REVIEW ARTICLE

Effect of extracorporeal membrane oxygenation on mortality rate of aluminum phosphate poisoning: A systematic review and meta-analysis

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Background: Aluminum phosphate (ALP) poisoning has a high mortality rate (MR) secondary to cardiogenic shock. Recently, extracorporeal membrane oxygenation (ECMO) showed a successful result in this issue. We conducted a systematic review and meta-analysis to compare the MR of patients with ALP poisoning who underwent ECMO versus those with conventional treatment. **Materials and Methods:** Two parallel databases' reviews were done to find the ECMO treatment-applied studies or conventional treatment-applied studies according to the PRISMA protocol. All studies in any languages and English conference abstracts were included for ECMO treatment-applied studies. Only English-language human observational studies, which reported MR, were included in conventional treatment-applied studies. All ETAS case reports were summarized and used as a newly generated cross-sectional study (NGCSS) for inclusion in the meta-analysis. **Results:** Out of 167 and 1043 records, 17 case reports (24 cases), 3 cross-sectional studies, and 9 conventional treatment-applied studies were selected. In meta-analysis NGCSS applied as the fourth cross-sectional ECMO treatment-applied studies. The overall MR of ECMO-treated cases (23% [95% confidence interval (CI): 7%–39%]) was significantly less than conventionally treated cases (60% [95% CI: 39%–63%]; $P < 0.001$). In ECMO-treated cases, the weighted mean difference (WMD) for age, blood pH, ALP dose, hospitalization, ECMO lag time, and ECMO duration were not statistically significant between survived and nonsurvived cases. However, WMD of cardiac ejection fraction (4.6%; 95% CI: 2.76%–6.39%; $P < 0.0001$), exposure to hospitalization lag time (−2.05; 95% CI: −4.05–0.14 h; $P = 0.06$), and length of hospital stay (16; 95% CI: 12.0–20.5 days; $P < 0.0001$) between survived and nonsurvived ETC were significant. **Conclusion:** ECMO reduced the MR of ALP-poisoned patients; however, it is a highly invasive and complicated procedure.

Key words: Extracorporeal membrane oxygenation, meta-analysis, pesticide, poisoning, survival rate

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INTRODUCTION

Aluminum phosphate (ALP) poisoning is a critical public health issue, especially in developing countries such as Iran, India, and Pakistan,[1-3] where it is commonly used as a fumigant. ALP poisoning has an alarmingly high mortality rate (MR), ranging from 70% to 100% in moderate-to-severe cases.[4,5] When ALP comes into contact with water, especially in the acidic environment of the gastric mucosa, it releases phosphine gas.[6] Phosphine disrupts the mitochondrial electron transport chain, leading to a loss of ATP production, increased oxidative stress, and, ultimately, cell injury.[7] Myocardial cells are particularly vulnerable, resulting

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in toxic cardiomyopathy, a key factor in ALP-induced mortality.[7,8]

Several treatments have been investigated to reduce the MR of ALP poisoning, including N-acetyl cysteine,[9] magnesium sulfate, calcium gluconate,[10] gavage of coconut oil and potassium permanganate,[11] sodium bicarbonate,[12] L-carnitine,[13] hemodialysis,[13] Intra-aortic balloon pump,[14] nanomicelle curcumin,[6] digoxin,[15,16] and glucagon.[15] Despite these efforts, none have proven definitively curative, highlighting the need for alternative approaches

Extracorporeal membrane oxygenation (ECMO) has emerged as a potentially lifesaving intervention for patients with circulatory failure due to poisoning.[17,18] ECMO provides cardiac and respiratory support, allowing time for the patient's heart and lungs to recover. About 160 reports were recorded in the literature for applying ECMO in poisoned cases from 1946 to 2020,[17] and the cases of its use in poisoning are increasing every day.[19,20] The American Heart Association recently in the last update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning recommended applying venoarterial ECMO in patients with cardiogenic shock or dysrhythmias that are refractory to other treatment measures as a lifesaving method.[21]

Although ECMO has shown promising results in case reports and a few cross-sectional studies for severe ALP poisoning,[20,22-28] no clinical trials have been conducted due to ethical and technical challenges. As the main cause of mortality of ALP poisoning is circulatory insufficiency, and ECMO may have a beneficial effect in this regard, this systematic review and meta-analysis aims to evaluate the efficacy of ECMO in reducing the MR of ALP poisoning by comparing it with conventional treatments. By synthesizing this information, we aim to provide a clearer understanding of ECMO's potential benefits and to guide future clinical practice.

LITERATURE REVIEW METHODOLOGY

This study is a systematic review and a meta-analysis. It has been carried out according to the PRISMA guidelines.[29] The research protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (ethical code IR.MUI.MED.REC.1402.275).

As there is not any clinical trial on applying ECMO for ALP poisoning, we have done two parallel databases review to find the studies that apply ECMO and studies that apply conventional treatment of ALP poisoning (Did not applied ECMO), to compare them.

Data sources

Bibliographic literature searches were conducted in the EMBASE, PubMed, Google Scholar, Web of Science, ProQuest, Science Direct, Springer, Scopus, and Cochrane from January 2000 to February 2023 for relevant articles. References lists of the selected articles were also searched.

Search strategy

Extracorporeal membrane oxygenation treatment-applied studies

We used the following keyword search techniques to find the relevant papers in all databases. The search techniques were modified according to the search tools of each database. The selected keywords were as follows: (ECMO OR "extracorporeal membrane oxygenation" OR "ECLS Treatment" OR "ECMO Treatment" OR "Extracorporeal Life Support" OR ECLS OR "Oxygenation, Extracorporeal Membrane" OR "Venoarterial ECMO" OR "Venoarterial Extracorporeal Membrane Oxygenation" OR "Venovenous ECMO" OR "Venovenous Extracorporeal Membrane Oxygenation") AND (Phosphines OR Aluminum phosphide) AND (Poison* OR intoxicant* OR overdose* OR toxicity) in Title, MESH/subject, and Abstract.

Conventional treatment-applied studies

We used the following keyword search techniques to find the relevant papers in all databases. The search techniques were modified according to the search tools of each database. The selected keywords were as follows: (Phosphines OR Aluminum phosphide) AND (Poison* OR intoxicant* OR overdose* OR toxicity) in Title, MESH/subject, and Abstract. To reduce the results, we filtered those results by "Clinical Study" and "Observational Study" in article type, "Human" in Species, and "English" in article language.

Inclusion and exclusion criteria

For ECMO appalling studies, all studies contain cross-sectional studies, case reports, clinical trials, case–control studies, and conference abstracts in any language were included. Nonhuman studies and review articles were excluded. We did not exclude any of the studies regarding their JBI scoring.[30]

For conventional studies: As we need the overall MR of ALP-poisoned cases who were treated by conventional treatment methods, all observational studies that report the overall MR of ALP-poisoned cases (cross-sectional studies) in the English language were included. All case reports, clinical trials, reviews, meta-analyses, and nonhuman studies were excluded. All included records were scored according to a checklist for analytical cross-sectional studies, critical appraisal tools for use in JBI systematic reviews.[30] Any documents with score< 5 were excluded

Screening and selection

The full citations of all extracted documents were imported

into an EndNote database and duplicated documents were excluded. Two reviewers independently screened the title and abstract of records to find the eligible documents. Then, the full text of selected records was evaluated by each of the two reviewers individually. They approved their selection according to the full text of documents and extracted data from papers. Finally, they organized an online meeting in the presence of the third researcher and discussed selected articles and extracted data. Discrepancies were resolved through discussion, and data were approved by all three researchers.

Data extraction

For ECMO-included studies, the checklists were designed for data extraction from studies, case reports, and cross-sectional studies. The extracted data from case reports and case series included: the author's name, year of publication of the paper and data of cases. The following data of each case was extracted: age, gender, number of pills taken, manner of intoxication, intent of intoxication, lag time to hospitalization, initial vital signs and clinical manifestations, the first venous blood gas analysis and serum lactate levels, electrocardiogram (ECG) abnormality, treatment of arrhythmias, the initial echocardiographic findings, especially ejection reaction (EF) of the left ventricle at admission and discharge, vasopressors, lag time to ECMO, ECMO settings, time to raise the EF to acceptable value, time to correct metabolic acidosis, ECMO duration, ECMO complications, length of hospital stay, outcome (mortality and survival), discharge condition, and follow-up.

