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REVIEW ARTICLE

Aluminum Phosphide Poisoning Mortality Rate in Iran; a Systematic Review and Meta-Analysis

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Abstract: **Introduction:** According to statistics provided by the forensic medicine facility of Iran, there are a high number of Aluminum phosphide (ALP) poisoning-related deaths in the country; while the mortality rate varies in different studies. This study aimed to determine a pooled estimate of ALP poisoning mortality rate in Iran. **Methods:** The present study was a systematic review and meta-analysis of the mortality rate of ALP poisoning in Iran. Through the quarry of Persian and English databases, using "aluminum phosphide", "phosphine", "rice pills", "poisoning", and "Iran" as keywords, and no time restrictions, studies reporting mortality rate in ALP poisoning cases were collected. The random-effects model was used to pool the proportions of mortality and age of survivors versus non-survivors. **Results:** 21 studies with 3432 cases of ALP poisoning were included in this meta-analysis. The pooled mortality rate of ALP poisoning in Iran was 39.6%, (95% CI: 31.5%-47.9%; I2 = 95%). Since there was significant publication bias, the trim-and-fill correction was conducted and the corrected pooled mortality rate was estimated to be 27.3% (95% CI: 18.9%- 36.5%), which is the rate that should be considered for clinical guidance. Morality rate in male and female patients was 62.3% (95% CI: 53.5%-70.8%) and 37.7% (95% CI: 29.2%-46.5%), respectively ($p < 0.01$). Survivors had significantly lower mean age than non-survivors (SMD: -0.26 (95% CI: -0.37 to -0.15); $p < 0.01$; I2=0%). **Conclusion:** According to this report, the Mortality rate of ALP poisoning in Iranian population is about 27%, with men having a higher fatality rate than women. Poisoning at a younger age is associated with better results.

Keywords: Aluminum phosphide; Poisoning; phosphine; Mortality; Iran

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1. Introduction

Aluminum phosphide (ALP), known as rice pill in Iran, is a very effective pesticide for commercial and industrial use. The high lethality of ALP is due to phosphine gas (PH3), which is released when ALP reacts with water. The resulting gas is colorless and has a distinct odor of garlic or rotten fish (1). Phosphine gas released in the stomach of individuals who have devoured this pill intentionally or accidentally, quickly gets absorbed into body organs and disrupts enzymatic activities, causes cell death and disrupts the function of almost all vital organs, namely brain, lungs, and liver (2). Symptoms of poisoning are due to the involvement of the cardiovascular, gastrointestinal, nervous, and pulmonary systems. The most common clinical signs and symp-

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toms of ALP poisoning are restlessness, irritability, dizziness, vertigo, tremors, diplopia, imbalance, cough, shortness of breath, abdominal colic, nausea, vomiting, in some cases black vomit, black stools, decreased cardiac output, irregular heartbeat, pulmonary edema, cyanosis, renal impairment, jaundice, enlarged liver and spleen, intestinal paralysis, seizure, and acute respiratory distress syndrome (1). Severe hypotension and shock are the most common symptoms of severe poisoning (3). Delayed symptoms of intoxication include pulmonary edema, hypocalcemic tetany, cardiovascular arrhythmia, liver damage, bradycardia, metabolic acidosis, thrombocytopenia, and methemoglobinemia (4). Treatment for ALP poisoning is only supportive treatment, as there is no known antidote available against it. The effectiveness of these treatments in poisoned patients depends entirely on the degree of poisoning and the time of arrival at the medical center; the mortality rate following ALP poisoning varies between different studies. Despite the ban on the public sale of rice pills since 2012, Iran has a high number of ALP poisoning cases (intentional or accidental). According to statistics provided by the forensic medicine facility of Iran, there is a high number of ALP poisoning-related deaths in the country (5). While many observational studies have reported the cases of ALP poisoning; there is no overall view about the mortality rate of ALP poisoning in the country. This study aimed to determine a pooled estimate of the ALP poisoning mortality rate in Iran.

2. Methods

2.1. Study design and setting

The present study was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. Scientific sources were searched by two independent researchers from 2000 to 2021. Search for articles and dissertations in Iranian sources were performed in the University Jihad Scientific Information Center (SID) database, and PubMed / MEDLINE, Scopus, EMBASE, and Web of Science databases with the keywords of “aluminum phosphide”, “phosphine”, “rice pills”, “poisoning”, and “Iran”. English and Persian articles were quarried. The reference list of all articles identified in the early stages was reviewed in order to access cited articles that were not found via electronic searches.

