Extracorporeal Membrane Oxygenation in Patients with Burns, Hero or Futile Medical Care? A Systematic Review and Meta-Analysis

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Research

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Abstract

Background

Severely burned patients, particularly when compounded with inhalation injuries, are at high risk for cardiopulmonary failure. Recently, promising studies have stimulated interest in using extracorporeal membrane oxygenation (ECMO) as a potential therapy for burn patients with refractory cardiac and/or respiratory failure. Several observational studies have been reported, but the findings in these vary.

Methods

In this study, we conducted a systematic review and meta-analysis using standardized mortality ratios (SMRs) to elucidate the benefits associated with the use of ECMO in patients with burn and/or inhalation injuries. A literature search using PubMed, EMBASE, MEDLINE, and the Cochrane Library were performed from inception to October 20, 2020. Clinical outcomes in the selected studies were compared.

Results

22 studies were included in the final review and analysis. 13 studies with a total of 75 patients were included in SMR quantitative analysis. The overall pooled mortality rate of burn patients receiving ECMO was 48%. The meta-analysis found that the observed mortality was significantly higher than the predicted mortality in patients receiving ECMO, with a pooled SMR of 2.07 (95% CI: 1.04–4.14). However, in the subgroup of burn patients with inhalation injuries, all patients receiving V-V ECMO had lower mortality rates compared to their predicted mortality rates, with a pooled SMR of 0.95 (95% CI: 0.52–1.73). Other subgroup analyses, including an adult group, pediatric group, V-V setting group, and a V-A setting group reported no benefits from ECMO; however, these results were not statistically significant. Interestingly, the pooled SMR values decreased as the selected patients' revised Baux scores increased (R=-0.92), indicating that the potential benefits from the ECMO treatment increased as the severity of patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

Conclusions

Our meta-analysis revealed that burn patients receiving ECMO treatment were at a higher risk of death. However, select patients, including those with inhalation injuries and those with the revised Baux scores over 90, would benefit from ECMO treatment. We suggest that burn patients with inhalation injuries or with revised Baux scores exceeding 90 should be considered for ECMO treatment and early transfer to an ECMO centre.

Highlights

1. This study is the first review and meta-analysis of burn patients receiving ECMO therapy based on SMRs.
2. Patients with burns receiving ECMO treatment were at high risk of death.
3. Select patients, including those with inhalation injuries and those with revised Baux scores over 90, may benefit from ECMO treatment.
4. The potential benefits from ECMO treatment increase as the severity of the patients with burns increases.

Introduction

Severely burned patients, particularly when compounded with inhalation injuries, are at high risk for cardiopulmonary failure [1]. Despite advances in burn care, the morbidity and mortality for these patients remain extremely high [2, 3]. Severe acute respiratory distress syndrome (ARDS) with refractory respiratory failure is one of the most dominant causes of death in patients with burns[2, 4]. ARDS results from smoke inhalation injuries, pneumonia, and an overwhelming cascade of airway inflammation, extraordinarily elevating the mortality rates in burn patients [5, 6]. Mechanical ventilation is the primary therapy to treat ARDS, which uses a lung-protective strategy to avoid superimposing additional damage on the already-injured pulmonary alveoli in order to let the “lung rest”. However, such ventilation is unable to provide life-saving respiratory support when a critical volume of the alveolar unit has failed [7]. Extracorporeal membrane oxygenation (ECMO) is considered as an alternative treatment to solve this problem without overstretching the injured lungs, and provides cardiac support, for extended periods, from hours to several weeks [8].

The two most common forms of ECMO are veno-arterial (VA) ECMO and veno-venous (VV) ECMO. VA-ECMO support is required for cardiac and/or respiratory failure; VV-ECMO provides adequate oxygenation and carbon dioxide removal in isolated refractory respiratory failure [7]. In early studies, the high incidences of bleeding and thrombotic complications were attributed to practitioners’ inexperience, resulting in unfavourable outcomes in ECMO-treated groups [9]. In recent years, ECMO has become more reliable with improvements in equipment, and increased practitioners’ experience has led ECMO to become an alternative tool to treat patients with severe cardiac and pulmonary dysfunctions [10, 11]. These promising studies have stimulated interest in using ECMO as a potential therapy for burn patients with refractory cardiac and/or respiratory failure.