The extracted data from cross-sectional studies include the following: authors' name, year of publication, age, gender, number of pills taken, lag time to hospitalization, lag time to ECMO, the initial EF, initial blood pH, initial SOFA score, MR, and length of hospital stay in both ECMO and conventionally treated groups and in survivor and nonsurvivor groups.

The authors' names, year of publication, sample size, MR, and number of survivors and nonsurvivors' groups were extracted.

Data synthesis and meta-analysis

Case reports

All extracted data of cases were imported into SPSS (version 21.0; SPSS Inc, Chicago, IL). The prevalence of male sex, glomerular filtration rate <30 ml/min/1.73 m^2, blood pH <7, tachycardia (heart rate >100), hypotension (systolic blood pressure <90), ECG abnormality, and mortality were calculated. Furthermore, the mean and standard deviation of age, lag time of ingestion and hospitalization, dose of ALP, SOFA score, blood pH, EF at admission, EF in discharge, and hospital stay were estimated. The calculation was also compared in survivor and nonsurvivor cases. The difference between the length of hospital stay and ECMO duration in survivor and nonsurvivor cases was evaluated by nonparametric Mann–Whitney U test.

Meta-analysis

To compare the mean value of variables such as age, blood pH, dose of ALP, ECMO duration, EF at admission, hospital stay, lag time to hospitalization, and lag to ECMO between survived and nonsurvived people, three cross-sectional studies[1,22,23] were included in the meta-analysis. To increase the power of data analysis, the participants of all case reports and case series studies were considered a new cross-sectional study and its results were combined with three aforementioned studies. Meta-analysis was conducted to estimate the combined mean difference of the above-mentioned variables. The mean difference in the studied variables was calculated and compared between survived and dead groups. The pooled effect size was estimated as the weighted mean difference (WMD) and 95% confidence interval (95% CI). Heterogeneity between studies was evaluated using Cochran's Q test and I-square (I^2) index; I^2 higher than 50% was considered high heterogeneity.[31] For obtaining the pooled WMD and their corresponding 95% CIs, a random effects model based on DerSimonian and Laird method was used due to high heterogeneity between included studies or fixed effect when heterogeneity was low in our meta-analysis.[32] None subgroup did not apply when high heterogeneity between included studies. We also estimated the MR between people treated with ECMO and those who did not experience this treatment approach. The result was reported as the MR in percent along with 95% confidence interval, and it was compared between two groups in the framework of a subgroup analysis. We also did a sensitivity analysis to examine the extent to which the estimated effect size might be influenced by a particular study. Publication bias was also evaluated by the visual inspection of funnel plots.[33] Furthermore, Egger's and Begg's regression tests were used for formal evaluation of publication bias.[33] When there is publication bias, we did a trim-and-fill analysis to correct the results. Statistical analyses were performed using STATA version 11.2 (STATA Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Extracorporeal membrane oxygenation-treated studies

Study selection

Based on the results of the search strategies in databases, 167 documents were imported into Endnote for ECMO-treated studies. After deleting duplicated records, 36 records remained. We could not find any clinical trial study.

After the exclusion of the ineligible records, 17 papers of case reports and 3 documents of cross-sectional study remained [Figure 1].

Case reports

By 15 documents and 2 conference abstracts (17 records), 24 cases were reported [Table 1]. All case reports reported one case, except two reports (2 and 7 cases on each of them[27,28]).

Table 1 and Supplementary Tables 1-4 summarize the findings of case reports. The earliest was published in 2014.[34] Half of the cases were male, and the mean age of them was 25.43 ± 17.94 years. The youngest case was 15 months[44] and the oldest was 67 years old.[24] Seven cases were children (<14 years). The most cases ingested the ALP tablets and 7 cases (%29.16) were exposed to phosphine gas through inhalation.[28,34,37,40,41]

Nausea and vomiting were common manifestations of the majority of cases [Supplementary Table 2]. Gastrointestinal manifestations, such as nausea, vomiting, and diarrhea, were the main presentation in children before shock and cardiovascular collapse [Supplementary Table 2].

As shown in Table 1, the mean of ingested doses of ALP in reported cases was 3.633 ± 2.60 g (500 mg to 5 g). Some cases inhaled phosphine gas from 48 h to several days before.[34,41,44] The longer was a 3-year-old baby who inhaled phosphine gas for several days due to placing the ALP under her bed to treat a bedbug infestation.[41]

The lag time between ingestion and hospitalization in cases who orally ingested tablets was 7.54 ± 5.17 h (median = 5 h).

The majority of cases had hypotension and tachycardia. They received the full doses of two or three vasopressors such as dopamine, epinephrine, norepinephrine, or milrinone. However, one case was normotensive[44] and two cases were bradycardic[35,45] [Supplementary Table 2].

Severe metabolic acidosis with low serum bicarbonate and high serum lactate levels was reported in almost all cases. The mean value of blood pH was = 7.05 ± 0.178.

As summarized in Tables 1 and 2 and Supplementary Table 3, the cardiac evaluations of cases before ECMO showed a severe cardiomyopathy. ST-T changes, QRS widening, and intraventricular conduction defects were seen in their ECGs. Various atrial and ventricular arrhythmia (such as prolonged ventricular fibrillation, polymorphic, intractable, or recurrent ventricular tachycardia, Torsades de pointes, atrial fibrillation, or wide-complex supraventricular tachycardia) were reported in the phosphine-intoxicated cases. In most cases, the arrhythmia was recurrent though they had been treated with cardioversion, defibrillation, magnesium sulfate, lidocaine, or/and amiodarone. In one case, wide-complex supraventricular tachycardia was resolved spontaneously.[44] Severe left ventricular or biventricular systolic dysfunction, or dyskinesia, as well as low left ventricular ejection fraction (EF) (mean = %21.3 ± %10.33, range ≤5%–35%) were found in echocardiography of cases at the start of hospitalization or just before ECMO.

The lag time between admission and ECMO performance was 1–22 h, and half of the cases underwent ECMO through <3.5 h (median = 3.5 h) [Supplementary Table 4]. In all cases, vascular access was through femoral vessels. The fellow rate of ECMO pumps was setting 2.1–4.5 L/Min. The mean of ECMO duration of cases was 5.51 ± 4.29 days (21 h to 16 days) [Supplementary Table 4]. The ECMO duration was numerically higher in survived cases (6.28 ± 4.4 days) than in nonsurvivors (2.25 ± 0.95 days) (PV = 0.091); however, it is not statistically significant. EF raised to an acceptable

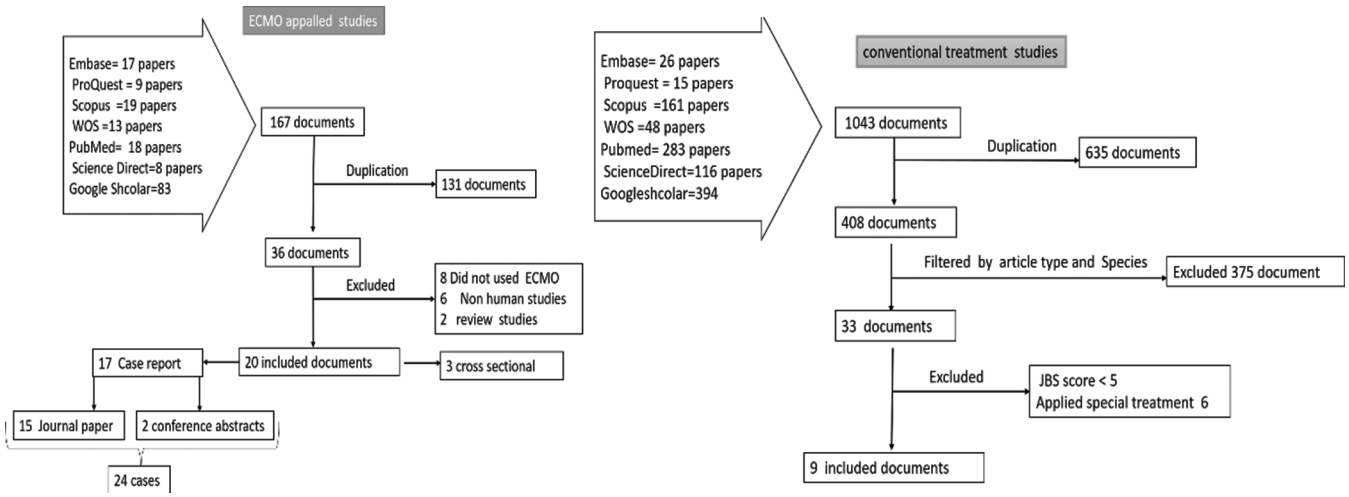

Figure 1: PRISMA flowchart for selection of articles in the systematic review and meta-analysis. WOS: Web of science, ECMO: Extracorporeal membrane oxygenation, JBS: JBI's score