The studies that reported cases of aluminum phosphide poisoning in Iran were selected in two stages. First, the abstracts of articles obtained in electronic searches were thoroughly reviewed, and irrelevant or duplicate studies were eliminated. In the second stage, the decision on the final inclusion of studies was made after reviewing the full text of the studies (Table 1). Information on study characteristics, quality, and results were extracted from each selected article.

The criteria for inclusion in the study was to evaluate patients with aluminum phosphide poisoning and present their mortality rate. Studies that only looked at the decedents were not included in this study. All articles that met the selection criteria were evaluated in terms of methodological quality.

The Newcastle-Ottawa Score (NOS) was used to evaluate the quality of the meta-included papers. NOS included three sections (case selection, group comparison, and exposure determination) and eight elements. The quality rating scale went from 0 (worst) to 9 (highest) (best). Studies with a score higher than 5 were included.

2.2. Data extraction

A pilot evaluation of the final full texts was performed to ensure inclusion of all data needed for final data synthesis to answer the study questions. Based on this evaluation, a checklist was provided for data extraction. This checklist included study ID, study design, province of study, duration of observation, the total number of cases (n), number of male and female cases, total mortality rate and mortality rate in each gender, and mean age of all participants, survivors, and non-survivors. A checklist of each study was filled by a single reviewer. Randomly, 5 studies were refilled by a second reviewer to ensure Inter-Rater reliability of checklists.

2.3. Data synthesis

We quantitatively examined the mortality rates of aluminum phosphide poisoning, the gender ratio of mortality, and the age of individuals. Mean age was pooled using the random effect model through calculation of Standard Mean Difference (SMD). The possibility of publication bias was checked using freeman-Tukey double arcsine transformation and Egger’s test in case of the binomial outcome of mortality. In case of publication bias, the trim-and-fill approach was used to address the issue. All statistical analyzes were performed using R statistical packages.

3. Results

As shown in the PRISMA flowchart (figure 1), finally, 21 studies with 3432 cases of ALP poisoning were included in this meta-analysis. There were about 1637 male and 1732 female poisoning cases (one study, Shadnia et al., 2007, did not report gender). Cases were evaluated from 2000 to 2021 (table 1).

3.1. Overall mortality rate

The pooled mortality rate of ALP poisoning in Iran was 39.6% (95% CI: 31.5% to 47.9%); with 95% heterogeneity ($p < 0.01$; figure 2).

Table 1: Studies included in the meta-analysis

Study* ID	Year**	N	Gender (n)		Age (year; mean ± SD)			
			Male	Female		Total	Survivor	Died
Majidi et al., 2021; (6); Urmia	2015- 2019	134	96	38	40	28.6±11.5	NA	NA
Navabi et al. 2018 (7); Kermanshah	2014- 2015	77	48	29	41	NA	28.7±10.2	31.3±10.7
Shadnia et al., 2007 (8);Tehran	2003	63	NA	NA	8	NA	NA	NA
Ataei et al., 2021 (9);Mashhad	2019- 2021	41	23	18	8	27.56±7.09	NA	NA
Mehrpour et al., 2008(10); Tehran	2006	45	24	21	32	27.3 ± 11.5	NA	NA
Rahbar et al., 2006 (11);Rasht	2000- 2003	116	63	53	68	29.47±14.79	NA	NA
Montazer et al., 2016 (12);Sari	2013-2014	52	14	38	16	23.4±9.2	NA	NA
Rahbar et al., 2013 (13);Rasht	2008-2009	104	66	38	93	33.8±14.69	NA	NA
Rahbar et al., 2011 (14);Rasht	2005-2006	102	68	34	77	29.75±14.34	NA	NA
Soltaninejad et al. 2012 (15);Tehran	2007- 2010	956	433	523	230	NA	24.5±8.19	27.32±11.31
Hassanian-Moghaddam et al. 2007 (16);Tehran	2005-2007	340	162	178	100	25.7± 9.2	NA	NA
Hosseinian et al., 2011 (17); Mazandaran	2007- 2008	102	46	56	19	28.5±12.4	28.66±12.75	24.92±9.51
Shokrzadeh et al., 2017(18);Gorgan	2008- 2015	53	37	16	16	NA	NA	NA
Farzaneh et al., 2015 (19);Ardabil	2006-2012	386	72	314	95	NA	NA	NA
Navabi et al., 2018 (7);Kermanshah	2014- 2015	118	75	43	41	NA	28.7±10.2	31.3±10.7
Shadnia et al., 2009 (20);Tehran	2000- 2007	471	246	225	146	NA	24.38 ± 8.81	30.87 ± 14.80
Mehrpour et al., 2009 (21);Tehran	2006- 2007	45	24	21	32	NA	NA	NA
Erfantalab et al., 2017 (22);Tehran	2014 - 2015	39	27	12	15	31.0±11.3	30.5±11.7 (17–65)	31.8±11.1 (23–61)
Mostafazadeh et al., 2011 (23) Tehran	2009	48	24	24	9	25.5±9.5	NA	NA
Tavakoli-Far et al., 2018 (24);Karaj	2006- 2011	67	36	31	30	NA	NA	NA
Shayeste et al., 2017 (25);Gorgan	2009- 2016	73	53	20	25	27.47±16.75	NA	NA

