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Review

Relationship Between Alcohol Co-Ingestion and Clinical Outcome in Pesticide Self-Poisoning: A Systematic Review and Meta-Analysis

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Abstract

Aim. Alcohol is a commonly co-ingested compound during self-poisoning with pesticides. Clinical experiences suggest alcohol co-ingestion (or withdrawal) makes patient management more difficult after self-poisoning and may contribute to poor clinical outcomes. We aimed to systematically review the world literature to explore the relationship between alcohol co-ingestion and outcome in pesticide self-poisoning.

Methods. We searched 13 electronic databases and Google scholar, conducted citation searching and a review of reference lists to find studies which investigated the relationship of alcohol with clinical outcome of pesticide self-poisoning in different countries. Thirteen studies, including 11 case series/reports and two cohort studies were considered for inclusion.

Results. Meta-analysis showed that alcohol co-ingestion in pesticide self-poisoning was associated with increased risk of death [odds ratio (OR) 4.9, 95% confidence interval (CI) 2.9–8.2 $P<0.0001$] and that alcohol co-ingested group required intubation eight times more often than non-co-ingested group in organophosphorus insecticide self-poisoning (OR 8.0, 95% CI 4.9–13.0 $P<0.0001$). Cases who co-ingested alcohol were older than non-alcohol group in two studies. One cohort study demonstrated that alcohol co-ingestion was associated with larger pesticide ingestions but did not itself affect the outcome.

Conclusions. This systematic review indicates that alcohol co-ingestion may worsen clinical outcome in pesticide self-poisoning.

INTRODUCTION

Pesticides self-poisoning is one of the three most important means of suicides in the world (World Health Organization, 2014), responsible for >100,000 deaths annually, accounting for about 20% of the global burden of suicide (Mew *et al*., 2017) and a major public health problem in many low- and middle-income countries (LMICs) (Naghavi, 2019). Deaths from pesticide poisoning make a major contribution to suicides in LMIC, particularly in rural areas (Gunnell *et al*., 2007; Mew *et al*., 2017) as it is widely available in the community. A range of pesticides contribute to varying case fatality from 0–42% (Eddleston *et al*., 2006b; Buckley *et al*., 2021).

Due to season-specific agricultural operations, the prevalence of pesticide poisoning varies throughout the year (Eddleston *et al*., 2006b; Senarathna *et al*., 2012). Pesticide poisoning remains a major concern among the youth in these rural areas due to low-socioeconomic status and problematic alcohol use in households (Fernando *et al*., 2021).

Sri Lanka has one of the highest alcohol consumption rates in the world (Jayasinghe and Foster, 2011; World Health Organization, 2019). Alcohol is a commonly co-ingested compound during self-poisoning with pesticides. Many deaths have been reported following poisoning in Asia that involved alcohol co-ingestion (Grmec *et al*., 2004). Alcohol is considered as an important risk factor for pesticide self-poisoning (Van Der Hoek and Konradsen, 2005; Konradsen *et al*., 2006) and may have contributed to poor clinical outcomes (Eddleston *et al*., 2009; Dhanarisi *et al*., 2018). Acute alcohol consumption is linked to poor impulse control, impaired judgment and probably altered taste, all of which increase the likelihood of ingestion of pesticides in excessive amounts (Eddleston *et al*., 2006a). Many men consume alcohol at the

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time of poisoning, and excessive amounts of ethanol can cause unconsciousness and increase the risk of toxicity. However, the relation with alcohol co-ingestion and patient outcome following pesticide self-poisoning is not widely addressed (Van Der Hoek and Konradsen, 2005; Eddleston *et al*., 2006a). Therefore, the aim of this systematic review is to review the literature to explore the relationship between alcohol co-ingestion and outcome in pesticide self-poisoning.

METHODS

Search strategy

We searched in Medline via PubMed, African Journals Online, Global Health Library, Index Medicus for the Eastern Mediterranean Region, Index Medicus for South-East Asia Region, Website of Indexing of Indian Medical Journals, KoreaMed, Latin American and Caribbean Health Sciences Literature (LILACs), Toxnet, Western Pacific Region Index Medicus, SLJOL and Clinicaltrials.gov without time limit. We conducted the review according to the guidelines and standards of Institute of Medicine (Eden *et al*., 2011) and PRISMA (Moher *et al*., 2015) for reporting. The protocol was created and registered through the International Prospective Register of Systematic Reviews (PROSPERO, Protocol No. CRD42020142163) (Liberati *et al*., 2009). The medical librarian (SP) was consulted regarding the development of the search strategy. The search terms, where possible, combined the concepts: pesticides OR self-poisoning AND (alcohol or ethanol) (Supplementary Table 1 for search strategy).

Study selection

After removal of duplicates from the retrieved articles, abstracts were screened using Rayyan Systems Inc. (Ouzzani *et al*., 2016). The inclusion and exclusion criteria for selecting studies are shown in Table 1. Studies which met the inclusion criteria were eligible for inclusion in the review. A two-stage screening process was undertaken independently by two reviewers (JD and TW). First, the titles and abstracts were screened by both reviewers to identify potentially eligible publications against inclusion and exclusion criteria. The citation was passed to the second stage, where a decision could not be made or there was a disagreement as to eligibility. In the second stage, each reviewer independently checked the full text of those articles and categorized as 'included,' 'unsure' or 'excluded' using Rayyan. Discrepancies were resolved by consensus, and a third reviewer (SP) adjudicated unresolved disputes. Reasons for rejections and exclusions of studies were recorded. The feasibility, appropriateness of data and ease of use were established as aforementioned in the study selection process through Rayyan.