Table 1: The gender, age, dose of ingested aluminum phosphate, manner and intent of poisoning, left ventricular ejection fraction at admission (ejection fraction*) and before extracorporeal membrane oxygenation weaning (ejection fraction##), length of hospital stay, and outcome of aluminum phosphate-intoxicated cases treated by extracorporeal membrane oxygenation

Case number	First author (year)	Sex	Age	Amount of ingestion	Manner/intent	EF* (%)	EF## (%)	Time to normal EF	ECMO duration	Length of hospital stay	Outcome	JBI scoring
1	Elabbassi *et al*. (2014)[34]	Male	6 years old	3 days inhalation	Inhalation/accidental	35	NR	NR			Survived	4
2	Merin *et al*. (2015)[28]	Male	5 years old	NR	Inhalation/accidental		NR	NR	7 days	21 days	Survived	6
3	Merin *et al*. (2015)[28]	Male	6 years old	NR	Inhalation/accidental		NR	NR	10 days	21 days	Survived	6
4	Sharma *et al*. (2015)[25]	Male	19 years old	3 g	Ingestion/NR	10–15	35–40	6 days	8 days	20 days	Survived	7
5	Mohan *et al*. (2015)[27]	Male	50 years old	2 tablets (3 g)	Ingestion/NR	28	42	3 days	44 h	22 days	Survived	4
6	Mohan *et al*. (2015)[27]	Female	40 years old	2 tablets (3 g)	Ingestion/NR	18	NR	NR	144 h	20 days	Survived	3
7	Mohan *et al*. (2015)[27]	Male	28 years old	2 tablets (3 g)	Ingestion/NR	22	NR	NR	96 h	34 days	Survived	4
8	Mohan *et al*. (2015)[27]	Male	17 years old	1 tablet (1.5 g)	Ingestion/NR	32	NR	NR	43 h	8 days	Survived	3
9	Mohan *et al*. (2015)[27]	Female	34 years old	2 tablets (3 g)	Ingestion/NR	22	NR	NR	48 h	43 day	Survived	4
10	Mohan *et al*. (2015)[27]	Male	46 years old	3 tablets (4 g)	Ingestion/NR	20	NR	NR	72 h	3 days	Nonsurvived	2
11	Mohan *et al*. (2015)[27]	Male	35 years old	2 tablets (3 g)	Ingestion/NR	18	NR	NR	72 h	3 days	Nonsurvived	2
12	Hassanian-Moghaddam *et al*. (2016)[35]	Male	28 years old	1.5 tablets (4.5 g)	Ingestion/NR	20	40	4 days	4 days	7 days	Survived	8
13	Mendonca *et al*. (2016)[36]	Male	6 years old	NR	NR/accidental	15	70	14 days	11 days	22 days	Survived	7
14	Chatterjee *et al*. (2017)[37]	Female	45 years old	2 weeks	Inhalation/accidental	Reduced	NR	NR	NR		Survived	4
15	Ekinci *et al*. (2017)[38]	Female	18 years old	1 tablet (0.5 g)	Ingestion/Sui	NR	NR	NR	21 h	22 h	Nonsurvived	5
16	Jaramillo-Stametz and Martin (2017)[39]	Female	45 years old	NR	Inhalation/accidental	NR	NR	NR			Survived	3
17	Hena *et al*. (2018)[40]	Female	3 years old	NR	Inhalation/accidental	26	35	16 days	16 days	36 days	Survived	8
18	Lehoux *et al*. (2018)[41]	Female	3 years old	Several days	Inhalation/accidental	<20	46	NR	15 days	30 days	Survived	7
19	Sharma *et al*. (2018)[24]	Female	67 years old	2 tablets	Ingestion/suicidal	20	35	1 day	3 days	10 days	Survived	7
20	Rao and Himaaldev (2020)[26]	Male	25 years old	3 tablets	Ingestion/NR	15–25	35–40	5 days	6 days	12 days	Survived	5
21	Daliri *et al*. (2020)[42]	Female	18 years old	1 tablet	Ingestion/NR	<5	55	2 days	5 days	45 days	Survived	7
22	Kumar *et al*. (2021)[43]	Female	29 years old	10 tablets (5 g)	Ingestion/NR	30–35	50	2 days	48 h	5 days	Survived	7
23	Lemoine *et al*. (2011)[44]	Female	15 months old	36 h inhalation	Inhalation/accidental	50	NR	NR	2 days	2 days	Nonsurvived	6
24	Farrar *et al*. (2022)[45]	Female	36 years old	8 tablets	Ingestion/suicidal	<10–20	42	NR	4 days	7 days	Survived	7

*EF=Left ventricular ejection fraction at admission, ##EF=Ejection fraction of left ventricle (%) before ECMO weaning. Maximum for JBI scoring=8. Case numbers 16 and 14 were conference abstract. The case number 15 was in Turkish language. NR=Not reported; ECMO=Extracorporeal membrane oxygenation; JBI=Joanna Briggs Institute; EF=Ejection fraction

Table 2: Different variables in the cross-sectional and case report studies reported the cases of aluminum phosphate treated by extracorporeal membrane oxygenation

Variables	First author (year) (reference)					
	Mohan *et al*. (2019)[22]		Mohan *et al*. (2016)[1]		Gami *et al*. (2022)[23]	Case reports*
	Conventional	ECMO	Conventional	ECMO	ECMO	ECMO
Number	32	35	30	15	124	24
Age (years)	35.3±12.4	34.8±11.5	29.1±12.7	34.0±8.9	35.74±6.83	25.43±17.94
Male sex, *n* (%)	29 (90.6)	27 (77.1)	18 (60)	11 (73.3)	93 (75)	12 (50)
Lag time (h)	6 (4-6)$	7 (4-10)$	7.6±5	8.9±3.4	2.68±0.36#	19.64±20.18
Dose of ALP (g)	3 (3-3.0)$	3 (3-4.5)$	2.1±1.5	2.1±0.9	8.1±5.4#	3.633±2.60
SOFA score	11 (10-12)$	10 (9-12)$				
GFR <30, *n* (%)	10 (31.3)	18 (51.4)				8 (33.3)
GFR <60, *n* (%)			13 (43.3)	8 (53.3)		
Blood pH	6.9 (6.9-7.2)$	7 (6.9-7)$			7.10±0.2	7.05±0.178
Blood pH <7, *n* (%)			8 (26.7)	15 (100)		7 (43.75)
EF at admission	30 (26.5-32)$	24 (22-28)$	27.2±4.0	27.1±2.9	15.2±5.0	21.3±10.33
EF in discharge	48 (47-49)$	52 (48-60)$	50.5±2.4	50±2.1		
hospital stay (days)	1 (1-1.0)$	12 (3-22)$	16.1±12.9	6.8±10		17.71±13.68
Tachycardia, *n* (%)			16 (53.3)	15 (100)	78 (62.90)	9 (81.81)
Hypotension, *n* (%)			22 (73.3)	15 (100)		13 (92.8)
ECG abnormality, *n* (%)			10 (33.3)	12 (80)	124 (100)	15 (93.75)
EF at follow-up			62±2.4	60.8±1.7	55.8±5.1	
Mortality, *n* (%)	27 (84.4)	14 (40.0)	26 (86.7)	5 (33.3)	15 (12.1)	4 (16.6)

*Case reports=data was extracted from case reports was summarized in Table 1, #Data were changed according to table unite, $Median with the IQR. EF=Ejection fraction (%); Hypotension=Systolic blood pressure at the time of presentation <90 mmHg; GFR=Glomerular filtration rate (mL/min/1.73 m^2); ECG=Electrocardiogram; IQR=Interquartile range; ECMO=Extracorporeal membrane oxygenation; ALP=Aluminum phosphate; SOFA=Sequential organ failure assessment

fraction on the 2nd–16th day of ECMO. The reported EFs before ECMO winning were 35%–70%. Although cardiac output gradually returned to normal, metabolic acidosis was resolved very fast (4 h to 2 days). However, one case had mild metabolic acidosis after winning.[26]

Infusion of the vasopressors was discontinued when pH was normal,[35] a few hours before pH became normal[24,27] or some days after winning.[27]

The mean of length of hospital stay of cases was 17.7 ± 13.7 days (range: 22 h to 45 days). It was significantly higher in survived cases (21.35 ± 12.63 days) than in nonsurvivors (2.21 ± 1.01 days) ($P < 0.001$, nonparametric).