* All study types were cross-sectional. ** Duration of observation. NA, not addressed.

3.2. Gender and mortality rate

The male and female mortality rates were pooled from 12 studies listed in figure 3a and 3b. Proportion of morality in male patients was 62.3% (95% CI: 53.5% to 70.8%); with 80% heterogeneity ($p < 0.01$). The proportion of mortality in female patients was 37.7% (95% CI: 29.2% to 46.5%); with 80% heterogeneity ($p < 0.01$).

As shown in the funnel plot in figure 4. freeman-Tukey double arcsine transformation and Egger's test revealed significant funnel plot asymmetry, indicating the possibility of publication bias or small-study effects, P<0.01. It reveals that studies are shifted to the right. Linear regression test of funnel plot asymmetry also confirmed asymmetry ($t = 2.23$, $df = 21$, $p = 0.0369$).

To address the publication bias, we utilized the trim-and-fill approach to look at the effect on the pooled estimate. After applying the trim-and-fill approach to account for missing studies, the result was a symmetrical Egger funnel plot, which is shown in figure 5, where the linear regression test of funnel plot asymmetry was not significant ($t = 0.17$, $df = 25$, $p = 0.8673$). The mortality rate that should be considered for therapeutic purposes is 27.3% (95% CI: 18.9% to 36.5%) as shown in the new forest plot in figure 6, with the pooled proportion corrected for publication bias.

3.3. Mean age and mortality rate

In a comparison of mean age of survivors versus non-survivors, a random effect model showed a significant difference between survivors versus non-survivors, where survivors had significantly lower age (SMD: -0.26, 95% CI: -0.37 to -0.15; p< 0.01; figure 7). Heterogeneity was not observed in the case of age comparison (I2=0%).

4. Discussion

This study showed a mortality rate of about 40% along with a publication bias. When we used trim-and-fill correction, mortality rate decreased to about 27%, which seems to be far from the reality. There is no proper official data available to facilitate reaching a final decision on mortality rate and in our knowledge, and this is the first study in Iran giving a comprehensive mortality rate for ALP poisoning. Also, there is a wide distance between the mortality rates of males and females, and averaging to find the overall mortality rate of ALP poisoning does not seem reliable.

Other studies have reported a 70–100% mortality rate, as reviewed by Meena et al. (26). A 59.3% mortality rate was reported in Mathai and Bhanu study in 2010 (27). But Iranian studies have reported a wider range of mortality rates as Abdollahi and Mehrpour (28) reported the mortality rate to vary

from 30 to 100%. But other factors, as well as the amount of consumed ALP, affect the results.

Unfortunately, due to factors such as high toxicity and high lethality of this substance and ease of access to this toxin, based on official reports a relatively high rate of poisoning is seen in the country, especially in some provinces such as Tehran, Gilan, Mazandaran, Golestan, and Lorestan, (5). Our meta-analysis also showed that most published studies are performed in these provinces.

Our study showed that the mortality rate of ALP poisoning in Iran was 39.6% with the proportion mortality being 62.3% in males and 37.7% in female patients. In the comparison of mean age of survivors versus non-survivors, there was a significant difference between survivors versus non-survivors, where survivors had a significantly lower age.