In earlier years, only a few case reports and case series have assessed ECMO in the context of burns and/or smoke inhalation [12–21]. Asmussen et al. in 2013 performed a systematic review of ECMO treatment for burn and smoke inhalation injuries. Due to the insufficient patient numbers from the available literature, along with limited evidence, the role of ECMO in patients with burn and inhalation injuries is unclear [2]. In recent years, several case series and retrospective studies have been performed, but the findings still vary [3, 22–32]. Randomised controlled trials of ECMO compared to conventional therapy might be the solution. However, burn patients with cardiac and/or respiratory failure are rare, making it difficult to perform randomizsd trials. Should a disaster occur, there may be many patients with major burns accompanied by cardiac and/or respiratory failure. However, a massive influx of burn patients would shock the workforce of hospitals in the surrounding area, making it difficult to conduct clinical studies at that moment. Medical ethics is another concerning issue in this regard.

Standardized mortality ratios (SMRs) indicate the mortality in a cohort relative to the mortality in a reference population. A meta-analysis of SMRs investigated the all-cause and cause-specific SMRs, eliminating the effect of differing patient characteristics in the two compared populations, and thus provides a better picture of the changes in survival [33, 34]. Because most of the available literature on burn patients being treated with ECMO are observational studies, and there is a lack of systematic studies evaluating cause-specific mortality, we conducted a systematic review of the literature and performed a meta-analysis on the available clinical data using SMRs. This was performed to elucidate the benefits associated with the use of ECMO in the patients with burn and/or inhalation injuries.

Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Search strategy

A systemic literature search was carried out in PubMed, EMBASE, MEDLINE, and the Cochrane Library databases on October 20, 2020 using the following search terms: “burn,” “burns,” “ARDS,” “adult respiratory distress syndrome”, “Extracorporeal Membrane Oxygenation,” “ECMO,” “inhalation injury,” “smoke,” and “respiratory failure.” All published articles were limited to human studies without language restrictions. All identified articles were screened for cross references.

Study selection

Review articles, observational controlled studies, letters, and case reports were included in the study. The titles and abstracts of all of the identified articles were screened and selected according to the following inclusion criteria: (1) participants were children or adults with a diagnosis of a thermal burn and/or smoke inhalation requiring ECMO as determined by a physician; (2) an identified group of patients who received ECMO as part of their therapeutic regimen; and (3) refer to disease severity in patients treated with ECMO using the revised Baux system, or with details provided for further calculation. For multiple studies using the same cohort, studies with the longest follow-up durations and that met the study inclusion criteria were selected. Studies meeting one of the following criteria were excluded from our analysis: (1) studies that were duplicate publications and (2) studies with appropriate data that could not be extracted based on the published results.

Two reviewers (Y.A. K. and Y.J. C.) independently examined the titles and abstracts of the articles independently. A subsequent full-text review was performed manually when the abstracts did not provide sufficient information. Any disagreements were discussed with a third reviewer (Y.J. H.) and resolved by consensus.

Outcome measures

The outcomes evaluated included patient mortality rates and SMRs. The revised Baux scoring system described by Osler et al. has been widely adopted using age, total body surface area burned, and inhalation injuries as predictors to produce outcome estimates on a continuous scale [35]. Revised Baux scores were calculated as age(years) + TBSA (%) + (17 * inhalation injury). Predicted mortality was calculated using a logistic regression model = $\frac{e^{-\ 8.8163+(0.0775*rBaux)}}{1+e^{-\ 8.8163+(0.0775*rBaux)}}$. For each study, the expected mortality was calculated by multiplying the number of cases by the revised Baux score predicted mortality rate.

Data extraction

Two reviewers (Y. A. K. and Y. J. C.) extracted the following data separately from all of the studies that met the inclusion criteria independently. The extracted data from the studies included the: study types, sample sizes, inclusion dates, treatment regimens, ages, sexes, countries, burn types, TBSA, presence of inhalation injuries or ARDS, ECMO settings, mortality status, mortality rates, revised Baux scores, and revised Baux score-based SMR with 95% CI. All the extracted data were crosschecked to rule out any discrepancies.

Data synthesis

The meta-analysis was performed using MetaXL version 5.2 following the PRISMA guidelines. We calculated the pooled crude mortality rate of patients receiving ECMO. The results were expressed as overall odds ratios (ORs) with associated 95% confidence interval (CI). For all studies that provided the revised Baux scores of patients, logistic regression calculations between the revised Baux scores and predicted mortality rates were performed. SMR was defined as the ratio of observed mortality to expected mortality, and the accompanying 95% CI was based on the methods used by Ury and Wiggins [34]. We produced a pooled SMR for ECMO treatment, with the results expressed as overall SMRs and associated 95% CIs. Subgroup analyses of different ECMO settings and paediatric patients were also performed.

Heterogeneity across studies was evaluated using the X^2 test, P values, and I^2 statistics. A random effects model was used for all analyses because of the large heterogeneity of the sample. Funnel plots were used to identify the present of publication bias [36]. When the mortality rate was zero, we added 0.5 to both the observed deaths and expected deaths and used the adjusted SMRs in our analysis.