Out of 24 reported cases, 20 cases (83.3%) survived and 4 cases (16.7%) nonsurvived[27,38,44] [Table 1]. One of the nonsurvivor cases was a 46-year-old man who ingested 4 g of ALP 12 h before hospitalization and was referred to the hospital with multi-organ failure. He had serum pH < 6.9 (HCO3 = 7) with high lactate serum level and EF = 20%. He underwent ECMO four hours after admission, but he did not survive after 3 days.[27] Mohen *et al*. also reported another 35-year-old man who ingested 3 g of ALP 5 h before hospitalization with similar metabolic acidosis (pH < 6.9, HCO_3 = 6, and lactate = 18) and EF (EF = 18%). He underwent ECMO 6 h after hospitalization but survived not more than 3 days.[27] Ekinci *et al*. reported an 18-year-old woman who ingested one tablet of ALP (500 mg) 2 h before hospitalization and underwent ECMO 1 hour later but could not survive more than 21 h due to refractory arrhythmia.[38] Lemoin *et al*. reported a 15-month-old girl who accidentally inhaled phosphine gas for 36 h and was referred to the hospital with nausea, malaise, abdominal pain, vomiting, and diarrhea.[44] She had hypotension, EF = 50%, and no metabolic acidosis. She became a candidate for treatment by ECMO; however, she did not survive more than 2 days due to focal seizure activity and minimal neurological function.

Thrombocytopenia (platelet count of 50,000/cc) and bleeding from cannula sites were reported in most of the cases. 41.6% of cases (10 cases) reported other complications including acute pulmonary edema, left-sided hemiplegia, seizure, respiratory failure, liver injury, respiratory failure, pancreatitis, disseminated intravascular coagulopathy, neurological injuries, ARDS, pleural effusion, fulminant hepatitis, septicemia, COVID-19, generalized necrosis of the gastrointestinal mucosa, profound psychological changes, dysphagia, and diarrhea.

Some of the cases were discharged with mild heart failure (low EF); nearly, all of them had normal EF in follow-up [Table 1 and Supplementary Table 4].

All cases were intubated and mechanically ventilated. Continuous renal replacement therapy (CRRT) or hemodialysis was reported in 13 cases due to persistent

metabolic acidosis with electrolyte imbalance or acute kidney injuries.[25-27,36,40,41,43,45]

Cross-sectional studies

We found 3 cross-sectional studies [Tables 2 and 3]. Mohan *et al*., in two studies, reported 112 ALP-poisoned cases who were candidates to undergo ECMO due to the severity of poisoning, but 62 cases, due to the impossibility of funding or lack of satisfaction with ECMO, were treated as conventional methods.[1,22] They reported that ECMO could significantly improve the survival of cases and the MR was reduced from 84.4%–86.6% to 33.3%–40% [Table 2].

The third cross-sectional study was reported by Gami *et al*.[23] They reported 124 cases underwent ECMO due to severe phosphine poisoning. They could reduce mortality to 12.1%. The authors of this study did not compare their results with any conventionally treated group.

Meta-analysis of effect of different indicators on extracorporeal membrane oxygenation-treated mortality

The mean values of age, blood pH, dose of ingested ALP, ECMO duration, EF at admission, lag time before hospitalization, and lag time from hospitalization to ECMO were compared between survived and dead patients who underwent ECMO. Comparing the waited mean difference (WMD) of age showed no significant difference between the two groups (survived and nonsurvived) 0.57 (95% CI: −5.13–6.28) (P = 0.844) [Figure 2]. The two groups were not significantly different in terms of WMD blood pH WMD = 0.02 (95% CI: −0.17–0.20; P = 0.862). The WMD of the dose of ingested ALP in survived cases was 0.5 g lower than in nonsurvived; however, it was not statistically significant (P = 0. 219).

The WMD of EF of survived cases at admission time was statistically higher (4.6%) (95% CI: 2.76%–6.39%) than nonsurvived cases (P < 0.0001). The Begg's test's result did not show publication bias (P = 0.136).

Comparing the WMD of ECMO duration showed no significant difference between the two groups (survived and nonsurvived) although the survived cases underwent ECMO 32.42 (95% CI: −8.08–73.9) h more than nonsurvived cases (P = 0.117).

Comparing the lag time between contact to ALP and hospitalization of different studies in survived and nonsurvived groups showed that the survived cases referred to the hospital sooner than nonsurvived cases (WMD = −2.05 (95% CI: −4.05–0.14) h, P = 0.066). However, the difference was not statistically significant. When the result was corrected for bias of publication, the WMD became statistically significant (P = 0.048).

Comparing the lag time between hospitalization to ECMO of different studies in survived and nonsurvived groups showed a statistically nonsignificant difference in WMD of the survived cases and nonsurvived cases (WMD = −2.00 [95% CI: −5.10, 1.10], P = 0.205) [Figure 3].

Comparing the WMD of hospital stay showed that the survivor has stayed 16 (95% CI: 12.0–20.5) days more than the nonsurvivor (P < 0.0001).

Conventional treatment studies

Study selection

Out of 1043 found documents in search of database for conventional treatment, 9 studies were included in the analysis [Figure 1].

Data extraction

The MR of studies with conventional treatment (without ECMO) is extracted and summarized in Table 4.

Meta-analysis for comparing the mortality rate of extracorporeal membrane oxygenation and nonextracorporeal membrane oxygenation-treated studies

To evaluate the effect of ECMO on mortality, we compared the MR between people treated with ECMO and the conventional method based on 4 cross-sectional studies of ECMO-treated patients (3 cross-sectional and 1 newly generated study from combining all case report studies) and 9 cross-sectional studies of conventional method-treated patients [Table 4]. The overall MR of ECMO treated cases was 23% (95% CI: 7%–39%) that significantly less than conventionally treated group (non-ECMO group) 60% (95% CI: 39%–63%) (P < 0.001) [Figure 2]. The funnel plot depicts some form of asymmetrical shape and the P value of Begg's test (0.921) and the P value of the slope of Egger's test (0.001) resulted in publication bias. Accordingly, trim-and-fill analysis was conducted to correct the results, and the results did not change [Figure 2]. The sensitivity analysis showed that none of the included studies has an influential effect on the combined estimated effect size.