Based on the reports by forensic medicine facility of Iran, most of the ALP-poisoning-related deaths were in the age group of 20-40 years, and most of them intended to commit suicide. Statistics from 2008 to 2011 show that death from rice pills were on the rise. There were 214 individual cases of mortality (105 women / 109 men) in 2008, 228 cases (104 women / 124 men) in 2009, 406 cases (202 women / 204 men) in 2010, and 463 cases (204 women / 259 men) in 2011 (5).

In a comparison of studies performed outside Iran, according to El-Sarnagawy's study, there was a strong link between mortality risk and young age, rural location, suicidal ingestion, increased toxic dose, and prehospitalization duration. They reported 44.7% deaths with ALP in 5 years (29). A study by Sheta showed that 43.3 percent of cases died (30). Compared to our study, better survival in Iranian poisoning cases could be due to the higher experience of Iranian health care providers in the management of ALP poisoning, as most case reports of successful treatment of ALP are being published by Iranians (31-33).

In a study by Alnasser et al., they evaluated ALP poisoning in Saudi Arabia over a nine-year period, the highest rate of death from AlP poisoning belonged to children, and it occurred most frequently during household fumigation. Delays in medical treatment and diagnosis may have had a role in the patients' death (34).

Poisoning due to the use of rice pills in Iran has led to the responsible organizations and institutions in the country taking measures to ban the import and restrict the sale of rice pills. Having comprehensive data on ALP poisoning mortality rate in our country could help us in policymaking regarding public sale of ALP for industrial purposes.

5. Limitations

A concern in this study was the possibility of publication bias. As a result, the findings of this study should be interpreted with caution, bearing the limitations in mind. Although our article search was limited to Iran, there was a low possibility of biased study retrieval due to the high number of studies; however, there might be a possibility of incomplete study retrieval as we did not find studies performed in the south of the country and medical dissertations and official and unofficial reports were not included. Reporting bias might also have affected our results as datasets with high mortality rates might have not be reported.

6. Conclusion

According to this report, the mortality rate of ALP poisoning in Iranian population is about 27%, with men having a higher fatality rate than women. Poisoning at a younger age is associated with better results.

7. Declarations

7.1. Acknowledgments

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7.2. Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

7.3. Conflict of interest statement

The authors have declared that no competing interests exist.

7.4. Author contribution

FB and NK conceptualized the study questions and performed revisions. FR and SA performed the searches. NH and NJM conducted the statistical analyses. Other authors provided the draft manuscript.

7.5. Ethical Considerations

All ethical principles are considered in this article.