Results

Study selection

The abstraction process is detailed in Fig. 1. After screening the titles and abstracts of 2261 publications, 74 articles were considered relevant. Of these, 52 were excluded after manual review of the full texts, thus leaving 22 articles (14 retrospective studies and 8 case series) eligible for final review and analysis, which are summarised in Table 1. In the SMR quantitative analysis, nine records were removed because due to incomplete and undetailed data.

Outcomes

The overall pooled mortality rate of burn patients receiving ECMO was 48.0% (95% CI: 0.405–0.556), while the pooled mortality rate in the paediatric subgroup was 41.4% (95% CI: 0.298–0.540); the adult subgroup's rate was 49.4% (95% CI: 0.375–0.613), the V-V setting subgroup's was 41.8% (95% CI: 0.333–0.508), and the VA-setting subgroup's was 41.1% (95% CI: 0.219–0.634).

The meta-analysis found that the observed mortality was significantly higher than the predicted mortality in patients receiving ECMO, with a pooled SMR of 2.07 (95% CI: 1.04–4.14) as shown in Fig. 2A. The funnel plot did not indicate any publication biases (Fig. 3). However, in the burn patients with inhalation injuries subgroup, all patients receiving V-V ECMO had a lower mortality than their predicted mortality, with a pooled SMR of 0.95 (95% CI: 0.52–1.73) as shown in Fig. 4C. Other subgroup analyses, including an adult group, paediatric group, V-V setting group, and V-A setting group, did not report any benefits from ECMO; however, these results were not statistically significant (Figs. 2 and 4). Interestingly, the pooled SMRs decreased as patients' revised Baux scores increased, with a high correlation (R= -0.92), as shown in Fig. 5. The pooled SMRs were less than one when the selected patients' revised Baux scores exceeded approximately 90, indicating that the potential benefits from ECMO treatment increased as the severity of patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

Assessment of bias

Funnel plots revealed no evidence of publication bias, as shown in Fig. 3. A random effects model was used for all analyses due to the large heterogeneity of the sample. According to the GRADE classification, we judged the quality of evidence of included studies. Subcategories of bias (such as indication, selection, allocation, performance, attrition or reporting bias) were not assessed.

Discussion

To the best of our knowledge, this study is the first review and meta-analysis of burn patients receiving ECMO therapy that is based on SMRs. The pooled all-cause mortality of burn patients receiving ECMO was 48%. The pooled overall SMR of 2.07 (95% CI: 1.04–4.14) suggested that ECMO recipients have significantly higher mortality rates compared to their predicted mortality rates calculated using their revised Baux scores. The use of ECMO may rather increase mortality in unsuitable patients. Moreover, our subgroup analysis showed no benefits in terms of patient survival when using ECMO in different settings or depending on different age populations. However, in the subgroup of burn patients with inhalation injuries who received V-V ECMO and those with major burn injuries with revised Baux scores exceeding 90, the observed mortality rates were lower than the predicted mortality rates, with a pooled SMR of 0.95 (95% CI: 0.52–1.73) and 0.90 (95% CI: 0.42–1.93).

SMRs based on generic mortality prediction models have been widely applied to predict deaths in the general population [37]. Various mathematical models have been developed and widely used to predict mortality as an outcome of burn injuries. They are associated with several factors, including age, TBSA, inhalation injuries, and so on [38]. Lots of prediction models such as the revised Baux score [39], Abbreviated Burn Severity Index [40], Total Burn Surface Index [41], Taiwan burn score [42], and the Belgian Outcome of Burn Injury study group [43] are well known systems that fulfill the published methodological standards for composite model construction and validation [38]. Several studies have reported that the revised Baux score system is more accurate for predicting survival not only in adult patients but also in paediatric patients [38, 39, 44–49]. Moreover, this model is simple to calculate and has good calibration and discriminatory power. As a result, our SMR calculations were based on the revised Baux score system when conducting the analyses in this study.

In recent decades, ECMO has become an essential tool in the care of patients with severe cardiac and pulmonary dysfunctions that are refractory to conventional management [10, 11, 50]. The indications and usage of ECMO as a treatment option have progressed strikingly. In addition, in the burn field, plastic surgeons and intensivists have tried to use ECMO as a rescue therapy for burn patients with severe cardiac or pulmonary dysfunctions. In earlier years, only a few case reports and case series of ECMO treatment in burn patients were reported. Several case series and retrospective studies have been reported recently. However, the consequently findings are still varied. Retrospective data from the Extracorporeal Life Support Organization (ELSO) international registry reported 58 adult burn patients from 1999 to 2015 with a hospital mortality rate of 57% [23]. Soussi et al. in 2016 reported 91% in-hospital mortality rate in 11 burn patients receiving ECMO therapy, suggesting that ECMO treatment for burn patients is not advisable [3]. However, in the last few years, several observational studies have revealed favourable outcomes from the use of ECMO [23, 25–31]. In this study, our meta-analysis revealed a pooled SMR of 2.07, suggesting a two-fold higher mortality rate compared to the predicted mortality in patients receiving ECMO therapy. Based on the results, ECMO is not recommended as a routine therapy for patients with burns.