Quality assessment

Two reviewers (JD and TW) conducted independent assessments on the quality of included studies. Where discordance between decisions was observed, this was resolved by consensus or discussion with a third review author (SP). For individual case series/reports, a quality assessment Tool of the National Institute of Health (NIH) was applied. This tool includes questions based on nine criteria to which either of the binary answers (Yes/No) was allotted. Based on the number of 'Yes' answers, a rating of good (7–9), fair (4–6) or poor (≤3) was awarded to each individual study and differences in quality ratings resolved by consensus. Studies for which the criteria were irrelevant were labeled as 'not applicable'.

For cohort studies, we applied the Newcastle-Ottawa Scale which consists of questions aimed at assessing three domains – selection, comparability and outcome where a system of awarding 'Stars' was used, to rate the quality of the study. Cohort studies with a quality rating of five stars or greater on the Newcastle-Ottawa Scale were included in the review. The results of the quality assessment are shown in Supplementary Tables 2 and 3.

Data extraction

Two reviewers (JD and TW) independently extracted data: publication details (title, author, year and country of study) type of study design, sample size, type of pesticide ingested, gender, age and study outcomes (pesticide/alcohol concentration measured, death) from eligible studies using a data extraction form and cross-checked for any errors (Table 2).

Data analysis and interpretation

Narrative synthesis of the findings of included studies was carried out by JD, TW, SS and FM. Data from four studies (Garammana *et al*., 2010; Gazzi *et al*., 2015; Min *et al*., 2015; Dhanarisi *et al*., 2018) were subjected to meta-analyses stratified by death and intubation (with alcohol co-ingestion vs. without alcohol co-ingestion) to obtain composite estimates of odds ratios (ORs) separately for each study and for all studies combined using GraphPad Prism v7 software (GraphPad, CA). Two case series (Eddleston *et al*., 2009; Mao *et al*., 2012) and a cohort study (Lee *et al*., 2017) that lacked death and intubation data for both alcohol and non-alcohol groups were not included in meta analyses.

RESULTS

Literature selection and study characteristics

In total, 3999 studies were identified through database searching. Based on the title and abstract screening, 3739 records were excluded due to lack of primary data and/or irrelevance to review objective. Of the resulting 60 eligible full texts, 14 studies met the inclusion criteria (Demeter *et al*., 1977; Warriner III *et al*., 1977; Ernouf *et al*., 1998; Al-Samarraie *et al*., 2009; Eddleston *et al*., 2009; Garammana *et al*., 2010; Yeh *et al*., 2010; Mao *et al*., 2012; Fuke *et al*., 2014; Gazzi *et al*., 2015; Min *et al*., 2015; Boumba *et al*., 2017; Lee *et al*., 2017; Dhanarisi *et al*., 2018), and thus were selected for inclusion in the review (Fig. 1). Of these 14 studies, 12 were case series/reports (6 case series and 6 case reports) and 2 were cohort studies. These cohort studies and case series were either prospective or retrospective in design. Supplementary Table 4 provides descriptive details of the included studies.

The methodological quality as measured by the NIH quality assessment tool was good or fair for all series/reports assessed except one study (Warriner III *et al*., 1977) due to lack of detail results (Supplementary Table 2) and the two cohort studies scored sufficient number of stars in the Newcastle- Ottawa Scale (Supplementary Table 3). There were no publication and reporting biases noted. Therefore, 13 studies were considered for inclusion in the final data synthesis which included 1439 patients.

Two-third of the studies were conducted in Asia (Sri Lanka, South Korea, Taiwan and Japan) and one-third in Europe

Table 1. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Language	English language only	Non-English
Years included	No range of years.	N/A
Publication type	Research published in peer-reviewed journals, government reports, WHO data and grey literature such as research reports and PhD theses	N/A
Type of data	Both qualitative and quantitative	N/A
Study design	All types of studies	Editorials, letters to editor
Study population	Patients with pesticides self-poisoning from general population (Age above 14 years)	Age below 14 years/ children
Setting	Global	N/A
Exposure/Outcome	Pesticides self-poisoning with alcohol exposure	Pesticide self-poisoning without alcohol exposure, occupational exposure

