Author's response to reviews

Title: Predictors of Poisoning-Related Fatality: A Hospital-Based Prospective Study

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Responses to Reviewers’ Comments

Reviewer 1

Comment 1. Make sure that the version to be submitted is revised thoroughly for grammatical errors: these make reading the paper over difficult and "put off" the reviewer.

Response: We have sent the manuscript out for English editorial service in the revision.

Comment 2. The authors would need to decide on exactly what they want to present in their results and make sure that the main points come out clearly - as the paper stands, the results are quite difficult to follow and there are too many issues that are presented.

Response: We agree with the reviewer’s comment and have deleted some minor issues in the Results section, such as information about numbers of exposure agents.

Comment 3. Together with the above point, it would be worthwhile to separate the results into different sections with separate subheading, e.g., Patient Demographic Details, Mortality - and other related headings. This has the effect of making it easier for the reader to follow the results and pick out key and important points.

Response: According to the reviewer’s comment, we have separated the Results into four sections with the subheadings of “Characteristics of the poisoning cases,” “Clinical status of the poisoning cases,” “Characteristics of the fatality cases,” and “Predictors for fatality.”

Comment 4. It may be worthwhile also to utilise graphs and charts to summarise some of the information, with text highlighting on pertinent facts. Tables with text alone is quite messy and hard to follow.

Response: According to the reviewer’s comment, we have added one chart (Figure 1) to present the data related to the distribution of implicated agents and omitted the related description in the text in the revised manuscript.

Comment 5. There is generally no need to continue repeating both numbers and proportions, e.g., on page 11 line 5, "...drugs (773/1548, 49.9%)..." this is messy and repetitious not adding much. You may want to stick more to percentages.

Response: In response to the reviewer’s comment, we omitted the fractions and showed most of the data in percentage only in the Results section of the revised manuscript.

Comment 6. The authors should be careful of your use of words like all and none especially when they represent a subpopulation - I was confused on some occasions about this use, e.g., page 11 paragrapg 2 line 3,"...traced in 71.6% of ALL patients..." which patients are referred to as "all."
Response: According to the reviewer’s comment, we minimized the use “all” in the revised manuscript and replaced “all the patients” by “the enrolled patients” when we mention all enrolled cases.

Comment 7. Where possible the authors should show the relative contributions of groups involved, e.g., when talking about the pesticides involved in fatal cases, the authors did not give the relative contributions of each; yet in the discussion they isolate paraquat as an important cause of fatality. But the results did not show that.

Response: We agree with the reviewer’s comment and have added the distribution of pesticides exposure involved in fatal cases in the section “Characteristics of fatality cases” as follows: Pesticides including paraquat, glyphosate, organophosphates, carbamates, and blasticidin-S were the agents most frequently involved in fatal exposures and accounted for 73.0% of the fatalities, and paraquat exposures led to the highest fatality rate (31 died among 43 exposed, 72.1%) and was the major agent involved in fatalities (46.3%).

Comment 8. The discussion was not written well. It read more like a literature review rather than a discussion – there was little effort made to address major results. The authors should attempt to discuss their results. As a general guide they can try answering the following: - what has other work from the country, region shown - what about work from other countries - why are there similarities and if differences, why are they there - what do the results mean and what impact will they have

Response: In response to the reviewer’s comment, we have revised the Discussion section to address the issues the reviewers raised. Furthermore, we added subheadings in this section in accordance with the Results section.

Comment 9. The authors should be careful to quote correctly what other researchers reported on, for example they state in their paper that Tagwireyi and colleagues reported that paraquat was a problem (ref. 42) - this is not correct.

Response: We thank the reviewer for the correction. We have revised it as “Pesticides exposure was also a major problem in Taiwan [2,21,22] and some countries [14,40,43,44]. Paraquat (24% w/v) is one of the most commonly used herbicides in Taiwan and has been the most common lethal agent of poisoning for a long time [2,26,45,46].” We have also checked the accuracy of other references again.

Comment 10. Conclusions have to follow from the results and discussion. The authors should ensure that all the things that they conclude - they have mentioned them elsewhere in their paper.

Response: According to the reviewer’s comment, we have made sure that all the
conclusions were based on information presented in the paper.

**Comment 11. The authors may need to change their title to reflect the other issues that they reported in - the way the title stands is quite misleading.**

Response: In response to the reviewer’s comment, we have changed the title to “Presentations of Patients of Poisoning and Predictors of Poisoning-Related Fatality: Findings from a Hospital-Based Prospective Study.”

**Reviewer 2**

**Comment 1**: The main quibble I have with this paper is the lack of detail on the completeness of data collection. That is it would be good to have a copy of the specific form used for data collection and the extent to which there were missing data for each field.