On the other hand, the substantial growth of patients treated with ECMO raises ethical issues regarding patient selection and when ECMO support should be halted. [51]. There is an increasing amount of studies demonstrating that careful patient selection is important to obtain the best results [51, 52]. Moreover, resource utilisation should be justified to minimise the economic burden on the health system [52]. In this study, different patient groups were analysed in order to determine the benefits from ECMO treatment. The results showed that the observed mortality in burn patients with inhalation injuries was lower than their predicted mortality, considering that the pooled SMR was 0.95. Other subgroup analyses, including an adult group, paediatric group, V-V setting group, and V-A setting group, found that ECMO treatment was not beneficial. It is also worth mentioning that the pooled SMR decreased as the patients' revised Baux scores increased, with a high correlation (R= -0.92), as shown in Fig. 5. The pooled SMR would cross over 1 when the patient's revised Baux exceeded approximately 90, indicating that the potential benefits from ECMO treatment increased as the severity of patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

Another pressing issue regarding ECMO is patient transfer. Several studies have reported that patients with severe acute respiratory failure should be transferred to an ECMO centre for further treatment. In burn patients, Dadras et al. and Eldredge et al. suggested early consideration of ECMO consultation in burn patients with severe ARDS and proposed the transfer of these patients. Based on our results, we suggest that burn patients with inhalation injuries or patients with revised Baux scores exceeding 90 should likely be considered for early transfer to an ECMO centre. We believe that the potential benefits from ECMO should always be weighed against the risks of transfer.

There were some limitations to this analysis. First, all included studies were case series or retrospective studies with a limited sample size. However, burn patients with cardiac and/or respiratory failure are nearly impossible to perform randomised trials due to ethical considerations and the rarity of the injuries with ECMO therapy. Second, SMRs that are based on prediction scoring systems such as in our study may have biases, other comorbidities and complications during hospitalisation were not evaluated as well. Last, since ECMO therapy is a rapidly evolving technology, older studies may follow different protocols or indications, causing different outcomes and selective biases.

Conclusions

This study revealed that burn patients receiving ECMO treatment were at high risk of death. As a rescue treatment, it should not be routinely used in all burn patients. However, select patients including those with inhalation injuries and patients with a revised Baux score exceeding 90, may benefit from ECMO treatment. The potential benefits from ECMO treatment increase as the severity of the patients with burns increases. We suggest that these patients consider early ECMO intervention and should consider being transferred to an ECMO centre.

Abbreviations

ECMO: Extracorporeal Membrane Oxygenation; ARDS: Acute Respiratory Distress Syndrome; VV: Veno Venous; VA: Venoarterial; SMR: Standardized mortality ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ELSO: Extracorporeal Life Support Organization; TBSA: total body surface area; confidence interval (CI)

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

None.

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Authors' contributions

YJC and YAK contributed to the study design, study selection, data extraction, quality assessment and writing of the manuscript. YCH and YAK analyzed the data and verified the analytical methods. TWC and HM revised the manuscript for important intellectual content. YAK and HM contributed to the final version of the manuscript and supervised the project. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of selected trials

Study (year)	Country	Study type	Age (Mean)	Case number (inhalation)	ECMO setting (VV/VA)	Mortalty	SMR (95% CI)
Goretsky et al. 1995 [12]	USA	Retrospetive	2.5	5(1)	0/5	2	15.74 (1.8-54.1)
Lessin et al. 1996 [13]	USA	Case series	1.45	2(2)	0/2	0	0.978 (0.223-7.799)
O'Toole et al. 1998 [14]	UK	Case series	1.6	2(2)	2/0	0	0.996 (0.227-7.939)
Pierre et al. 1998 [15]	USA	Retrospetive	4.33	5(3)	N/A	2	24.69(2.82-84.83)
Kane et al. 1999 [16]	USA	Retrospetive	2.5	12(4)	N/A	4	N/A
Masiakos et al. 1999 [17]	USA	Retrospetive	N/A	3(N/A)	N/A	2	N/A
Chou et al. 2001 [18]	Taiwan	Case series	30.3	3(2)	2/1	1	1.589 (0.064-8.043)
Thompson et al. 2005 [19]	USA	Case series	33	2(2)	2/0	0	0.894 (0.204-7.129)
Nehra et al. 2009 [20]	USA	Retrospetive	4.45	10(N/A)	N/A	7	N/A
Askegard-Giesmann et al. 2010 [21]	USA	Retrospetive	N/A	36(6)	17/19	17	N/A
Hughes et al. 2015 [22]	USA	Case series	30	3(3)	3/0	0	0.308 (0.07-2.457)
Soussi et al. 2016 [3]	France	Retrospetive	51	11(6)	3/8	10	N/A
Burke et al. 2017 [23]	USA	Retrospetive	N/A	58(14)	44/14	33	N/A
Hsu et al. 2017 [24]	Taiwan	Retrospetive	43.3	6(6)	2/4	5	0.946 (0.306-2.172)
Nosanov et al. 2017 [25]	USA	Retrospetive	38.9	30(8)	N/A	16	N/A
Kennedy et al. 2017 [26]	USA	Case series	46	2(0)	2/0	0	N/A