N/A: not applicable

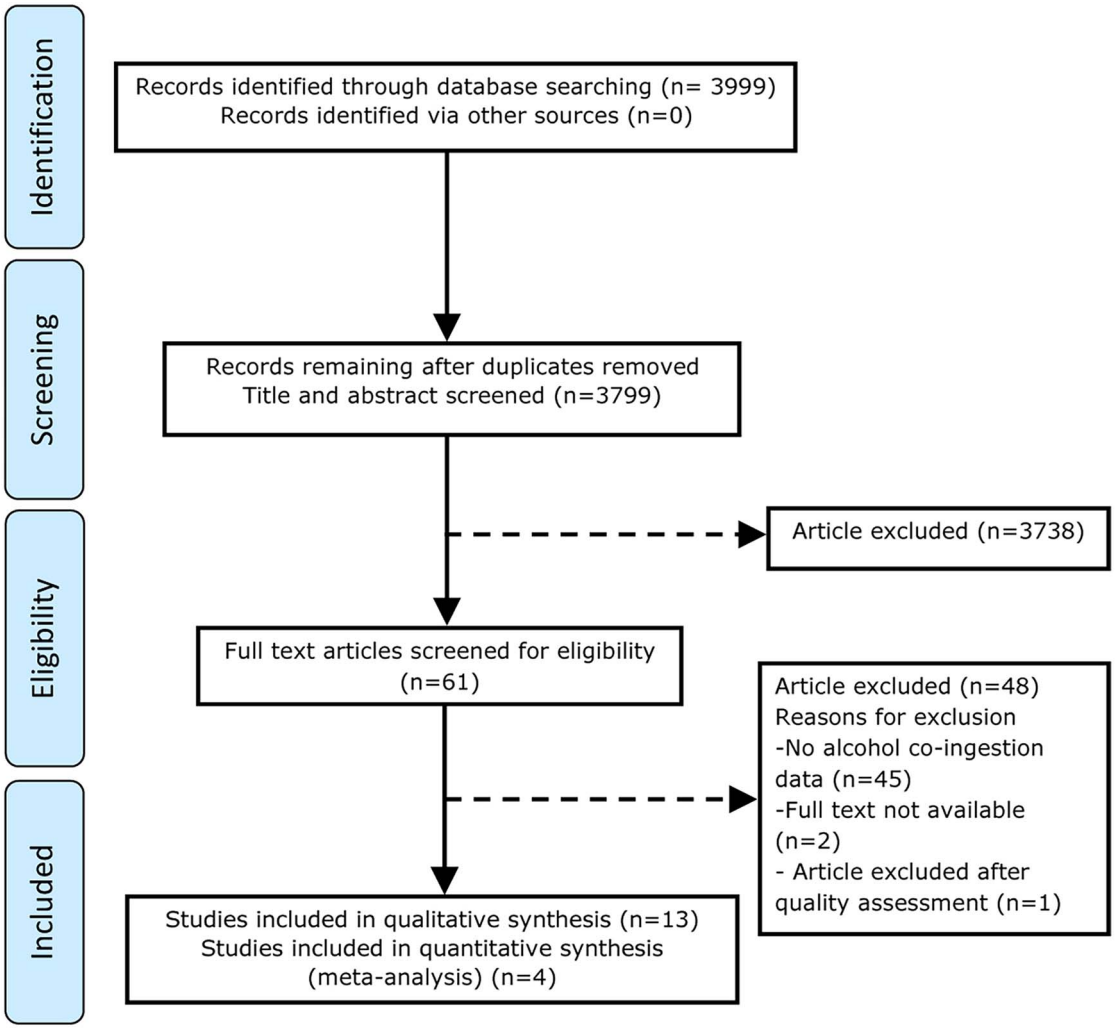

Fig. 1. PRISMA flow diagram illustration included and excluded studies in the systematic review.

(Norway, France, Greece, Belgium and Romania). Majority of the studies were on organophosphorus (OP) insecticides (Eddleston *et al*., 2009; Min *et al*., 2015; Lee *et al*., 2017; Dhanarisi *et al*., 2018) followed by the neonicotinoid insecticide imidacloprid (Yeh *et al*., 2010; Fuke *et al*., 2014), carbamate insecticide ethiofencarb (Al-Samarraie *et al*., 2009) and organochlorine insecticide endosulfan (Demeter *et al*., 1977).

Alcohol co-ingestion and demographic characteristics

Four studies reported alcohol co-ingestion predominatly in males (Eddleston *et al*., 2009; Min *et al*., 2015; Lee *et al*., 2017; Dhanarisi *et al*., 2018). The patients in cases with alcohol co-ingestion were older than non-co-ingested group in two studies (Eddleston *et al*., 2009; Dhanarisi *et al*., 2018).

Table 2. Characteristics of included studies

Author/Year	Country	Study design	Age group/ age (years)	Sample size (*n*)	Type of pesticide ingested	Absolute or estimated pesticide concentration measured (Yes/ No)	Absolute or estimated alcohol concentration measured (Yes/ No)	Outcome Measures
Lee *et al.* (2017)	South Korea	Retrospective cohort study	42–71	135 (93 males)	OP	Yes	Yes (Survivors: 80 [0–167] non-survivors: 192 [97–263] mg/dL)	Increased risk of death (non-survivors had a 2-fold greater BAC, compared with the survivors; 192 [97–263] vs. 80 [0–166.75] mg/dL, $P < 0.001$) Increased duration of intubation (non-survivors; 19 [82.6%] vs. survivors; 68 [60.7%], $P = 0.046$) Decreased pseudocholinesterase levels (non-survivors; 226 [126–663] vs. survivors;177 [120–667] $P = 0.763$)
Min *et al.* (2015)	South Korea	Retrospective cohort study	Median ALC+: 59, ALC−: 55	136 (93 males)	OP	Yes	Yes (161 [89–209] mg/dL)	Increased risk of death (ALC+; 28/95 [39.0%], ALC−; 2/41 [4.9%] $P = 0.002$) Increased duration of intubation (ALC+; 71/95 [74.7%], ALC−;16/41 [4.9%] $P < 0.001$) Increased risk of aspiration pneumonia (ALC+; 23/95 [24.2%], ALC−; 3/41 [7.3%] $P = 0.021$) Increased duration of hospital stays (ALC+; 15.0 [5.0–24.0], ALC−; 10 [5.0–24.0] days $P = 0.654$) Decreased pseudocholinesterase levels (ALC+; 171.5 [143.5–697.0], ALC−; 274.0 [790–810.0] U/L $P = 0.738$)
Garammana *et al.* (2010)	Sri Lanka	Prospective case series	14–78 (median: 28)	110 (83 males)	Bispyribac	Yes	No	Death (ALC+; 2/16 [12.5%], ALC−; 1/107 [0.9%]) Decreased consciousness (From total deaths, 02 patients [66.6%] were associated with alcohol co-ingestion and low GCS [3 and 12])
Dhanarisi *et al.* (2018)	Sri Lanka	Prospective case series	Median ALC+: 32, ALC−: 48	243 (182 males)	Profenofos	Yes	No	Increased risk of death (ALC+; 10/64 [15.6%], ALC−;10/179 [5.6%]; $P = 0.013$) Increased duration of intubation (ALC+; 13/64 [20.3%], ALC−; 16/179 [8.9%]; $P = 0.016$) Increased duration of hospital stays (ALC+; 3.6 [2.0–7.8], ALC−; 3.1 [1.9–5.0) days; $P = 0.112$) Decreased acetylcholinesterase levels (ALC+; 0 [0–293.3], ALC−; 0 [0–0.8] mU/μmol Hb $P = 0.0559$)
Eddleston *et al.* (2009)	Sri Lanka	Prospective case series	Median ALC+: 39, ALC−: 25	72 (55 males)	Dimethoate	Yes	Yes (15 [0–115] mg/dL)	Increased risk of death (non-survivors BAC; 0.94 [0.52–1.30] vs. survivors BAC; 0.0 [0.00–1.04] g l^{-1}, $P = 0.018$) Decreased butyrylcholinesterase levels (ALC+; 1561 [837–2829], ALC−; 1252 [216–2829] mU ml^{-1} $P = 0.20$)