DISCUSSION

In this systematic review and meta-analysis study, we evaluated the effect of ECMO on the MR of ALP poisoning. We found 198 reported cases underwent ECMO that 164 of them were survived, while most of them had high indexes of severity such as high SOFA score, multi-organ failure, severe metabolic acidosis, or cardiogenic shock. Several treatments were evaluated to improve the prognosis of phosphine intoxication, and none of them could significantly increase the survival of cases.[6,29,53,54] According to the current meta-analysis, the use of ECMO in severe ALP-poisoned

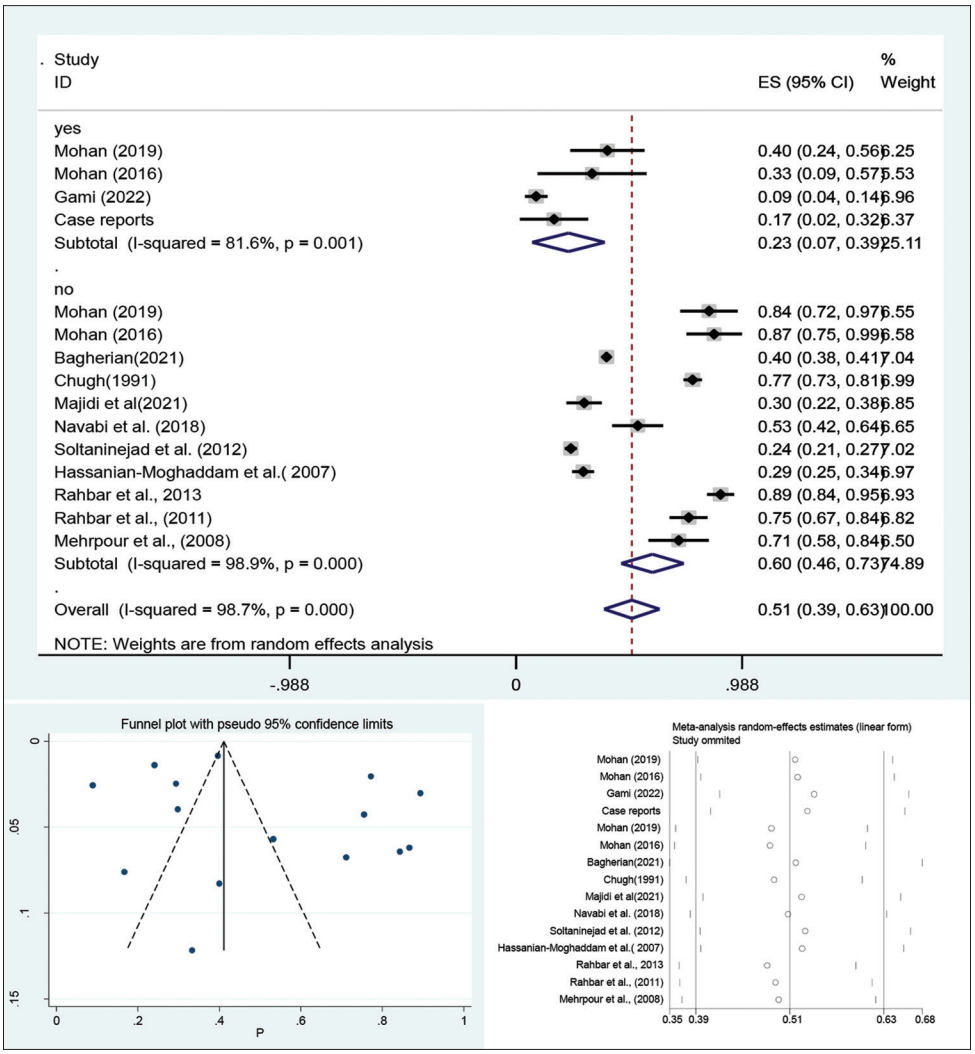

Figure 2: Comparing the overall mortality rate of aluminum phosphate-poisoned cases who were treated with or without extracorporeal membrane oxygenation (yes or no, respectively). The funnel plot and slope of Egger's test showed a publication bias. The trim-and-fill correction method could not change the results. ES: Effect size, CI: Confidence interval

Table 3: Different variables in survivor and nonsurvivor cases of cross-sectional reported the aluminum phosphate poisoning treated by extracorporeal membrane oxygenation

Variables	First author (year) (reference)							
	Mohan *et al.*(2019)[22]		Mohan *et al.* (2016)[1]		Gami *et al.* (2022)[23]		Case reports*	
	Survivor	Nonsurvivor	Survivor	Nonsurvivor	Survivor	Nonsurvivor	Survivor	Nonsurvivor
Number	21	14	10	5	113	11	20	4
Age (years)	35.5±10.9	33.8±12.8					25.5±18.1	25.1±19.6
Male sex *n* (%)	16 (76.2)	11 (78.6)					10 (50.0)	2 (50.0)
Lag time to hospitalization (h)	6 (4.5-9.25)$	8 (2.5-13.5)$	7.3±2.6	12.0±2.6	1.67±0.34	5.17±0.67	21.3±21.5	13.8±15.4
Dose of ALP (g)	3 (2.25-3.75)$	3.75 (3-4.5)$			2.8±2	2.7±1.8	3.9±2.8	2.5±1.8
Blood pH	7 (6.9-7.1)$	6.9 (6.87-7)$			7.13±0.3	7.10±0.4	7.05±0.16	7.07±0.29
EF at admission	24 (22-29)$	22 (18-25)$	26.2±4.8	19.6±1.7	15.2±5	10±4.5	19.9±8.5	29.3±17.8
Hospital stay (days)	20 (10-24.5)$	3 (1.75-15.75)$	22.8±10.3	2.6±0.5			21.4±12.6	2.2±1.0
Lag time to ECMO (h)	8.9±3.3	9.8±6.2	3.5±3.2	3.8±0.8	2.4±0.17#	7.1±0.83#	5.2±6.1	6.2±5.6
ECMO duration (h)	67±35.9	42.1±26.9	60±35	62.4±13.1			148.8±106.1	54.0±23.0

*Case reports=data was extracted from case reports was summarized in Table 1, #Data were changed according to table unite, $Median with the IQR, ##Renal dysfunction=eGFR <30 mL/min/1.73 m^2. ALP=Aluminum phosphate; EF=Ejection fraction (%); Hypotension=Systolic blood pressure at the time of presentation <90 mmHg; eGFR=Estimated glomerular filtration rate (mL/min); ECG=Electrocardiogram; ECMO=Extracorporeal membrane oxygenation; IQR=Interquartile range

cases could reduce the MR from 60% (39%–63%) to 23% (CI = 7%–39%).

Although there are some narrative reviews about the use of ECMO in ALP poisoning,[53,55] because there is a