Ainsworth et al. 2018 [27]	USA	Retrospetive	36	12(4)	12/0	6	0.805 (0.184-6.418)
Chiu et al. 2018 [28]	Taiwan	Case series	21.8	5(5)	4/1	2	6.557 (2.404-14.098)
Szentgyorgyi et al. 2018 [29]	UK	Retrospetive	34.4	5(5)	5/0	1	0.644 (0.073-2.215)
Eldredge et al. 2019 [30]	USA	Retrospetive	5.9	8(3)	8/0	1	N/A
Mehran et al. 2019 [31]	Germany	Case series	46	8(7)	7/1	3	2.173 (0.087-10.999)
Josep et al. 2019 [32]	USA	Retrospetive	34	17(2)	17/0	8	7.086 (3.062-13.86)

ECMO: Extracorporeal Membrane Oxygenation; VV: Veno Venous; VA: Venoarterial; SMR: Standardized mortality ratio

Figures

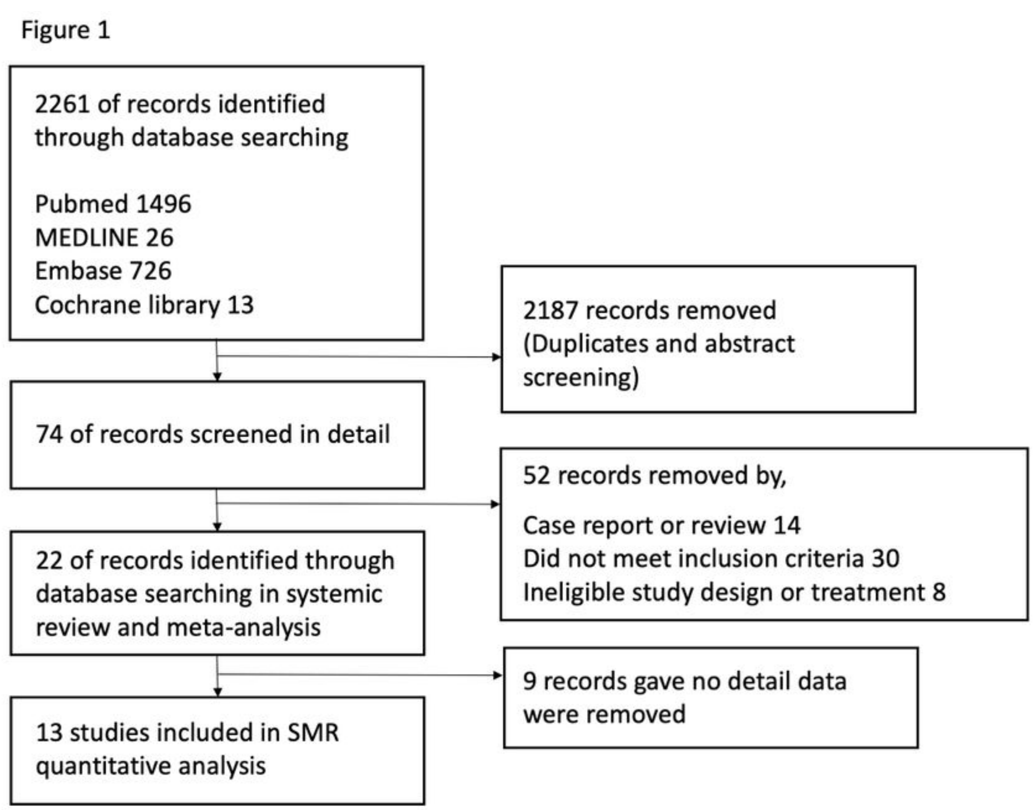
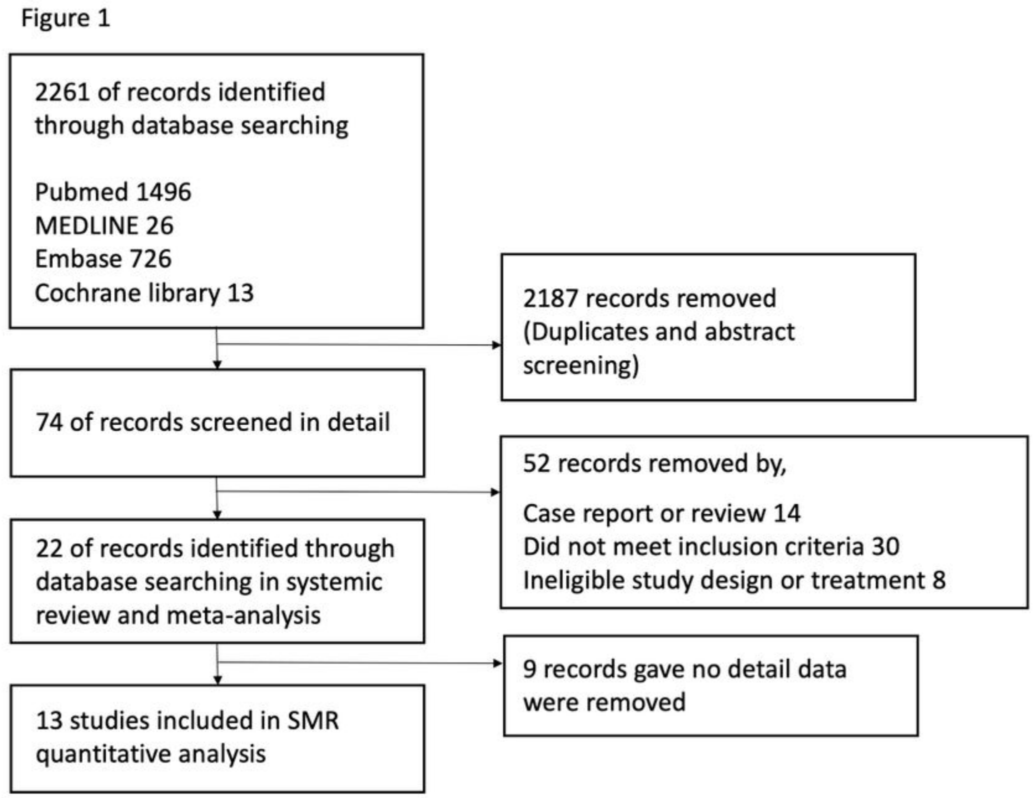


