning nomogram (probably the most famous nomogram in emergency medicine) to your introduction.
Response: Thank you. We have added the reference in the manuscript, please see page 6 line 77 and reference 5.
4. Last paragraph of the introduction needs to be re-written to express the goal of the study not what the study actually achieved.
Response: Thank you. We have revised the manuscript as per reviewer’s request, please see page 6 line 82-83.
5. Serum amylase and Lactic acid are significantly different between cohorts. Please explain and add this to limitations and/or discussion section.
Response: Thank you. We have revised the manuscript as per reviewer’s request, please see page 17 line 286-288.
6. As a side-note, the gender balance seems quite even between men and women in both cohorts - this may or may not be worth commenting on depending on prior studies’ gender balance.
Response: Thank you for your suggestion. We will consider this in future studies.

Replies to Reviewer 2
Main points
1. Pls revise the title to be explicit about the subject matter, mentioning both insecticides and self-poisoning (the authors usefully excluded patients who did not ingest the insecticides from the analysis). The title could be: Prognostic Nomogram for the Severity of Acute Organophosphate Insecticide Self-Poisoning”. Many OP insecticides are not organophosphates-so the term organophosphorus insecticides is more accurate.
Response: Thank you. We have revised the manuscript as per reviewer’s request. Please see title page.
2. Nomograms have been used widely for 40 years in toxicology, a fact that appears to have been
missed by the authors who state: “The nomogram has been predominantly used in other (non-toxicology) clinical areas... This encouraged the use of a nomogram in the field of toxicological diseases.” The authors need to recognise work on paracetamol (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4500323/) and paraquat (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2659600/) nomograms in the introduction of their paper. I am unsure why these are missed.

Response: Thank you for pointing out this critical issue, this part of introduction has been revised as per your suggestion. Please see page 6 line 76-81.

3. The authors confuse variables with parameters (which are the boundaries for variables). Pls revise parameters to variables as appropriate in the paper.

Response: Thank you for pointing out this critical issue. We have revised the information in Table 1 and Table 2.

4. Other prognostic modelling for acute OP self-poisoning is not acknowledged or reviewed in the paper, other than the statements: “These variables were established to be linked with poor prognosis of AOPP patients in certain earlier studies.9, 20-24” (Of note, reference 24 is an in vitro paper and does not provide any evidence on prognosis. Seems to be an error) and “First, due to the retrospective design of this study, some valuable parameters such as symptoms and certain clinical risk scores (Glasgow coma scale, Peradeniya Organophosphorus Poisoning Scale, etc.) were inaccessible. Thus, the discrimination of this nomogram and other risk scoring systems was not compared.” Just because the weak retrospective design of the study prevented collection of these data and therefore direct comparison, does not mean that they should be ignored. The AUC for GCS less than or equal to 13 is 0.84, similar to the AUC for this nomogram which is more expensive to collect. Similarly there are data on Peradeniya Organophosphorus Poisoning which should be included in this paper. See https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2493062/. There should be discussion of the other studies and their weaknesses/strengths/AUCs rather than presenting these data in isolation.

Response: (1) We are incredibly grateful to the reviewers for revising the paper so carefully. The miss arranged reference has been removed and further rechecked the references thoroughly to avoid any such mistake and made appropriate changes (ref 14, 16 and 17). (2) Indeed pre-existing scoring systems are great in predicting patient’s mortality. We added a paragraph in page 15 and 16 line 261-268.

5. Two other key variables that need discussing and ideally including into the analysis are time to presentation and OP insecticide (or class) ingested. Including all patients who present within 24 hours incorporates a great deal of variability - since patients presenting late will often have a poorer prognosis. The authors point out the importance of starting treatment early: “Quick assessment of patients’ severity and prognosis, as well as instantaneous and suitable therapy are vital.” This variable should be collected from dataset and included in the analysis. The prognosis paper above (in #4) and ref 14 in the manuscript report the key importance of the particular OP ingested in determining the outcome (and therefore prognosis). Were these data collected in the medical records? Again this should be incorporated into the analysis and discussed in the paper.

Response: Thank you for your suggestion, these are indeed important limitations of our study. The medical records of enrolled hospital had some vague description on patients’ complaints, for example, “orally intake Ops half a day”, which means some patients don’t have record of the specific type of Ops, accurate hours of Ops intake, or even doses of OPs. So, we could not acquire accurate information as per your request. Please see revised manuscript page 15, line 256-260.

6. Further missing variables are a history of alcohol dependence, level of alcohol intoxication on arrival at hospital, and obesity, since these will affect outcome: obesity: https://pubmed.ncbi.nlm.nih.gov/24856742/
alcohol: https://pubmed.ncbi.nlm.nih.gov/20002086/

Response: Thank you. Please see revised manuscript page 15 and 16, lines 261-265.

7. The authors state in the discussion: “The outcomes of this study established the benefits of the nomogram used as a support tool for decision making by emergency physicians in AOPP patients.”
The paper does not provide any data that this nomogram benefits patients. This needs to be tested, so this statement is incorrect. The abstract is more accurate in its conclusion: “A convenient severity evaluation nomogram for AOPP patients was developed, which could be used by physicians in making clinical decisions and predict ING patients’ prognosis.” Benefit from its use, versus other variables, has not been shown. Clinical management of these patients requires careful resuscitation, use of antidotes, and monitoring. It is not clear yet that prediction of prognosis can be turned into improve management that results in better outcome.

Response: This sentence was replaced by “This study established a nomogram to be used as a support tool for predicting severe AOPP cases.” Please see revised manuscript page 16, line 281-282.

8. The authors state that the nomogram uses: “objective data, immediately available on presentation”. This is probably not true since it will take some time (hours) to provide accurate albumin concentrations even if the white cell count and cholinesterase activity can be measured at the bedside. Pls revise. This is important since GCS can be assessed immediately on presentation, while I do not think this score can be done on admission.