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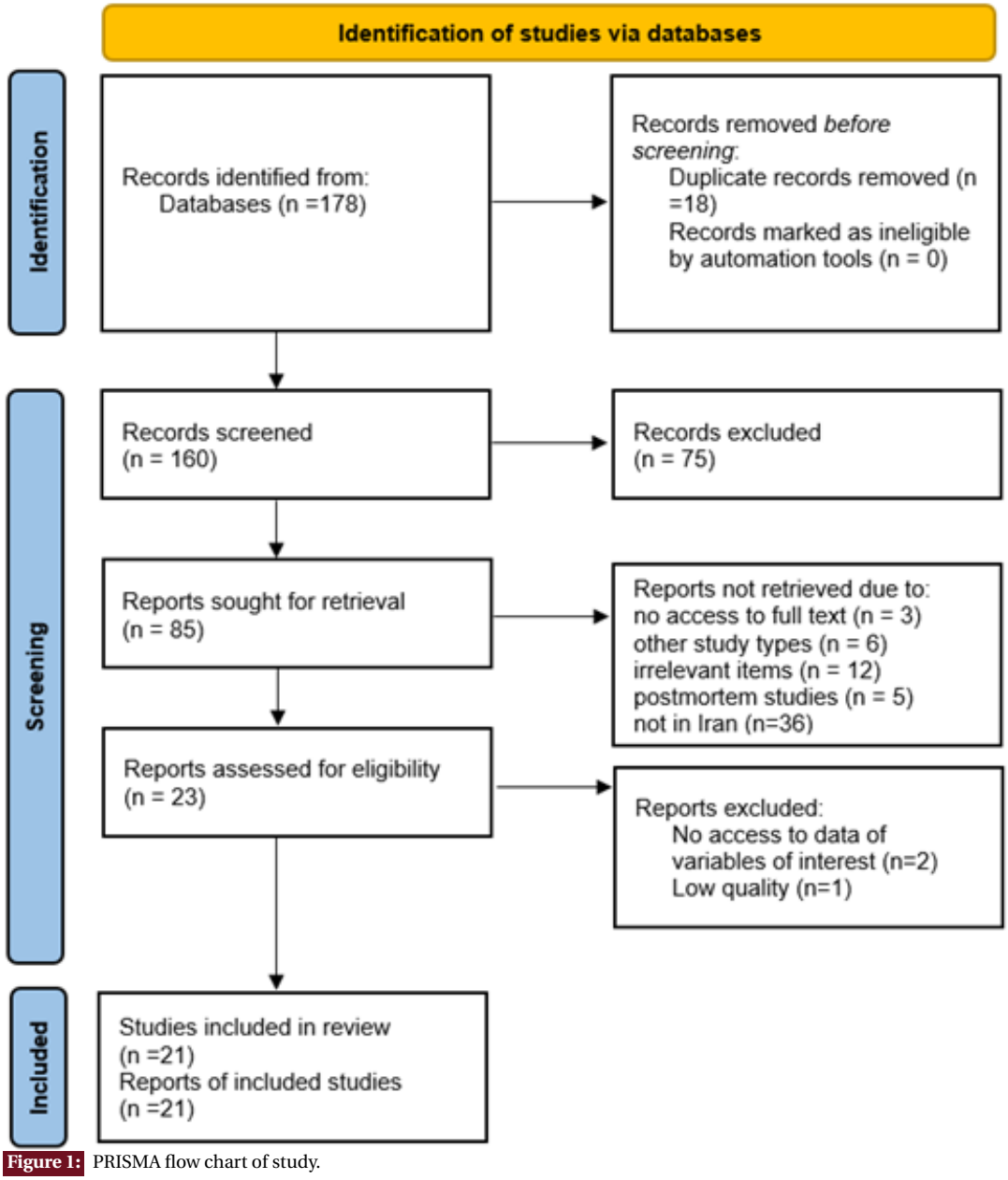

Figure 1: PRISMA flow chart of study.