Figure 1

Flow diagram of search strategy and study selection processes for the systemic review and meta-analysis



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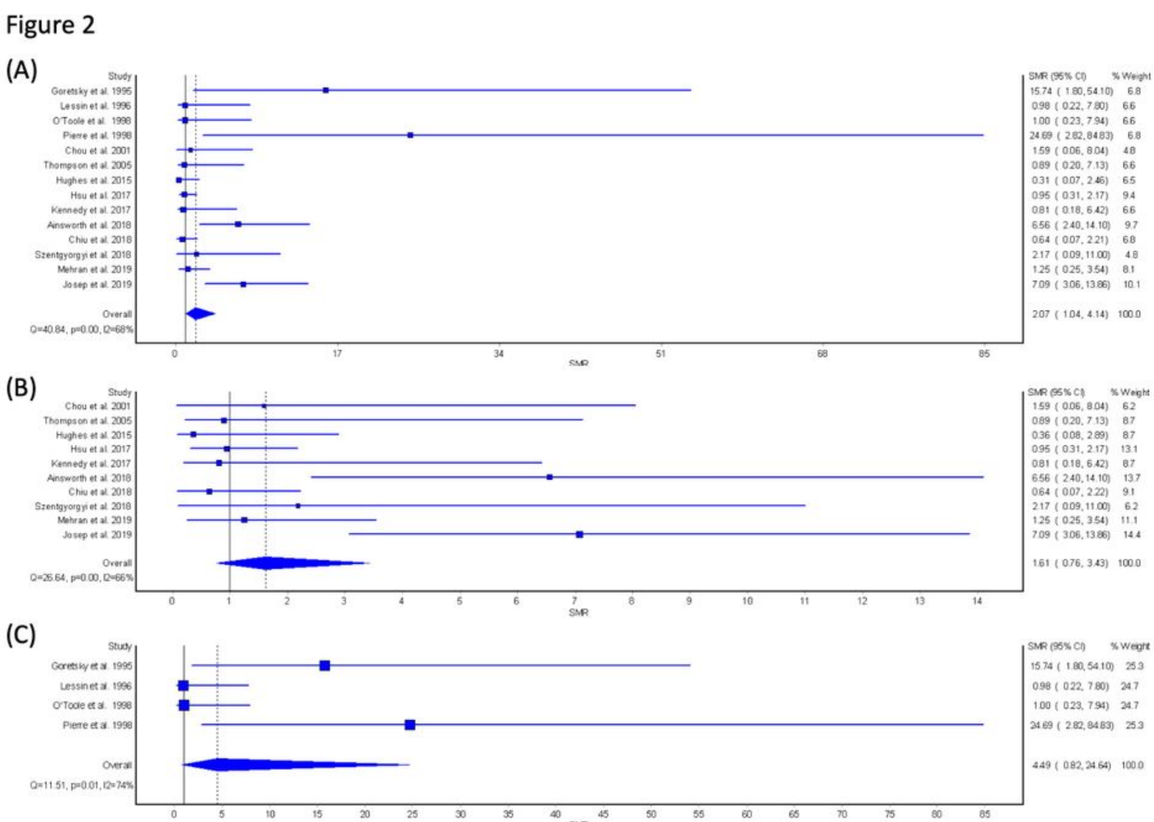
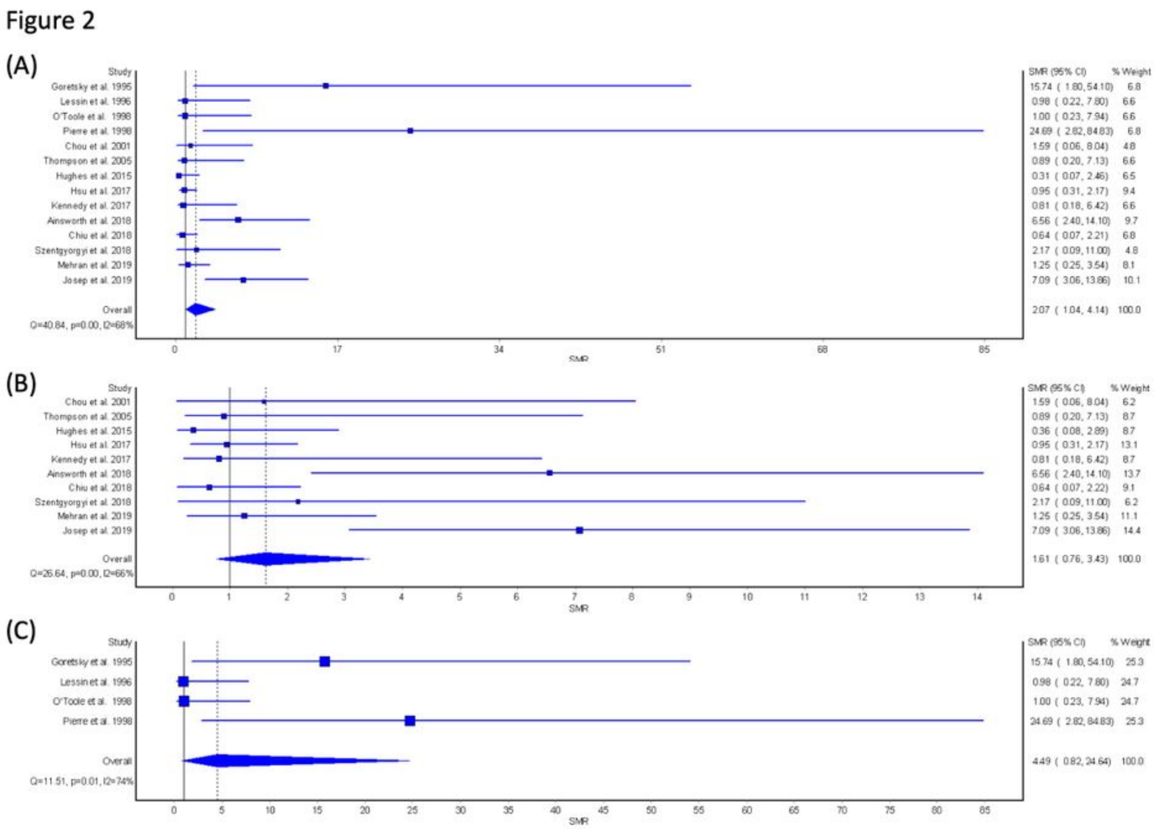


Figure 2

For all studies that provided the revised Baux scores of patients, logistic regression calculations between the revised Baux scores and predicted mortality rates were performed. A pooled SMR for ECMO treatment, with the results expressed as overall SMRs and associated 95% CIs. The observed mortality was significantly higher than the predicted mortality in patients receiving ECMO, with a pooled SMR of 2.07 (95% CI: 1.04-4.14) (A); adult group and paediatric group did not report benefits from ECMO (B) and (C). CI: confidence interval