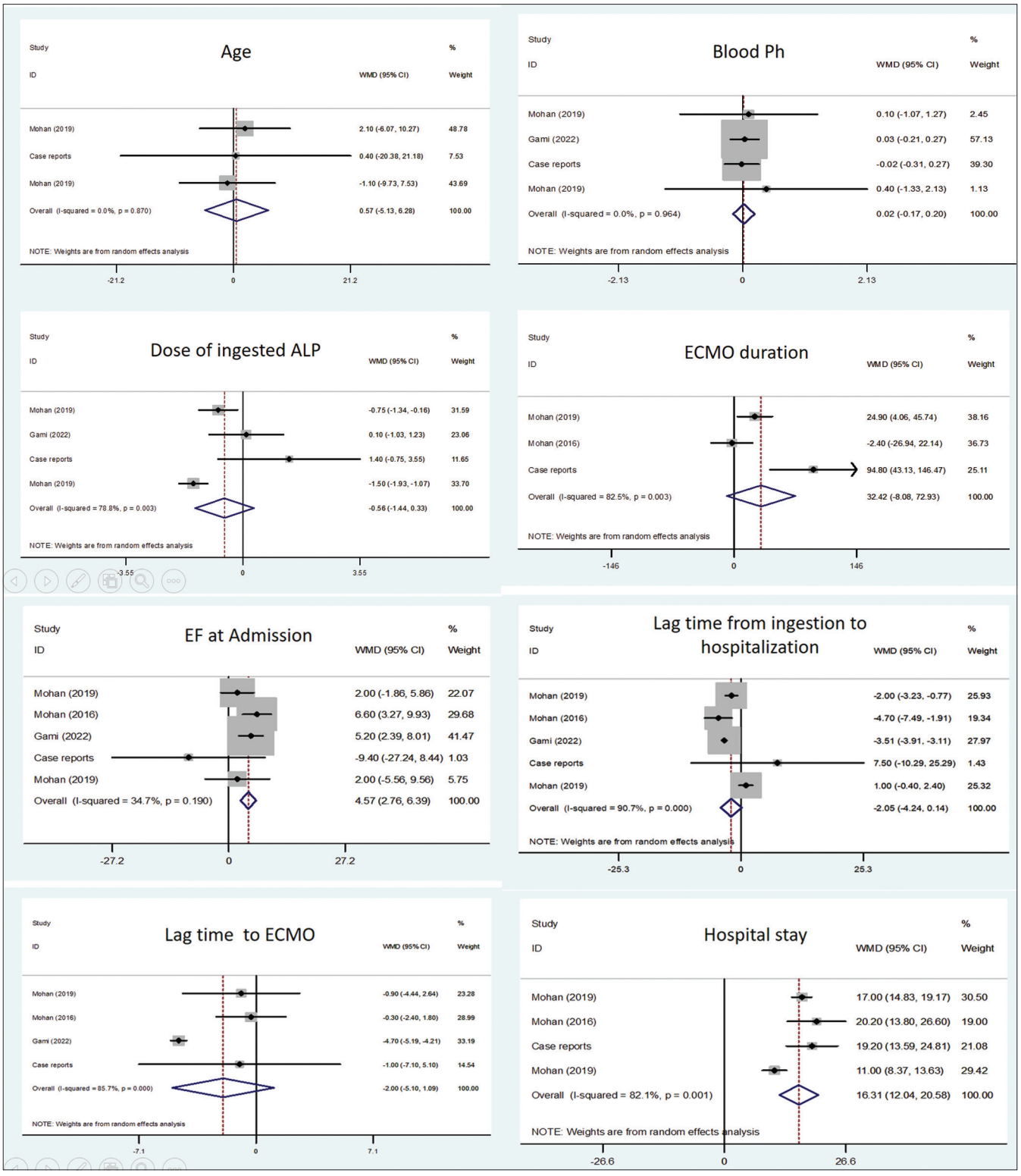

Figure 3: Meta-analysis of the waited mean difference of age, blood pH, dose of ingested aluminum phosphate, extracorporeal membrane oxygenation (ECMO) duration, ejection fraction at admission, lag time before hospitalization, lag time from hospitalization to ECMO, and hospital stay on in survived and nonsurvived groups who underwent ECMO. ALP: Aluminum phosphate, ECMO: Extracorporeal membrane oxygenation, EF: Ejection fraction

limited number of cross-sectional studies and there is not any clinical trials, it has not been any meta-analysis Thus, the current research is the first meta-analysis on this issue, and we try to increase the number of included studies in analysis with newly generated cross-sectional study.

Table 4: The sample size and mortality rate of patients with aluminum phosphate intoxication in the cross-sectional studies

First author (year)	JBI scoring	ECMO	*n*	Survived	Death	Mortality rate (%)
Mohan *et al*. (2019)[22]	7/8	Yes	35	21	14	40.00
Mohan *et al*. (2016)[1]	7/8	Yes	15	10	5	33.33
Gami *et al*. (2022)[23]	6/8	Yes	124	113	11	8.87
Case reports*	5/8	Yes	24	20	4	16.67
Mohan *et al*. (2019)[22]	7/8	No	32	5	27	84.38
Mohan *et al*. (2016)[1]	7/8	No	30	4	26	86.67
Bagherian *et al*. (2021)[5]	6/8	No	3432	2073	1359	39.6
Chugh *et al*. (1991)[4]	6/8	No	418	96	322	77.20
Majidi *et al*. (2021)[46]	7/8	No	134	94	40	29.85
Navabi *et al*. (2018)[47]	6/8	No	77	36	41	53.25
Soltaninejad *et al*. (2012)[48]	7/8	No	956	726	230	24.06
Hassanian-Moghaddam *et al*. (2007)[49]	6/8	No	340	240	100	29.41
Rahbar Taramsari *et al*. (2013)[50]	5/8	No	104	11	93	89.42
Rahbar Taromsari *et al*. (2011)[51]	6/8	No	102	25	77	75.49
Mehrpour *et al*. (2009)[52]	5/8	No	45	13	32	71.11

*Case reports=one study created from all of the case reports in Table 1. JBI score=Joanna Briggs Institute criteria for systematic reviews; ECMO=Extracorporeal membrane oxygenation

Phosphine produces reactive oxygen species (ROS) secondary to mitochondrial dysfunction. ROS overproduction and mitochondrial dysfunction lead to cardiomyopathy.[56] Thus, the main symptoms of ALP poisoning are hypotension, metabolic acidosis, and reduced EF.[53,57] However, ALP-induced mitochondrial dysfunction is reversible and the duration and severity of poisoning are related to phosphine dose, glutathione and other antioxidant storage of cells.[53] Phosphine half-life is 5 h in air and 28 h in dark environments.[58] Phosphine-induced cardiomyopathy is also reversible.[34,59,60] Similar to most reversible poisoning, if the cases could tolerate hypotension and acidosis when ALP is eliminated from the body he/she would be recovered.[22] Thus, cardiorespiratory bridge therapy with early resuscitation and ECMO could be a good choice for phosphine intoxication, especially if a profound myocardial dysfunction and cardiogenic shock are present.[22] ECMO has been mainly suggested for conditions where the potentially reversible underlying problem carries a very high rate of mortality despite conventional therapy,[61,62] especially recently recommended by the American Heart Association for management of poisoned patients with cardiogenic shock or dysrhythmias.[21] All researchers reported that the left ventricular dysfunction of ALP-intoxicated cases returned to near normal at discharge or through 6 months of follow-up [Supplementary Table 4].

VA-ECMO is an invasive, high-theca, and high-risk procedure that may be accompanied by life-threatening complications.[61] Although ECMO could significantly improve the survival and prognosis of ALP-poisoned cases, the biggest limitation of this method is its high technology and experience. Cole *et al*.[20] reviewed all cases reported to the National Poison Data System and treated with ECMO. They revealed that no case of ECMO had been reported in rural regions of the United States. Mohan *et al*.[1] also mentioned that the complication of ECMO procedure in the initial few cases was much higher than in the latter cases. ECMO has life-threatening complications that could increase the mortality of ALP poisoning. Thus, experience in performing ECMO in ALP-poisoned cases is important.[63]

The overall MR of ECMO in nonpoisoned cases was reported as 41%–59.8%.[63,64] Results of a Nationwide Cohort Study reported that as the traumatic patients had lower cardiac and other underlying problems, the results of ECMO in the trauma group had better outcomes than others.[63] However, the overall mortality of ECMO in poisoned cases was reported 20%–30%[20,55] which was about two times lower than nonpoisoned cases. The overall MR of ECMO-treated ALP-intoxicated cases, as per our results, is 23% (CI = 7%–39%).

In two cross-sectional studies conducted by Mohan *et al*.,[1,22] the conventional group did not undergo ECMO, primarily due to financial constraints of the family, and most of them belonged to low/medium socioeconomic status. The researchers believed that the lower socioeconomic status of the conventional group cases might be a confounding factor for poor outcomes. Because unknown comorbidity and malnutrition could change the outcome of cases.

The survivor cases had longer hospital stays (WMD = 16 days more than nonsurvivors). It has been reported that death from ALP poisoning would happen mostly within 24 h secondary to cardiovascular failure and through 48–72 h later due to hepatic failure.[65]

Similar to other studies,[61] thrombocytopenia and bleeding were the most common side effects of ECMO used in the treatment of ALP poisoning. Thrombocytopenia may be a

consequence of ALP poisoning,[66,67] or drug-treatment as well as blood exposure to the circuit surface.[61] Bleeding is also a common problem in ECMO procedures and may be related to the malfunction of platelets,[61] thrombocytopenia, heparin administration, and/or shock or severe acidosis-induced disseminated intravascular coagulopathy.[68-70] Limb ischemia due to thromboembolic complications was also reported in other applications of ECMO as well as ALP poisoning.[69,71,72] A large cannula (>20 Fr), malposition of the cannula, female gender, and younger patients are the risk factors of this complication.[61,72] In our review, two females (18 and 36 years old) out of 24 found cases reported leg ischemia,[28,34] and one of them was cannulated by a multi-stage 21-Fr venous access.[34]

CRRT or hemodialysis was reported in 13 cases out of 24 founded cases due to persistent metabolic acidosis with electrolyte imbalance or acute kidney injuries.[25-27,40,41,36,43,45] Acute kidney injury which needs renal replacement therapy is frequently observed in patients supported with ECMO.[73] However, suggested mechanisms of kidney injuries by ECMO are reduced renal oxygen delivery and/or inflammatory damage of the kidney.[73] ALP could induce renal injury due to cellular toxicity or secondary to shock.[74] Mohan *et al*.[22,27] reported that nearly half of the cases who supported with ECMO had moderate-to-severe acute kidney injuries; however, only 2 cases were placed on CRRT.