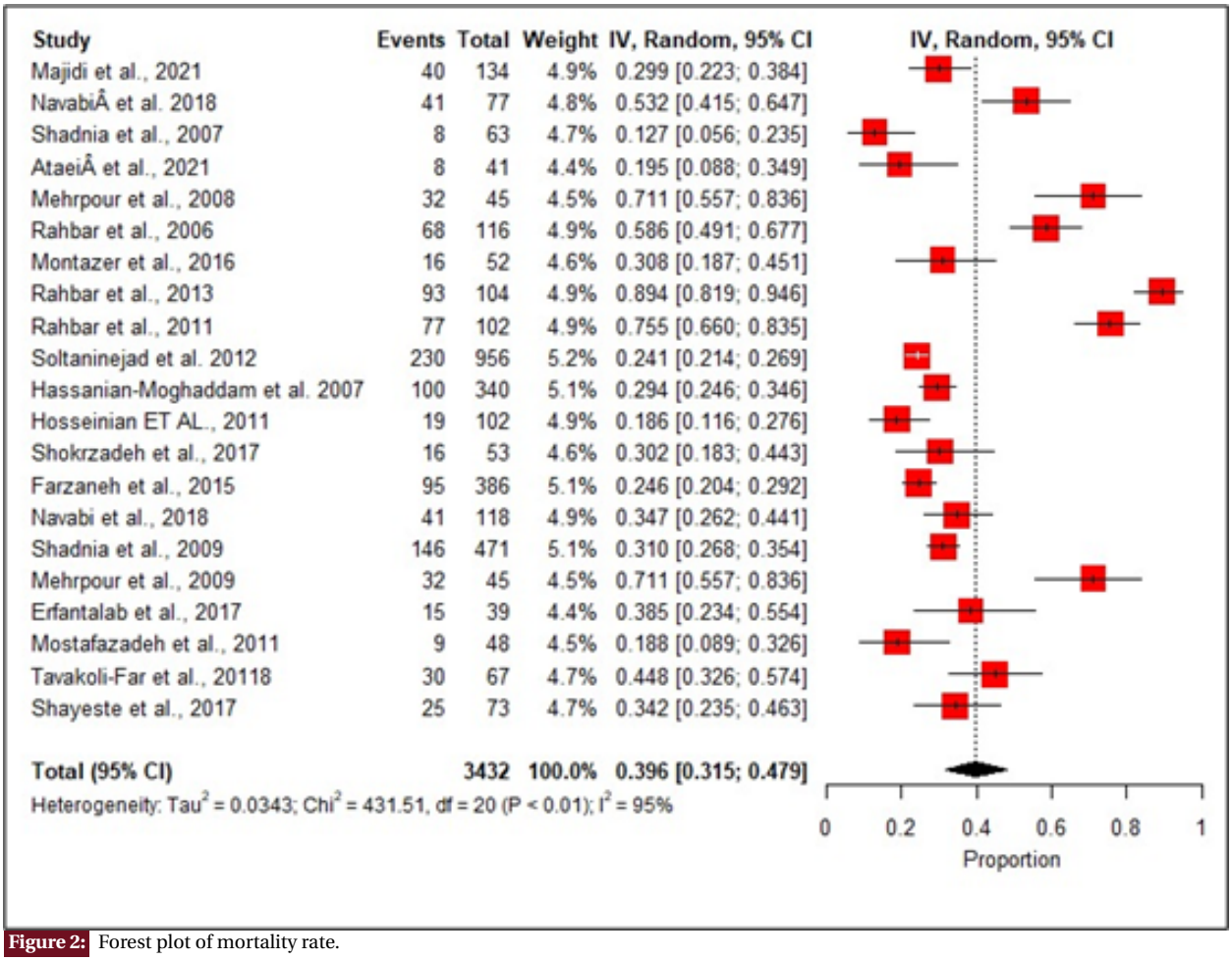

Figure 2: Forest plot of mortality rate.

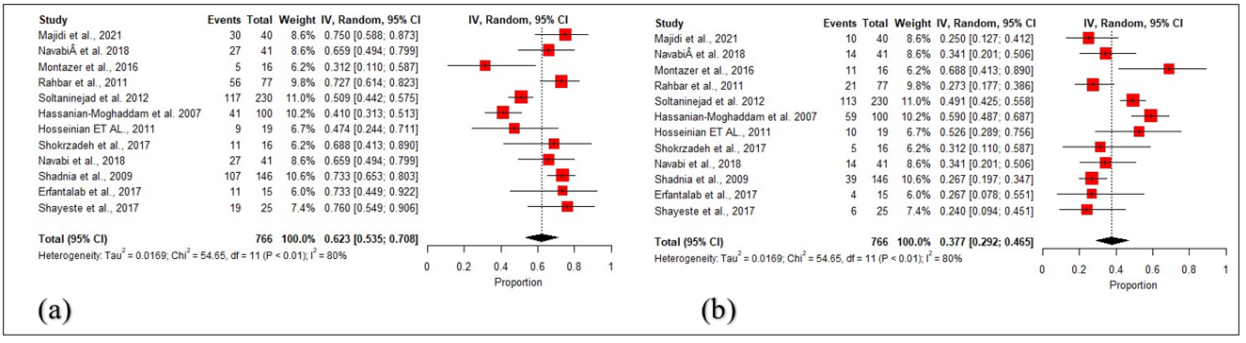

Figure 3: Forest plot of mortality rate based on gender, (a) male, (b) female.

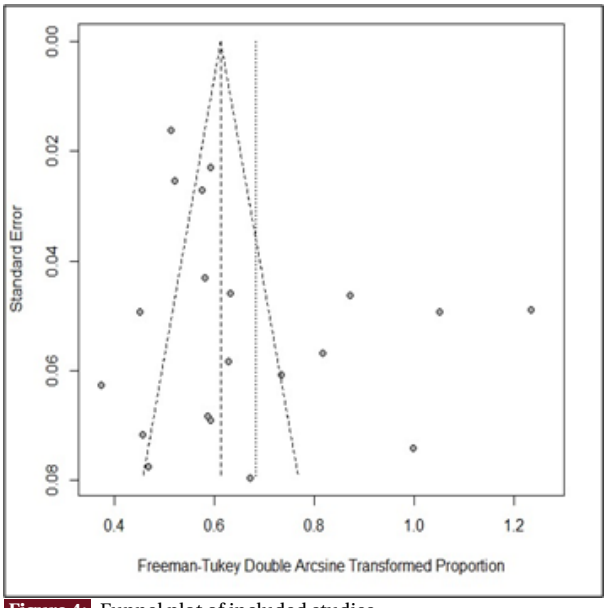

Figure 4: Funnel plot of included studies.