Response: Thank you for your suggestion. The albumin concentration may take 2-3 hours in our hospital. We removed ‘immediately available’ in that sentence.

9. “The treatment of AOPP patients was not standardized owing to the retrospective design of this study.” Although the treatment was not standardised, it still needs describing. How was atropine given? What other drugs were given? Management needs to be carefully described in the methods section.

Response: Thank you. Treatment of AOPP patients was described as reviewer requested in page 9, line 124-135.

10. The analysis reports that a raised serum creatinine was initially included in the analysis and albumin was included. However, table 1 shows that many of the patients with severe poisoning had normal creatinine and albumin concentrations since the upper quartiles were within the normal range (although these are not provided - it would be useful to see these). Why do the authors think that a small reduction in albumin is linked with poor outcome? I understand raised lactate and low pH = poor perfusion. Less sure about raised WCC. Can the results be discussed in terms of mechanism of the poisoning and poor outcome. What was high pCO2 on admission (=hypoventilation) not associated with poor outcome? Was the blood gas taken on air or on oxygen?

Response: (1) Albumin was selected by multivariable logistic regression. Albumin could form serum albumin adducts in the presence of organophosphorus compounds (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793267/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747771/). This has been discussed in the discussion on page 15, line 243-244.

(2) No abbreviation “WCC” was used in the paper, do you mean “WBC”? WBC has been proved a useful predictor in AOPP (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5896186/).

(3) PCO2 was associated with severe AOPP in univariable logistic regression; however, after adjusted for other associated variables, PCO2 was not selected for multivariable logistic regression.

(4) Blood gas was taken regardless of oxygen therapy as revised in page 9, line 143.

11. In section: “Independent prognostic factors in the primary cohort”. What increase/decrease in WCC, Hb, albumin, etc, was associated with the Odds ratios? eg what incremental increase in creatinine was associated with an OR of 1.26?

Response: Thank you. The incremental increase or decrease in variables was marked as units in the first column in table 2. For example, “white blood cells (×109/L)” and OR =1.09, means when WBC increased 1×109/L, the risk of developing severely poisoning of a patient was 1.09. “sCr (per 0.1 mg/dL)” and OR = 1.26, means when sCr increased 0.1 mg/dL, the risk of developing severely poisoning of a patient was 1.26.

Minor

1. In the definition of hypotension in the markers of severity, the authors state: “Patients with a blood
pressure of <90/60 mmHg and requiring vasopressor administration, BESIDES dopamine and norepinephrine were considered as hypotension.

Does this mean that patients with low blood pressure requiring dopamine and norepinephrine were not considered hypotensive? This does not seem correct - possible typo?
Response: Thank you. This sentence has been revised in this version of the manuscript.

2. “The patients included in this study comprised those who were severely poisoned”.
I think this is a typo since the patients included those who were severe (~25%) and those who were not severely poisoned.
Response: Thank you. This sentence has been revised in this version of the manuscript.

3. Table 1 - sex is usual term. Which sex is presented in the table? Male or female?
Response: Thank you. Gender was replaced by “male” in table 1.

4. “An estimated 200,000 people are killed every year”. This statement needs a citation but is probably out of date. This was true in the late 1990s, but is now more likely to be around 100,000 - see Mew et al (https://pubmed.ncbi.nlm.nih.gov/28535450/)
Response: Thank you. This sentence has been revised in this version of the manuscript.

5. “Limited studies exist on the management of AOPP patients.15, 16”. I am not sure this accurately summarises the situation. There have been many studies. Including just one on penehyclidine (ref 16), plus a recent review is superficial. Pls provide a comprehensive review of studies, that might include Bajracharya et al, but there are many others.
Response: Thank you. This sentence has been revised in this version of the manuscript.

6. “A five-variable risk-prediction nomogram”. It is a six variable model.
Response: Thank you. This sentence has been revised in this version of the manuscript.

7. figure 1 - combined is spelt incorrectly on both sides.
Response: Thank you. This has been revised in this version of the manuscript.

Replies to Reviewer 3
1. In Table 1 and 2, for the gender variable, it was not mentioned whether Female or Male was used as baseline.
Response: Thank you. Gender was replaced by “male” in table 1 and table 2.

2. It is not clear what is the point of Figure 3. What do the three curves stand for? It is challenging to differentiate the curves “apparent” with the “Ideal”. More details is needed for Figure 3.
Response: Thank you. In the original figure 3, the ideal line was marked in blue, which was not clear in the black-white version of the manuscript. A description for three lines in figure 3 was added in figure legends.

3. From Table 1, it seems that the outcome is a categorical variable with four different levels (severely poisoned, in-hospital deaths, hypotension, ventilator support). This table is a little confusing, as it almost made me think that the response is a multi-level categorical variable. I realized the table listed only the different scenarios for the “severe” patients, but not the “non-severe” patients. And the response is in fact a binary variable of “severe” or “non-severe”. The authors are suggested to make this point more clear in Table 1, and avoid any confusions that may cause.
Response: Thank you. To avoid the confusion, the word “outcomes” was removed, and the ‘percentage of different complications in severely poisoned patients’ was emphasized by line indent. Please see revised Table 1.

4. What is the p-value for in Table 1?
Response: Thank you. P-values in table 1 have been checked.

**VERSION 2 – REVIEW**

| REVIEWER             | Zang, Yong                        |
|----------------------|-----------------------------------|
|                      | Indiana University School of Medicine, Biostatistics |
| REVIEW RETURNED      | 01-Feb-2021                       |
| GENERAL COMMENTS | The authors have addressed all my questions, and I have no future comments. |