Response: As this study was conducted in Taiwan, the form used for data collection was in Chinese. If the reviewer or the Editor would like to take a look at the questionnaire, we will be more than happy to provide it. However, it will take a substantial effort to translate it into English and occupy a large space in the paper. On the other hand, we have reported the number of participants who provided information in the column “Subtotal (%)” n Tables 1 and 2 for each field. With the total number of participants reported in the titles of these tables (N = 1512), the readers can easily know the extent to which there were missing data for each field. Therefore, we prefer reporting the number of participants providing data for each field to translating the whole and then including it in the manuscript.

**Comment 2**: Prospective studies of poisoning admissions can be very useful and may serve many different purposes - identifying problematic poisons, providing evidence to guide diagnosis or prognosis, providing data on the natural history of particular poisonings etc... One of the issues with such databases is quite a lot of data on patients has to be collected to come up with new findings. So the authors are reporting on two years worth of data from their centre. They seem to have done a good job of collecting and analysing the data and the results should help them guide their practice and priorities for public health interventions. Unfortunately, there is not that much in this paper to grab the interest of readers from elsewhere. The main broad conclusions - i.e. that paraquat is very toxic, that old age and abnormal vital signs on admission indicate a worse prognosis - are not new findings. Moreover, the specific quantified odds ratios may not be applicable elsewhere – e.g. the strong association of respiratory abnormalities with death might only apply in areas where paraquat is a leading cause of death (for further explanation see Buckley NA, Dawson AH, Whyte IM. Diagnostic Data in Clinical Toxicology: Should We Use A Bayesian Approach? Journal of Toxicology -Clinical Toxicology 2002;40(3):213-222.)

This is not to say this study shouldn’t be published - it should - but the authors should give some thought to how they might in this or future studies make the presentation of
their data more relevant and applicable to a wider audience.

Response: We are glad to learn that the reviewer suggests this study be published. We did collect a lot of information through this study, and it is difficult to put all the useful information into one paper. This paper focuses on the predictors of poisoning-related fatality, and we agree with the reviewer’s comment that the main broad conclusions (i.e. that paraquat is very toxic, that old age and abnormal vital signs on admission indicate a worse prognosis) are not new findings. However, there were few prospective studies conducted in EDs to confirm these findings, and therefore this paper adds to the supports of such knowledge in the practice in EDs. In most clinical settings, not just in the EDs, there are difficulties in obtaining accurate information on the poisons ingested, and the main issue that we would like to present in this paper is that some easy-to-obtain variables are good predictors for fatality. While we also agree the reviewer’s comment that the specific quantified odds ratios may not be applicable in some other places, we believe it is important to generate those estimates, so that the stability (statistical significance) of the observation can be evaluated (through 95% confidence intervals in this manuscript). Besides, this comment in fact applies to almost all published epidemiological papers.

As suggested by the reviewer, we plan to performed further analyses and discuss related issues from different aspects, and this paper will provide the general background information for further analyses if it gets published. We share the thought of the reviewer that our data should be relevant and applicable to a wider audience and have argued in the Conclusions that the results of this study should act as a reminder to clinicians, public health professionals and the general public of the serious consequences of exposures to paraquat.

Review 3

Comment 1: ‘Poisoning was defined as exposure to drugs or any environmental substances resulting in an ED visit…’ Does this include adverse drug effects of prescribed medication??


Comment 2: What proportion of patients admitted to the hospital with poisoning were recruited to this study?

Response: In the first sentence of Methods, we stated that this is a prospective study involving recruited consecutive cases, which means that we recruited all cases of poisoning exposure during the study period.
Comment 3: ‘All enrolled patients were carefully tracked throughout the hospitalization and follow-up periods to document final outcomes. ….. Those who died of poisoning exposures during the hospitalization or within a short time after discharge ….’ How were patients followed up after hospital discharge? How successful was this follow-up - what was the drop out?

Response: We had assistants who took the response of following the condition of enrolled patients during hospitalization and after discharge. Those who were discharged with stable condition were routinely followed by the psychiatric or toxicological outpatient clinic for at least once, and therefore, we know each patient’s condition after discharge from the chart of the patient. If the patients could not return to the out patient clinics, the assistant would follow up patients or their friends and relatives by phone. According to the practice of the two EDs, friends or relatives who brought the patient to the ED are required to leave at least one phone number to be recorded in the chart. Therefore, we have successfully followed up all the enrolled patients.

Comment 4: How was suicide intent assessed? Through which scale? How accurate was it in ill or unconscious patients?