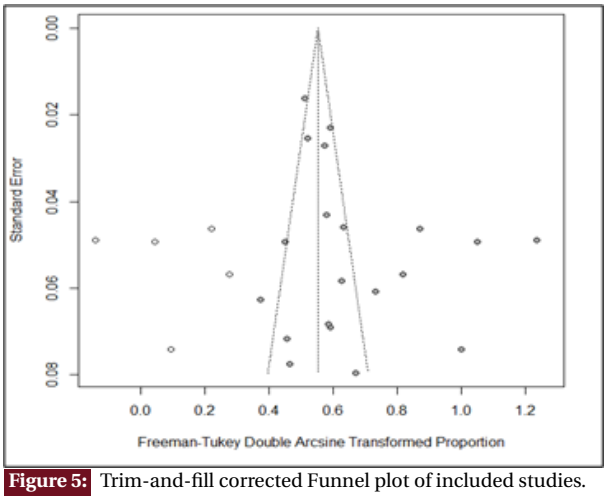

Figure 5: Trim-and-fill corrected Funnel plot of included studies.

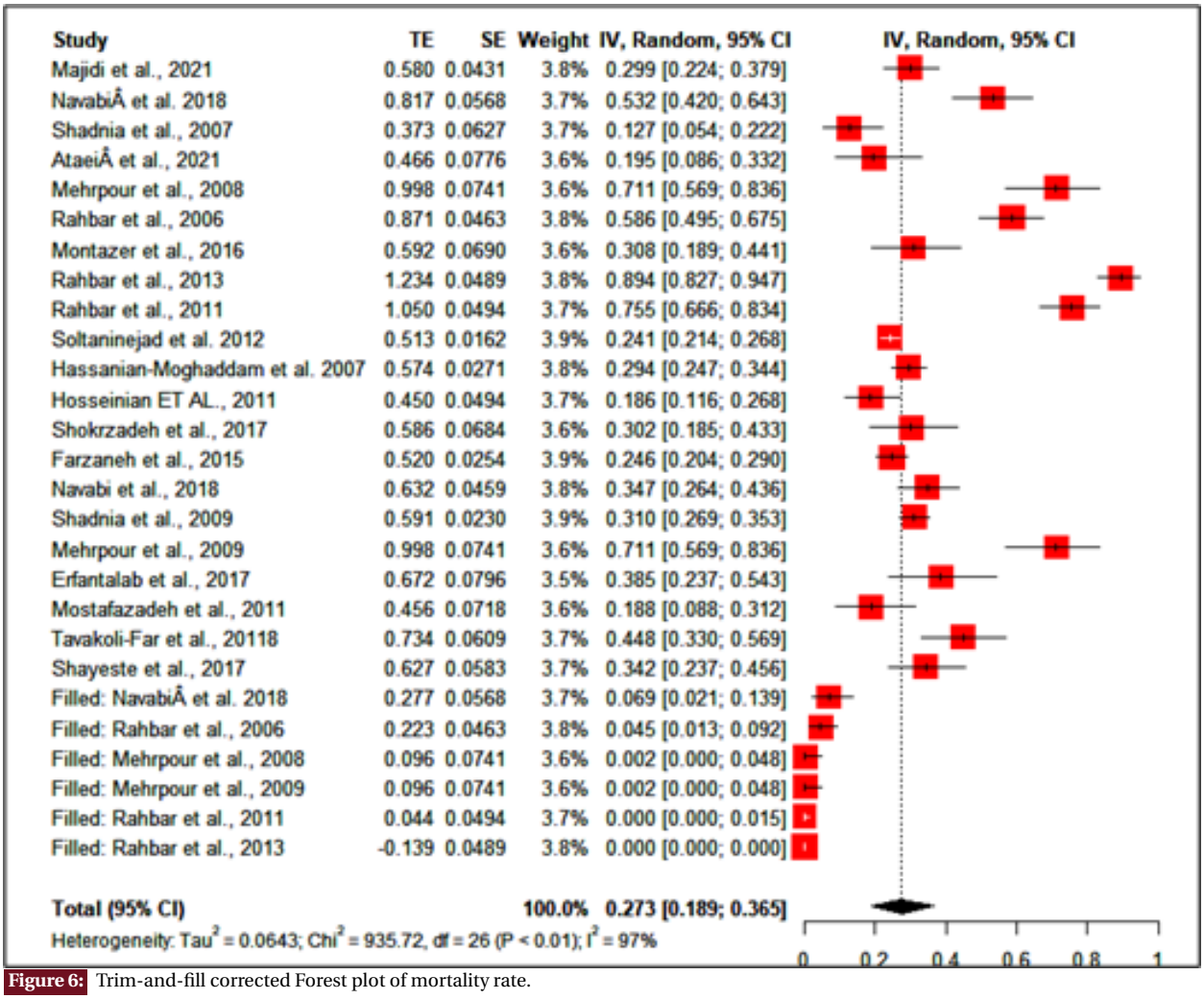