(*Continued*)

Table 2. Continued

Author/Year	Country	Study design	Age group/ age (years)	Sample size (*n*)	Type of pesticide ingested	Absolute or estimated pesticide concentration measured (Yes/ No)	Absolute or estimated alcohol concentration measured (Yes/ No)	Outcome Measures
Mao *et al.* (2012)	Taiwan	Observational case series	46 (IQR: 33–63)	131 (90 males)	Glufosinate	Yes	No	Decreased risk of death (severe/fatal ALC+; 1 [3%], non-severe ALC+; 21 [25.6%] $P = 0.004$)
Gazzi *et al.* (2015)	Romania	Retrospective case series	20–29	606 (264 males)	Cholinesterase inhibitors	Yes	No	Increased risk of death (65.2% of death were associated with alcohol co-ingestion) Disorders of consciousness (73.9% of death were associated with disorders of consciousness)
Fuke *et al.* (2014)	Japan	Case report	70	_	Imidacloprid	Yes	Yes (105 lg/ml)	Death
Ernouf *et al.* (1998)	France	Case report	47	_	Paraquat	Yes	Yes (3.34 g/L)	Death
Boumba (2017)	Greece	Case report	52	_	Pyrethroids in combination with mirtazapine	Yes	Yes (0.75 g/L)	Death
Yeh *et al* (2010)	Taiwan	Case report	67	_	Imidacloprid	No	Yes (104 mg/dL)	Arrhythmia and multiple organ failure within hours of intake death
Al-Samarraie *et al.* (2009)	Norway	Case report	56	_	Ethiofencarb	Yes	Yes (0.12 g/100 ml)	Death
Demeter *et al.* (1977)	Belgium	Case report	28	_	Endosulfan	Yes	Yes (1.81 g/L)	Death

ALC+: alcohol was co-ingested; ALC-: alcohol was not co-ingested; BAC: blood alcohol concentration; NA: not available

Alcohol co-ingestion and other clinical characteristics

Only two studies reported the length of hospital stay by alcohol co-ingestion showing no significant difference in length of hospital stay between patients reporting alcohol co-ingestion and those not co-ingesting alcohol (Min *et al*., 2015; Dhanarisi *et al*., 2018) (Supplementary Table 4). Alcohol ingestion was associated with larger ingestions of OP insecticide dimethoate in the only study in which pesticide concentrations were measured where alcohol was positively associated with dimethoate concentration ($P = 0.002$) (Eddleston *et al*., 2009). No significant difference was observed between alcohol and non-alcohol groups regarding the amount of pesticide ingested in two studies (however, dose was not confirmed by measuring blood concentration in these studies) (Min *et al*., 2015; Dhanarisi *et al*., 2018). One study in dimethoate poisoning reported slightly higher median BuChE activity in patients with alcohol detectable in blood on admission than in those with no alcohol detectable in blood [1561 mU ml^{-1} (Interquartile Range (IQR) 837–2829) vs. 1252 mU ml^{-1} (IQR 216–2829); P = 0.20; normal range 3000–6000 mU ml^{-1}] (Eddleston *et al*., 2009). However, none of the OP poisoning studies reported a significant difference between alcohol co-ingested patients and non-co-ingested patients regarding cholinesterase activity ($P > 0.05$) (Min *et al*., 2015; Dhanarisi *et al*., 2018). Only two studies reported the level of consciousness. These studies showed that >50% of patients who died were associated with alcohol intake and disorders of consciousness/low Glasgow Coma Scale (GCS) (Garammana *et al*., 2010; Gazzi *et al*., 2015). According to one study, out of the total three deaths, two individuals had low GCS (3 and 12) and had also consumed alcohol, whereas the third death patient had a GCS of 13 without alcohol (Garammana *et al*., 2010). The other study reported that more than half of fatalities occurred in patients who ingested alcohol (65.2%) with disorders of consciousness (73.9%) (Gazzi *et al*., 2015).

Alcohol co-ingestion and risk of death

Alcohol co-ingestion was associated with a higher risk of death than those who did not co-ingest alcohol in pesticide self-poisoning including OP insecticides, the herbicide bispyribac and other pesticides. Forest plots of the effect of alcohol co-ingestion on death could be produced only for four studies (Garammana *et al*., 2010; Gazzi *et al*., 2015; Min *et al*., 2015; Dhanarisi *et al*., 2018) (Fig. 2, Supplementary Table 4). Meta-analysis showed that alcohol co-ingestion in pesticide self-poisoning was associated with increased risk of death (OR 4.9, 95% CI 2.9–8.2 $P < 0.0001$). There was strong association between blood alcohol concentration (BAC) and outcome in OP self-poisoning (Eddleston *et al*., 2009; Lee *et al*., 2017). In one study (Eddleston *et al*., 2009), patients who died had a higher admission median alcohol concentration than survivors and the risk of death was higher amongst individuals who consumed alcohol ($P = 0.018$).