Regarding the meta-analysis comparing the survived and nonsurvived cases, the most important factors in effect of ECMO on survival of cases were lag time between ingestion of ALP and hospitalization. However, the lag time between hospitalization and ECMO did not affect survival. The EF before ECMO was also statistically significantly lower in nonsurvivor than survived cases (4.5%). It seems that the primary EF could affect on efficacy of ECMO. It seems that although ECMO is an effective treatment for ALP poisoning, other suggested conventional treatments could improve prognosis and should be performed.

Although about one-third (29%) of the cases were less than 14 years old, the survival of ALP-poisoned cases by ECMO was not related to age. The overall (nonpoisoned) ECMO survival rate of adults and children is nearly similar (25%–37% and 40%–60%, respectively);[64,75] however, the complication in children is higher.[61,72] Most of the ALP adults intoxicated were not old age, thus it seems that age could not affect the survival of ALP-poisoned cases by ECMO; however, age is an important factor in influences on short-term survival in patients with cardiogenic shock.[76]

Some studies reported the effect of variables such as the dose of ingested AIP on the prognosis of cases treated by ECMO.[1,22] However, the meta-analysis of this study did not show such effects.

We could not evaluate and compare the effect of the other possible factors such as gender,[61,72] primary blood pressure, cardiac arrest, and the other treatments performed for cases in the survived and nonsurvived cases. However, primary blood pH did not affect the survival of ECMO-treated cases.

Limitations

The cross-sectional studies, which did not use ECMO, reported all cases of ALP poisoning (all severity); however, the studies that used EMCO reported only moderate-to-severe cases. Therefore, we were not able to separate the treatment results (survival or nonsurvival) of the patients in the conventional treatment studies based on the severity of poisoning.

We excluded non-English studies for conventional treatment that may induce a selection bias.

Furthermore, the conventional treatment protocols of different studies were not similar, especially since there is no acceptable treatment protocol for ALP poisoning and it is case and physician-dependent. Only a few studies that applied ECMO mentioned the use of conventional treatment. Thus, we could not match and compare the effect of different conventional treatments on survival of cases.

To increase the number of studies that can be used in meta-analysis, we tried to create a new cross-sectional study by combining the results of case report studies. The results of the newly generated study are similar to other cross-sectional studies and also the statistical method could not define a significant publication bias between new generated study and other included studies. However, we believe that the majority of authors and journals have a much greater tendency to publish positive results from new treatment protocols than failures, and this leads to a selection bias.

CONCLUSION

ALP-induced cardiogenic shock is a severe life-threatening condition. ECMO reduced the MR of ALP-poisoned patients, although it is a highly invasive and complicated procedure. It may create a new perspective on the survival of ALP-poisoned patients. The lag time of poisoning to hospitalization and pretreatment EF are the most important factors in reducing the mortality of this poisoning. Additional studies are needed to accurately determine the indications, contraindications, risk factors for failure, and the need for other treatments along with ECMO for the use of ECMO.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: The gender, age, dose of aluminum phosphate ingestion, manner and intent of poisoning, and lag time to time to hospitalization of aluminum phosphate-intoxicated cases treated by extracorporeal membrane oxygenation

Case number	First author (year) (reference)	Sex	Age	Amount of ingestion	Manner	Intent	Time to hospitalization
1	Elabbassi (2014)[1]	Male	6 years old	3 days inhalation	Inhalation	Accidental	3 days
2	Merin (2015)[2]	Male	5 years old	NR	Inhalation	Accidental	NR
3	Merin (2015)[2]	Male	6 years old	NR	Inhalation	Accidental	2 days
4	Sharma (2015)[3]	Male	19 years old	3 g	Ingestion	NR	4 h
5	Mohan (2015)[4]	Male	50 years old	2 tablets (3 g)	Ingestion	NR	10 h
6	Mohan (2015)[4]	Female	40 years old	2 tablets (3 g)	Ingestion	NR	5 h
7	Mohan (2015)[4]	MALE	28 years old	2 tablets (3 g)	Ingestion	NR	6 h
8	Mohan (2015)[4]	Male	17 years old	1 tablet (1.5 g)	Ingestion	NR	10 h
9	Mohan (2015)[4]	Female	34 years old	2 tablets (3 g)	Ingestion	NR	10 h
10	Mohan (2015)[4]	Male	46 years old	3 tablets (4 g)	Ingestion	NR	12 h
11	Mohan (2015)[4]	Male	35 years old	2 tablets (3 g)	Ingestion	NR	5 h
12	Hassanian-Moghaddam (2016)[5]	Male	28 years old	1.5 tablets (4.5 g)	Ingestion	NR	0.5 h
13	Mendonca (2016)[6]	Male	6 years old	NR	NR	Accidental	1 day
14	Chatterjee (2017)[7]	Female	45 years old	2 weeks	Inhalation	Accidental	NR
15	Ekinci (2017)[8]	Female	18 years old	1 tablet (500 mg)	Ingestion	Suicide	2 h
16	Jaramillo-Stametz (2017)[9]	Female	45 years old	NR	Inhalation	Accidental	48 h
17	Hena (2018)[10]	Female	3 years old	NR	Inhalation	Accidental	35 h
18	Lehoux (2018)[11]	Female	3 years old	Several days	Inhalation	Accidental	NR
19	Sharma (2018)[12]	Female	67 years old	2 tablets	Ingestion	Suicide	5 h
20	Rao (2020)[13]	Male	25 years old	3 tablets	Ingestion	NR	NR
21	Daliri (2020)[14]	Female	18 years old	1 tablet	Ingestion	NR	20 h
22	Kumar (2021)[15]	Female	29 years old	10 tablets (5 g)	Ingestion	NR	NR
23	Lemoine (2011)[16]	Female	15 months old	36 h inhalation	Inhalation	Accidental	36 h
24	A Farrar (2022)[17]	Female	36 years old	8 tablets	Dissolved in water	Suicide	NR

Case numbers 16 and 14 were conference abstract. The case number 15 was in Turkish language. NR=Not reported

Supplementary Table 2: Initial clinical and laboratory findings of aluminum-intoxicated cases who underwent extracorporeal membrane oxygenation

Case ID*	Nausea and vomiting	Other manifestations	GCS	RR	PR	BP	Vasopressor/inotrope	Ph.	HCO3 (mg/dL)	Lactate (mmol/dL)
1	Yes	Fatigue	NR	Tac.P	Tac.c	HypoT	Milrinone (0.25/kg/min)	NR	NR	NR
2	Yes		NR	NR	150	88/49	Inotropic support	7.27	15.9	10
3	NR		NR	NR	124	80/40		7.30	14.8	10.4
4	Yes	Respiratory distress	NR	28	108	80/50	Dopa (10 μg/kg/min), Epi (0.1 μg/kg/min)	M.A.		High
5	Yes		NR	32	130	62/44	Dopa (20 μg/kg/min), NEP (8 mg/h)	7.00	8.0	17
6	NR		NR	NR	NR	NR	NR	6.9	6.0	19
7	NR		NR	NR	NR	NR	High-dose	6.90	10.0	16
8	NR		NR	NR	NR	NR	High-dose	7.00	8.0	15
9	NR		NR	NR	NR	NR	NR	6.80	5.0	16
10	NR	Multi-organ dysfunction	NR	NR	NR	NR	NR	6.90	7.0	15
11	NR		NR	NR	NR	NR	NR	6.90	6.0	18
12	Yes		15	30	Brad.C	60/NR	Epi	7.07	12.8	47
13	Yes		NR	NR	NR	NR	NEP (0.1 μg/kg/min), Epi (5 μg/kg/min)	M.A.		9
14	Yes	Dyspnea	NR	NR	NR	NR	Inotropic support	NR	NR	NR
15	NR		NR	NR	NR	NR	NR	NR	NR	NR
16	Yes	Abdominal pain, Flu like	15	NR	NR	NR	NR	NR	NR	NR
17	Yes	Weakness and tired	NR	Tac.P	152	66/46	Dopa, Epi.	7.34	11.2	3.1
18	Yes	Lethargy, flu like	15	NR	155	60/40	Dopa (10 μg/kg/min)	NR	NR	NR
19	Yes	Diarrhea, weakness, altered sensorium	8	35	85	80/60	Dopa, Epi, NEP	7.09	8.9	15
20	No	Dyspnea	NR	NR	NR	HypoT	High-dose	NR	NR	NR
21	Yes	Severe headache	5	NR	Brad.C	HypoT	Epi (0.05 μg/kg/min), NEP (0.5 μg/kg/min)	M.A.		16.5
22	NR		15	NR	NR	HypoT	NEP (5 μg/kg/min), Epi (2 μg/kg/min), vasopressin (0.04 units/h)	7.16	13.5	9
23	Yes	Respiratory distress, cyanosis, lethargy, prolonged capillary refill time, cool extremities	NR	40	179	110/89	Dopa, Epi	7.41	14.0	3.4
24	NR	Mottled skin	14	Tac.P	Tac.c	80/50	NEP (35 μg/min), Epi (35 μg/min)	7.10	16.0	13.8