Figure 6: Trim-and-fill corrected Forest plot of mortality rate.

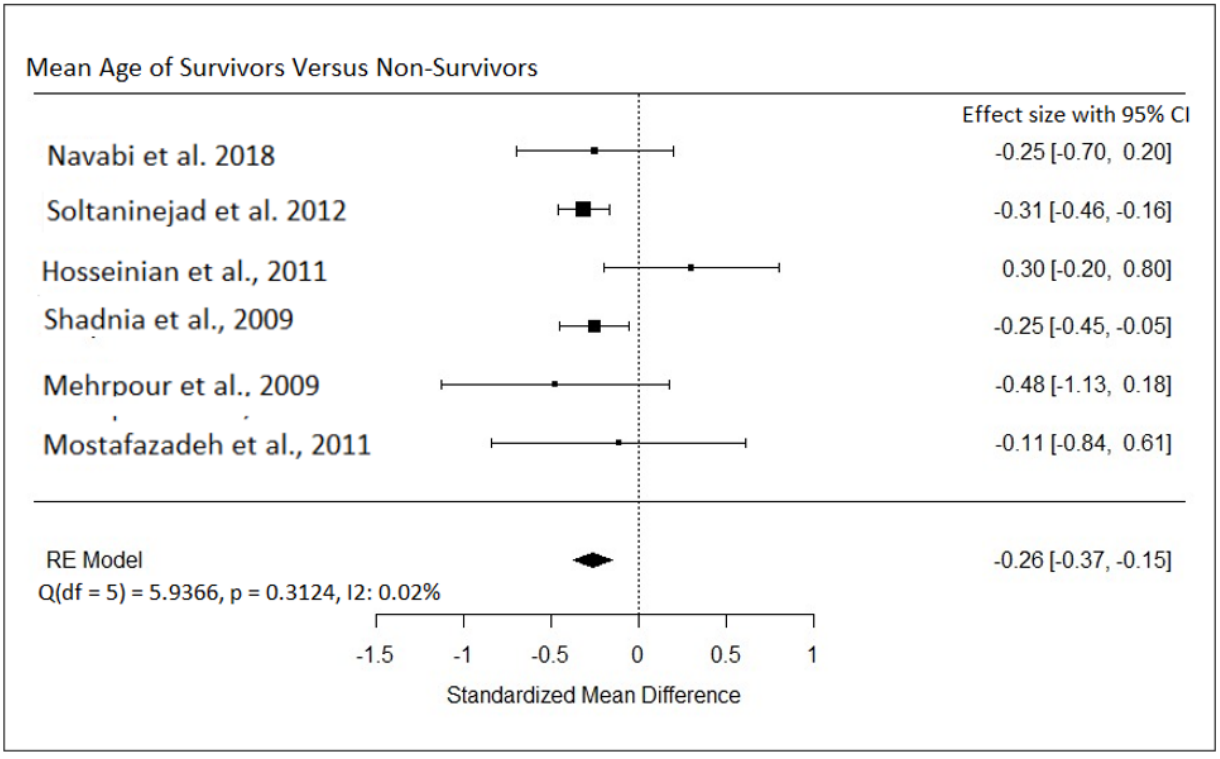

Figure 7: Forest plot of mean age of survivors versus non-survivors.