Another study (Lee *et al*., 2017), not included in meta-analysis due to no death data reported for alcohol and non-alcohol groups separately, found a BAC of 173 mg/dL to be a significant risk factor for fatal OP poisoning; the patients who died had a 2-fold greater BAC, compared with the survivors ($P < 0.001$).

Only two studies reported alcohol co-ingestion and fatality by gender. One study ($n = 72$) on dimethoate poisoning reported a single death (6%) among females ($n = 17$) but none of the women in the study had co-ingested alcohol (Eddleston *et al*., 2009). Another study of profenofos self-poisoning showed that 50% of deaths from total deaths ($n = 20$) were associated with alcohol co-ingestion among males ($n = 10$) (Dhanarisi *et al*., 2018). However, other studies have not reported number of deaths for males and females separately.

Only one study showed that the alcohol co-ingestion was associated with reduced mortality for glufosinate herbicide self-poisoning where alcohol co-ingestion was inversely associated with the risk of developing severe/fatal outcome with this poison (OR 0.1, 95% CI <0.1–0.5) (Mao *et al*., 2012).

Alcohol co-ingestion and tracheal intubation/ventilation

Only two studies reported the association between alcohol co-ingestion and risk of intubation/ventilation (Min *et al*., 2015; Dhanarisi *et al*., 2018) (Supplementary Table 4). Meta-analysis showed that alcohol co-ingested group required intubation eight times more often than non-co-ingested group in OP self-poisoning (OR 8.0, 95% CI 4.9–13.0 $P < 0.0001$) (Fig. 2). More aspiration pneumonia was observed in the group poisoned with organophosphate insecticide with alcohol in one study (Min *et al*., 2015).

Case studies

Published case reports of six fatal poisonings in men postulated that the pesticide's interaction with alcohol may have been a contributing factor for death (Demeter *et al*., 1977; Ernouf *et al*., 1998; Al-Samarraie *et al*., 2009; Yeh *et al*., 2010; Fuke *et al*., 2014; Boumba *et al*., 2017) (Supplementary Table 4). They reported co-ingestion of alcohol with six different pesticides (imidacloprid, paraquat, endosulfan, ethiofencarb, alpha-cypermethrin and deltamethrin) (Demeter *et al*., 1977; Ernouf *et al*., 1998; Al-Samarraie *et al*., 2009; Fuke *et al*., 2014; Boumba *et al*., 2017). One case study reported an ingestion of alcohol mixed with imidacloprid causing acute multiorgan failure including kidney injury, acute lung injury, hypotension, metabolic acidosis and arrhythmia within hours of ingestion. This study suggests that imidacloprid can be bio-transformed in various parts of the body by aldehyde oxidase to highly toxic metabolites causing organ damages and effects of alcohol in the activity of aldehyde oxidase may also contribute to multiorgan failure (Yeh *et al*., 2010).

DISCUSSION

This review provides the first quantitative summary of the world literature on the relationship between alcohol co-ingestion and clinical outcome in pesticide self-poisoning using meta-analysis to estimate the increased risk of death and intubation associated with alcohol co-ingestion. Alcohol co-ingestion was associated with a 4.9-fold increase in risk of mortality and an 8-fold increase in risk of intubation. The increased risk of poor outcome with alcohol co-ingestion may be due to greater suicidal intent (Oh *et al*., 2014; Conner and Bagge, 2019), underlying health conditions (Eddleston *et al*., 2005; Mohamed *et al*., 2009; Wijerathna *et al*., 2019) and