*Case ID was reported in Table 1. BP=Blood pressure (mmHg) systolic/diastolic; Brad.C=Bradycardia; Brad.P=Bradypnea; Dopa=Dopamine; Epi=Epinephrine; GCS=Glasgow Coma Scale; HypoT=Hypotension; M.A.=Metabolic acidosis; NEP=Norepinephrine; NR=Not reported; PR=Pulse rate (beats/min); RR=Respiratory rate (cycle/min); Tac.c=Tachycardia; TacP=Tachypnea

Supplementary Table 3: Initial electrocardiogram and echocardiography findings of aluminum-intoxicated cases who underwent extracorporeal membrane oxygenation

Case ID*	EKG	Arrhythmia	Arrhythmia treatment	EF (%)	Echocardiography findings
1	NR	NR		35	NR
2	NR	Prolonged VF, polymorphic VT	Defibrillation, MgSO4		Moderate LV dysfunction
3		VF, polymorphic VT	Defibrillation, MgSO4		Biventricular failure
4		PVC		10–15	Severe LV systolic dysfunction
5	Intraventricular conduction defect	Intractable VT	Cardioversion, MgSO4	28	Severe LV systolic dysfunction
6		Recurrent VT	Cardioversion, MgSO4	18	Severe LV systolic dysfunction
7		Recurrent VT	Defibrillation, MgSO4	22	Severe LV systolic dysfunction
8		Non		32	
9		AF	Defibrillation	22	
10				20	
11				18	
12	ST changes, wild QRS	AF, VT	Defibrillation	20	NR
13	NR	TdP	Defibrillation, amiodarone	15	
14	NR			Reduced	
15	NR	Refractory arrhythmias		NR	NR
16	NR			NR	
17	ST changes	VT, TdP	Lidocaine, MgSO4	26	Severe LV systolic dysfunction
18	NR	NR	NR	<20	
19	ST-T changes			20	
20	ST changes, wild QRS	Arrhythmia	MgSO4	15–25	LV systolic dysfunction
21	Wide QRS	VF	Defibrillation	<5	LV akinesia
22	NR			30–35	
23	ST changes, wild QRS	Wide-complex supraventricular tachycardia	Resolved spontaneously	50	LV systolic dysfunction LV dyskinesia
24	NR			<10–20	Biventricular systolic dysfunction

*Case ID reported in Table 1. AF=Atrial fibrillation; EF=Left ventricular ejection fraction at admission; IVCD=Intraventricular conduction defect; LV=Left ventricular; MgSo4=Magnesium sulfate; NR=Not reported; PVC=Premature ventricular contraction; TdP=Torsades de pointes; VF=Ventricular fibrillation; VT=Ventricular tachycardia

Supplementary Table 4: Extracorporeal membrane oxygenation settings and parameters, outcome, and follow-up aluminum-intoxicated cases who underwent extracorporeal membrane oxygenation

Case ID*	Lag time#	PUMP fellow (L/min)	Type of dialysis (duration)	EF## (%)	Time to normal EF	Time to normal PH	ECMO duration	Time of vaso pressor off	Length of hospital stay	Outcome	Other complications$$	Discharge condition	Follow-up (time)
1	NR	NR	CRRT (NR)	NR	NR	NR		NR		Survived		NR	
2	2	NR	NR	NR	NR	NR	7 days	NR	21 days	Survived		Complete recovery	Completely normal (2 months)
3	2	NR	NR	NR	NR	NR	10 days	NR	21 days	Survived		Complete recovery	Completely normal (2 months)
4	NR	<4	CRRT (NR) and HD (3 times)	35–40	6 days	NR	8 days	8 day	20 days	Survived			
5	5	2.5	NR	42	3 days	6 h	44 h	12 h	22 days	Survived	Acute pulmonary edema	EF: 41%, general good condition	Completely normal (6 months)
6	3	2.1	NR	NR	NR	8 h	144 h	24 h	20 days	Survived		EF=42%	Completely normal (6 months)
7	22	2.6	CRRT (2 days)	NR	NR	12–24 h	96 h	12–24 h	34 days	Survived		EF of 38%	Completely normal (2 months)
8	2	3	NR	NR	NR	12–24 h	43 h	12–24 h	8 days	Survived		EF=35%	Good recovery, EF=48% (NR)
9	3	2.2	CRRT (8 cycles)	NR	NR	10–12 h	48 h	7 days	43 day	Survived		EF=35%	Completely normal (8 months)
10	4	2.8	CRRT (NR)	NR	NR	NR	72 h	NR	3 days	Nonsurvived	DIC		
11	6	2.9	CRRT (NR)	NR	NR	NR	72 h	NR	3 days	Nonsurvived			
12	NR	3.6–3.8	NR	40	4 days	3 days	4 days	3 days	7 days	Survived		Complete recovery	Completely normal (NR)
13	6	2.8	CVHD (3 days)	70	14 days	NR	11 days	NR	22 days	Survived	Left-sided hemiplegia	Left-sided hemiplegia	NR
14	NR	NR	NR	NR	NR	NR	NR	NR		Survived	Multi-organ failure	Complete recovery	NR
15	1	NR	NR	NR	NR	NR	21 h	NR	22 h	Nonsurvived			NR
16	NR	NR	CRRT (NR)	NR	NR	NR		NR		Survived			NR
17	NR	NR	CRRT (23 days) and HD (1 time)	35	16 days	NR	16 days	NR	36 days	Survived	Seizure, respiratory failure, liver injury, pulmonary edema	Mild heart failure	Completely normal (6 months)
18	NR	100 mL/kg/min	CRRT (15 days)	46	NR	12 h	15 days	NR	30 days	Survived	Liver injury, pulmonary edema	Referred to a rehabilitation facility	Completely normal (? months)
19	NR	3	Not done	35	1 day	4 h	3 days	24 h	10 days	Survived			NR
20	NR	4.5	HD (NR)	35–40	5 days	After weaning	6 days	NR	12 days	Survived	Respiratory failure, liver injury, pancreatitis, DIC. pulmonary edema	Complete recovery	NR
21	2	3.5	CRRT (NR)	55	2 days	2 days	5 days	4 days	45 days	Survived	Listed *in* footnote#,*	NR	Mild respiratory complications (3 months)
22	5	3.5	CRRT (NR)	50	2 days	12 h	48 h	NR	5 days	Survived		Complete recovery	NR
23	14	NR	NR	NR	NR	NR	2 days	NR	2 days	Nonsurvived	Seizure, neurological injuries		
24	NR	4	CRRT (39 h)	42	NR	39 h	4 days	NR	7 days	Survived	DIC	Complete recovery	NR

#,*ARDS, plural effusion, liver injury, fulminant hepatitis, massive gastrointestinal and vaginal bleeding, septicemia, COVID-19, generalized necrosis of the gastrointestinal mucosa, profound psychological changes, dysphagia, diarrhea, *Case ID reported in Table 1, #The lag time between admission and ECMO (hours), $$Except AKI, arrhythmia, and ECMO complications, ##EF=Ejection fraction of left ventricle (%) before ECMO weaning. CO=Cardiac output; CRRT=Continues renal replacement therapy; CVHD=Continuous venovenous hemodialysis; DIC=Disseminated intravascular coagulopathy; HD=Hemodialysis; NR=Not reported; ECMO=Extracorporeal membrane oxygenation; EF=Ejection fraction

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