Response: According the practice of the two EDs, all poisoning cases receive consultation with a psychiatrist or a social worker. The suicide intent was assessed by the consulted psychiatric doctor or social worker. For those who were unable to be assessed in the ED, the consultation would be performed after their condition stabilized. In the study area, few patients were brought to the EDs without any friend or relative accompanied. On most of the critically ill or died-on-arrival patients, we could get information from their friends, relatives, emergency paramedical technicians, and/or policemen.

Comment 5: Information on the concomitant use of alcohol could only be known in 62.4% patients, and 17.3% of them used alcohol in the episode.

How was this information obtained - alcohol breath meter? Blood level?

Why was alcohol use on admission not recorded for all patients? I wonder what biases this relatively low number brings into the study? Was it not possible to get the information from unconscious patients or fatal cases, markedly biasing this analysis?

What proportion of patients had alcohol dependency, or withdrawal later in their hospital admission? What proportion of patients were regular users of alcohol?

Response: Alcoholism in Taiwan is not as common as in many other countries, and therefore the blood alcohol level is not routinely checked for patients admitted to the EDs. During the study period, we did not find any case in which alcohol was the only agent for intoxication. Only 62.4% of enrolled patients provided information of concomitant use of alcohol, and 17.3% of them admitted or were found to consume alcohol in the episode. In addition to the fact that it is often impossible to get the information from unconscious
patients or fatal cases, some patients are unwilling to provide such information due to various reasons. In addition, because alcohol consumption is not a focus of this manuscript, we did not perform further analyses for related issues and thus unable to provide precise answers to the questions rose by the reviewer. Nonetheless, from years of experience in clinical practice in the region, we know that patients with alcohol dependency constitute a very small proportion of patients of poisoning, and few patients of poisoning present withdrawal symptoms later in their hospital admission. We recognized this limitation in the Discussion of the original manuscript and added a clear statement in the revised manuscript in response to the reviewer’s comment.

Comment 6: According to the previous report of PCC, the poisoning-related fatality rate was estimated around 5.7% in Taiwan [2], and our study found it to be was 4.3%, a very close figure. The study does not address deaths that occurred before hospital admission. The case fatality ratio is therefore an in hospital CFR.

Response: We agree with the reviewer’s comment that the case fatality ratio reported in our paper is an in hospital CFR; we enrolled the patients who died on arrival but not the patients who died but were not sent to the hospitals. Therefore, not all the deaths that occurred before hospital admission were included in our study. Nevertheless, this is a common feature of hospital-based studies, and the PCC in Taiwan did not include all patients who died before admission, either.

Comment 7: A major limitation of the paper is that the criteria have not been independently validated using another data set. This needs to be acknowledged at the end of the discussion.

Response: We agree with the reviewer’s comment and have put it in the last paragraph of “Discussion” as follows: As in other studies, difficulties in obtaining complete information in some cases would limit some of our results and limitations in generating the results of this study to other regions should also be considered. Another limitation is regarding the prospective validation using another data set. Even in the same area, the pattern of poisoning may vary over time, and therefore, updating the epidemiology data regularly to recognize the trends of specific agents and validate risk factors are important to the setting of prevention strategies.

Minor issues: The studies of regional epidemiology cited in the introduction are rather random. Regional variation in poisoning admissions has been comprehensively reviewed (Eddleston 2000, QJM 93:715-731) ‘Among the agents, pesticides had the highest fatality rate’ Since there is no time denominator (per year, etc), the case fatality cannot be a rate. It is either a proportion or ratio (probably, the latter is better since the abbreviation CFR can be kept). This is a common mistake that is discussed by Schulz in the Lancet (see Lancet 2002; 359: 57–61).

Response: We agree with the reviewer’s comment that the regional epidemiology studies cited in the introduction seem random. Just like the author described in the article (Eddleston M, 2000, Q J Med 93: 715-731) “The data presented above are very patchy. I
have been unable to find studies for many countries, in particular those of South America and Africa. Few countries have more then one study, resulting in a picture of the situation in only one place at one time and differ between regions, these snapshots may not be representative of the current problems…” we suffered from the same problem while searching references for our manuscript. The pattern and causal agents of poisoning vary from region to region, and even from time to time in the same region. Whereas Eddleston (2000) provides a comprehensive review of articles on regional variation in poisoning admissions published between 1980 and 1999, we used the references published between 1991 and 2005, mostly between 2000 and 2005. Although they seem to be patchy and random, we believe they reflect the recent situation. As to the use of fatality “rate” or “ratio”, we follow the “A Dictionary of Epidemiology” 4th Ed. (Last, 2001 p. 24). Although it may be not entirely accurate scientifically, the term can convey the correct meaning, just like the term “prevalence rate” (should be a proportion, not a “rate”) that is frequently used in the medical literature and the term “currency exchange rate” (should be a ratio, not a “rate”) that is often used in our daily life.