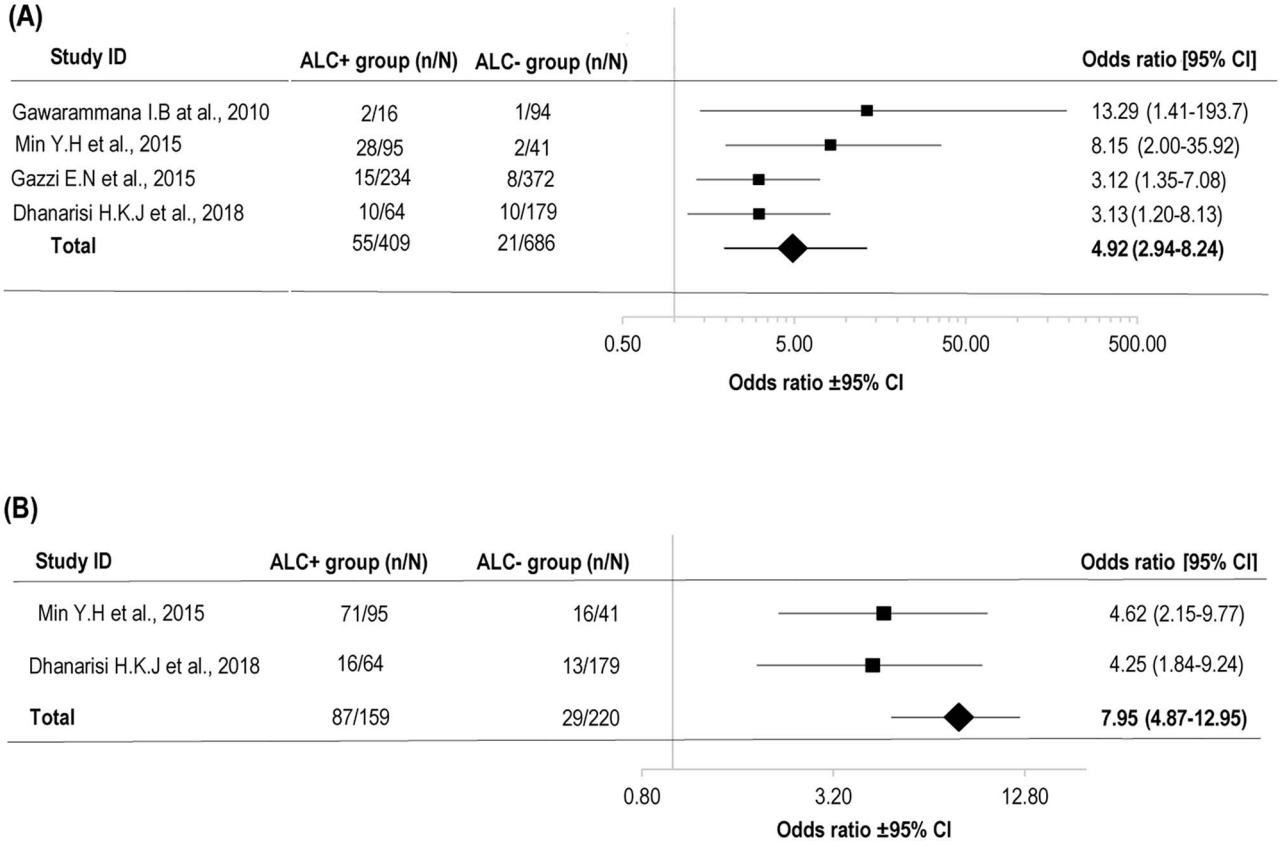

Fig. 2. Forest plots for overall survival showing the alcohol co-ingestion and (A); death (B); intubation AIC+: alcohol co-ingestion; AC−: absence of alcohol co-ingestion.

increased volume of ingestion of pesticide (Eddleston *et al.*, 2009).

Out of 14 studies those met the eligibility criteria, we have included only 13 articles on alcohol co-ingestion and outcome in pesticide self-poisoning after quality assessment (1 was excluded due to poor quality according to quality assessment tool). Most of the included studies were carried out in Asia since high prevalence of pesticide self-poisonings (of 89% of global suicides) is reported from the Asian and Western Pacific regions (Eddleston and Phillips, 2004; Pearson *et al.*, 2017; Mew *et al.*, 2017). Only four studies explored the direct relationship between alcohol co-ingestion and pesticide self-poisoning (Eddleston *et al.*, 2009; Min *et al.*, 2015; Lee *et al.*, 2017; Dhanarisi *et al.*, 2018).

The relationships between alcohol co-ingestion, poison dosage and BAC varied between the studies that measured alcohol. The alcohol intoxication can contribute to the clinical outcome with fatalities and it is observed that alcohol consumption is associated with high pesticide concentrations. Co-ingestion of alcohol may increase the tendency to ingest large amount of insecticide thereby increasing risk of death (Eddleston *et al.*, 2009). Furthermore, this risk was reduced by controlling the insecticide concentration, indicating that deaths were not due to the direct toxic effects of alcohol but to the higher ingestions by intoxicated individuals. Alternatively, alcohol co-ingestion may alter the pharmacokinetics of pesticides by altering the metabolism of OP leading to slow elimination from the body (Buratti and Testai, 2007; Jang and Harris, 2007). Acute alcohol ingestion can inhibit CPY450 enzyme function (Mattila, 1990; Chan and Anderson, 2014) and may potentially alter metabolism of pesticides. Alcohol concentrations may also be high that they are likely to dominate modulation of CYP450 activity (Busby *et al.*, 1999).

Interestingly, a study demonstrated that higher blood concentrations of alcohol were associated with higher blood dimethoate concentrations and had worse outcomes (Eddleston *et al.*, 2009). However, the blood alcohol did not appear to directly affect outcome; instead, alcohol intoxication appeared to result in greater dimethoate ingestion (and perhaps increased absorption) and worse outcome.

Overall, older age (>50 years) is associated with alcohol consumption in most of the studies (Eddleston *et al.*, 2009; Min *et al.*, 2015; Lee *et al.*, 2017; Dhanarisi *et al.*, 2018). Males outnumbered the female in terms of alcohol co-ingestion probably due to influence of cultural norms in those specific societies (Hettiarachchi and Kodithuwakku, 1989; Eddleston *et al.*, 2005). Males made up the higher number of deaths in alcohol co-ingestion than females (Eddleston *et al.*, 2009; Dhanarisi *et al.*, 2018).

Patients co-ingested with alcohol exhibited more severe complications with longer hospitals stays, more intubations and ventilation compared with non-ingested group. However, most of the studies did not specifically mention the contribution of alcohol on these outcomes. Respiratory failure is one of the leading causes of death due to acute intoxication of pesticides, and alcohol is one of the most commonly abused drugs that may induce respiratory failure (Gazzi *et al.*, 2015; Min *et al.*, 2015; Lee *et al.*, 2017; Dhanarisi *et al.*, 2018).

Although a study has postulated that the presence of a significant BAC could be considered as a secondary

contributory factor to the fatal outcome of pesticide self-poisoning (Boumba *et al.*, 2017), the data presented are insufficient to conclude how this secondary contributory factor would be responsible for increased fatal outcomes.

There was only one study which postulated that the alcohol co-ingestion could be beneficial in reducing the severe toxic effects of oral herbicide glufosinate exposure. The alcohol co-ingestion was inversely associated with the severe/fatal toxicity (OR 0.1, 95% CI 0.1–0.5, $P = 0.004$) (Mao *et al.*, 2012). However, there is no sound data to demonstrate the exact mechanism of the protective effect of alcohol in this study.

Several studies showed that lower GCS scores (consciousness) were associated with alcohol intake (Alexander *et al.*, 2004; Rundhaug *et al.*, 2015). A decreased level of consciousness correlates to increased morbidity (Upadhyay *et al.*, 2017), mortality (Garammana *et al.*, 2010; Gazzi *et al.*, 2015) and makes management of pesticide-poisoned patients more difficult possibly by elevating the depressive effects of pesticide on conscious level and respiratory drive (Eddleston *et al.*, 2009).

The prevalence of methanol poisoning has increased in some countries, but we have studied ethanol which is a most commonly co-ingested compound and methanol co-ingestion is relatively uncommon with pesticide poisoning.

Limitations of the review

This systematic review includes only the articles published in English. Except in one cohort study (Eddleston *et al.*, 2009), other studies are limited by the lack of measurement of blood alcohol and pesticide concentrations which would have helped explicate the comparative role of the pesticide and alcohol to outcome. Other limitation in these studies is that they did not quantify chronic exposure to alcohol, a likely confounder in understanding the relationship between acute alcohol use and pesticide poisoning. Only one study reported the drinking history measures (Dhanarisi *et al.*, 2018) but it did not assess the association between drinking history measures and the outcomes. Cultural and social aspects of drinking patterns may play a role in the relationship between alcohol and outcome in deliberate pesticide self-poisoning.

CONCLUSION

It is evident that alcohol co-ingestion leads to increased risk of death and intubation, worsening hospital outcomes in pesticide self-poisoning. In addition, our results indicate that alcohol co-ingestion is associated with male gender, older age and higher plasma concentrations/dose in patients' self-ingestion with pesticide. Larger studies looking at different pesticide types are required to assess this further along with quantifying the effect of chronic exposure to alcohol.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Alcohol and Alcoholism* online.

AUTHOR CONTRIBUTIONS

Hand-searching, screening, data extraction, was performed by JD, TW and SP. FM, IG, FS and ME gave guidance on project design, data extraction, analysis and methodological assessments. JD and TW drafted the manuscript. JD, TW, SP, FM, ME, FS and VM revised and edited the manuscript. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

The data underlying this article are available in the article and in its online supplementary materials.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

References

Alexander S, Kerr ME, Yonas H *et al.* (2004) The effects of admission alcohol level on cerebral blood flow and outcomes after severe traumatic brain injury. *J Neurotrauma* **21**:575–83.

Al-Samarraie MS, Karinen R, Rognum T *et al.* (2009) Lethal poisoning with ethiofencarb and ethanol. *J Anal Toxicol* **33**:389–92.

Boumba VA, Rallis GN, Vougiouklakis T. (2017) Poisoning suicide with ingestion of the pyrethroids alpha-cypermethrin and deltamethrin and the antidepressant mirtazapine: a case report. *Forensic Sci Int* **274**:75–8.

Buckley NA, Fahim M, Raubenheimer J *et al.* (2021) Case fatality of agricultural pesticides after self-poisoning in Sri Lanka: a prospective cohort study. *Lancet Glob Health* **9**:e854–62.

Buratti FM, Testai E. (2007) Evidences for CYP3A4 autoactivation in the desulfuration of dimethoate by the human liver. *Toxicology* **241**: 33–46.

Busby WF, Ackermann JM, Crespi CL. (1999) Effect of methanol, ethanol, dimethyl sulfoxide, and acetonitrile on in vitro activities of cDNA-expressed human cytochromes P-450. *Drug Metab Dispos* **27**:246–9.

Chan L-N, Anderson GD. (2014) Pharmacokinetic and pharmacodynamic drug interactions with ethanol (alcohol). *Clin Pharmacokinet* **53**:1115–36.

Conner KR, Bagge CL. (2019) Suicidal behavior: links between alcohol use disorder and acute use of alcohol. *Alcohol Res* **40**. https://doi.org/10.35946/arcr.v40.1.02.

Demeter J, Heyndrickx A, Timperman J *et al.* (1977) Toxicological analysis in a case of endosulfan suicide. *Bull Environ Contam Toxicol* **18**:110–4.

Dhanarisi HJ, Gawarammana IB, Mohamed F *et al.* (2018) Relationship between alcohol co-ingestion and outcome in profenofos self-poisoning–a prospective case series. *PLoS One* **13**: e0200133.

Eddleston M, Phillips MR. (2004) Self poisoning with pesticides. *BMJ* **328**:42–4.

Eddleston M, Gunnell D, Karunaratne A *et al.* (2005) Epidemiology of intentional self-poisoning in rural Sri Lanka. *Br J Psychiatr* **187**: 583–4.

Eddleston M, Buckley NA, Gunnell D *et al.* (2006a) Identification of strategies to prevent death after pesticide self-poisoning using a Haddon matrix. *Inj Prev* **12**:333–7.

Eddleston M, Karunaratne A, Weerakoon M *et al.* (2006b) Choice of poison for intentional self-poisoning in rural Sri Lanka. *Clin Toxicol* **44**:283–6.

Eddleston M, Gunnell D, Von Meyer L *et al.* (2009) Relationship between blood alcohol concentration on admission and outcome in dimethoate organophosphorus self-poisoning. *Br J Clin Pharmacol* **68**:916–9.

Eden J, Levit L, Berg A *et al.* (2011) Standards for initiating a systematic review. In *Finding What Works in Health Care: Standards For Systematic Reviews*. Washington (DC): National Academies Press (US).

Ernouf D, Boussa N, Legras A *et al.* (1998) Acute paraquat poisoning: increased toxicity in one case with high alcohol intake. *Hum Exp Toxicol* **17**:182–4.

Fernando K, Jayamanna S, Weerasinghe M *et al.* (2021) Risk factors for deliberate self-harm in young people in rural Sri Lanka: a prospective cohort study of 22,000 individuals. *Ceylon Med J* **66**: 87–95.

Fuke C, Nagai T, Ninomiya K *et al.* (2014) Detection of imidacloprid in biological fluids in a case of fatal insecticide intoxication. *Leg Med* **16**:40–3.

Garammana BI, Roberts DM, Mohamed F *et al.* (2010) Acute human self-poisoning with bispyribac-containing herbicide nominee®: a prospective observational study. *Clin Toxicol* **48**:198–202.

Gazzi EN, Sorodoc V, Jaba IM *et al.* (2015) Profile of adult acute cholinesterase inhibitors substances poisoning–a 30 years analysis. *Open Med* **10**:278–84.

Grmec Š, Mally Š, Klemen P. (2004) Glasgow coma scale score and QTc interval in the prognosis of organophosphate poisoning. *Acad Emerg Med* **11**:925–30.

Gunnell D, Eddleston M, Phillips MR *et al.* (2007) The global distribution of fatal pesticide self-poisoning: systematic review. *BMC Public Health* **7**:1–15.

Hettiarachchi J, Kodithuwakku GC. (1989) Self-poisoning in Sri Lanka: factors determining the choice of the poisoning agents. *Hum Toxicol* **8**:507–10.

Jang GR, Harris RZ. (2007) Drug interactions involving ethanol and alcoholic beverages. *Expert Opin Drug Metab Toxicol* **3**:719–31.

Jayasinghe NR, Foster JH. (2011) Deliberate self-harm/poisoning, suicide trends. The link to increased alcohol consumption in Sri Lanka. *Arch Suicide Res* **15**:223–37.

Konradsen F, van der Hoek W, Peiris P. (2006) Reaching for the bottle of pesticide – a cry for help. Self-inflicted poisonings in Sri Lanka. *Soc Sci Med* **62**:1710–9.

Lee YH, Oh YT, Lee WW *et al.* (2017) The association of alcohol consumption with patient survival after organophosphate poisoning: a multicenter retrospective study. *Intern Emerg Med* **12**:519–26.

Liberati A, Altman DG, Tetzlaff J *et al.* (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* **6**:e1000100.

Mao Y-C, Hung D-Z, Wu M-L *et al.* (2012) Acute human glufosinate-containing herbicide poisoning. *Clin Toxicol* **50**:396–402.

Mattila MJ. (1990) Alcohol and drug interactions. *Ann Med* **22**:363–9.

Mew EJ, Padmanathan P, Konradsen F *et al.* (2017) The global burden of fatal self-poisoning with pesticides 2006-15: systematic review. *J Affect Disord* **219**:93–104.

Min YH, Park SM, Lee KJ *et al.* (2015) Effect of alcohol on death rate in organophosphate poisoned patients. *J Korean Soc Clin Toxicol* **13**:19–24.

Mohamed F, Dawson AH, Roberts D. (2009) Factors influencing variability in clinical outcomes from imidacloprid self-poisoning. *Clin Toxicol* **47**:836–7.

Moher D, Shamseer L, Clarke M *et al.* (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* **4**:1–9.

Naghavi M. (2019) Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the global burden of disease study 2016. *BMJ* **364**:l94.

Oh SH, Lee KU, Kim SH *et al.* (2014) Factors associated with choice of high lethality methods in suicide attempters: a cross-sectional study. *Int J Mental Health Syst* **8**:1–5.

Ouzzani M, Hammady H, Fedorowicz Z *et al.* (2016) Rayyan – a web and mobile app for systematic reviews. *Syst Rev* **5**:1–10.

Pearson M, Metcalfe C, Jayamanne S *et al.* (2017) Effectiveness of household lockable pesticide storage to reduce pesticide self-poisoning in rural Asia: a community-based, cluster-randomised controlled trial. *Lancet* **390**:1863–72.

Rundhaug NP, Moen KG, Skandsen T *et al.* (2015) Moderate and severe traumatic brain injury: effect of blood alcohol concentration on Glasgow coma scale score and relation to computed tomography findings. *J Neurosurg* **122**:211–8.

Senarathna L, Jayamanna SF, Kelly PJ *et al.* (2012) Changing epidemiologic patterns of deliberate self poisoning in a rural district of Sri Lanka. *BMC Public Health* **12**:1–8.

Upadhyay S, Bhalerao N, Pratinidhi SA. (2017) Study of level of consciousness and electrolyte abnormalities in patient admitted to intensive care unit (ICU). *Int J Contemp Med Res* **4**:1739–42.

Van Der Hoek W, Konradsen F. (2005) Risk factors for acute pesticide poisoning in Sri Lanka. *Trop Med Int Health* **10**:589–96.

Warriner RA III, Nies AS, Hayes WJ Jr. (1977) Severe organophosphate poisoning complicated by alcohol and turpentine ingestion. *Arch Environ Health* **32**:203–5.

Wijerathna TM, Gawarammana IB, Mohamed F *et al.* (2019) Epidemiology, toxicokinetics and biomarkers after self-poisoning with Gloriosa superba. *Clin Toxicol* **57**:1080–6.

World Health Organization. (2014) *Preventing Suicide: A Global Imperative*. World Health Organization, Geneva, Switzerland.

World Health Organization. (2019) *Global Status Report on Alcohol and Health 2018*. World Health Organization, Geneva, Switzerland.

Yeh I-J, Lin T-J, Hwang D-Y. (2010) Acute multiple organ failure with imidacloprid and alcohol ingestion. *Am J Emerg Med* **28**: 255.e1–3.