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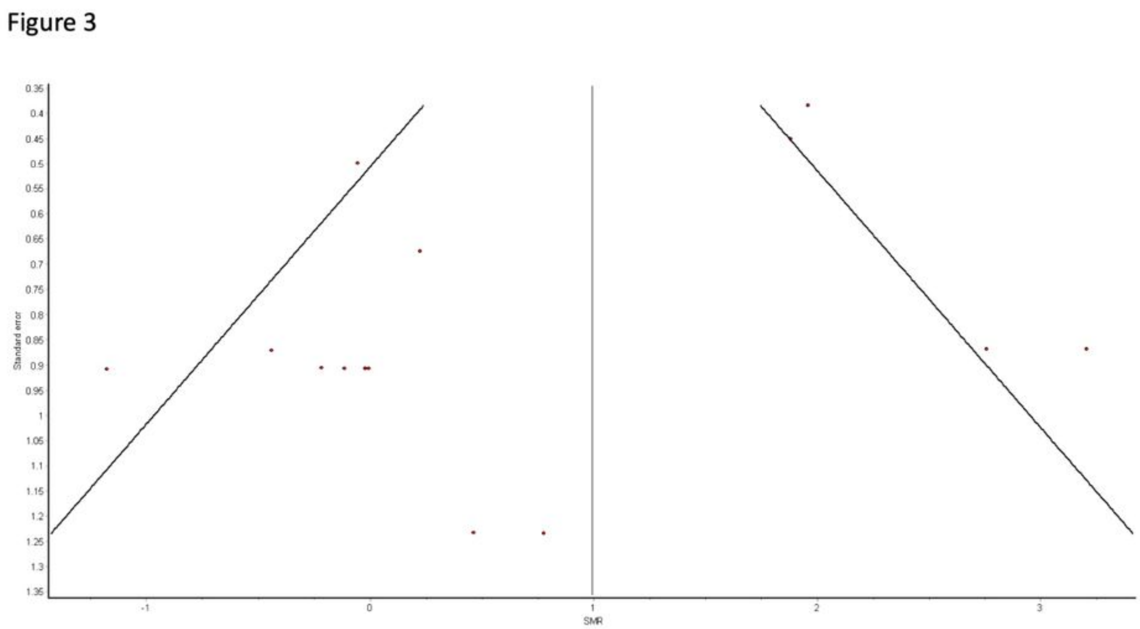
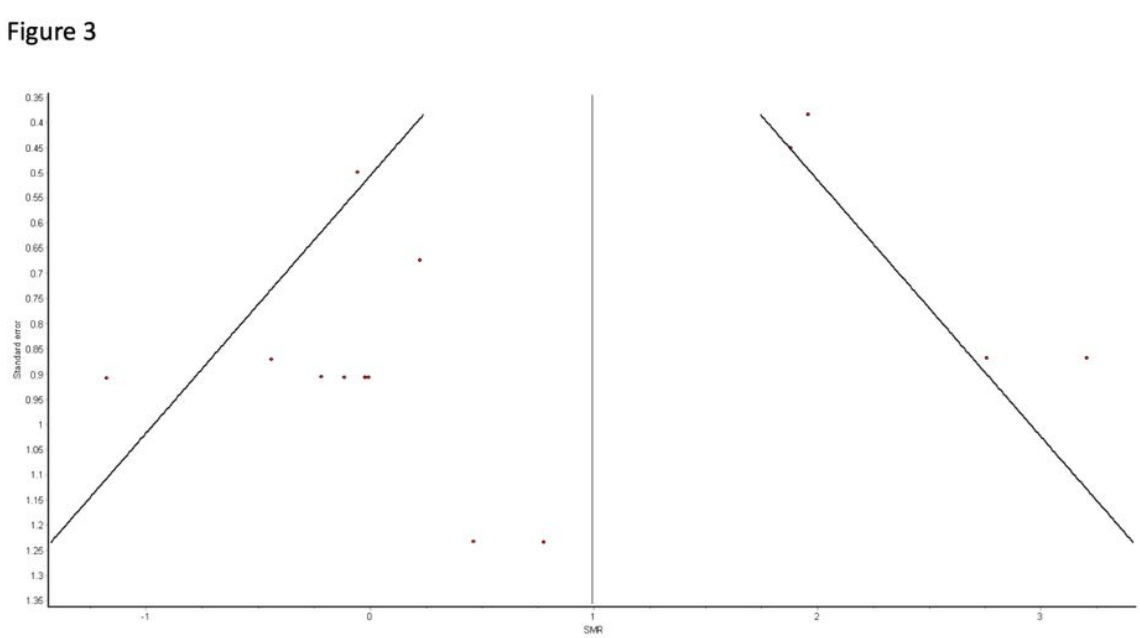


Figure 3

Funnel plot of pooled studies



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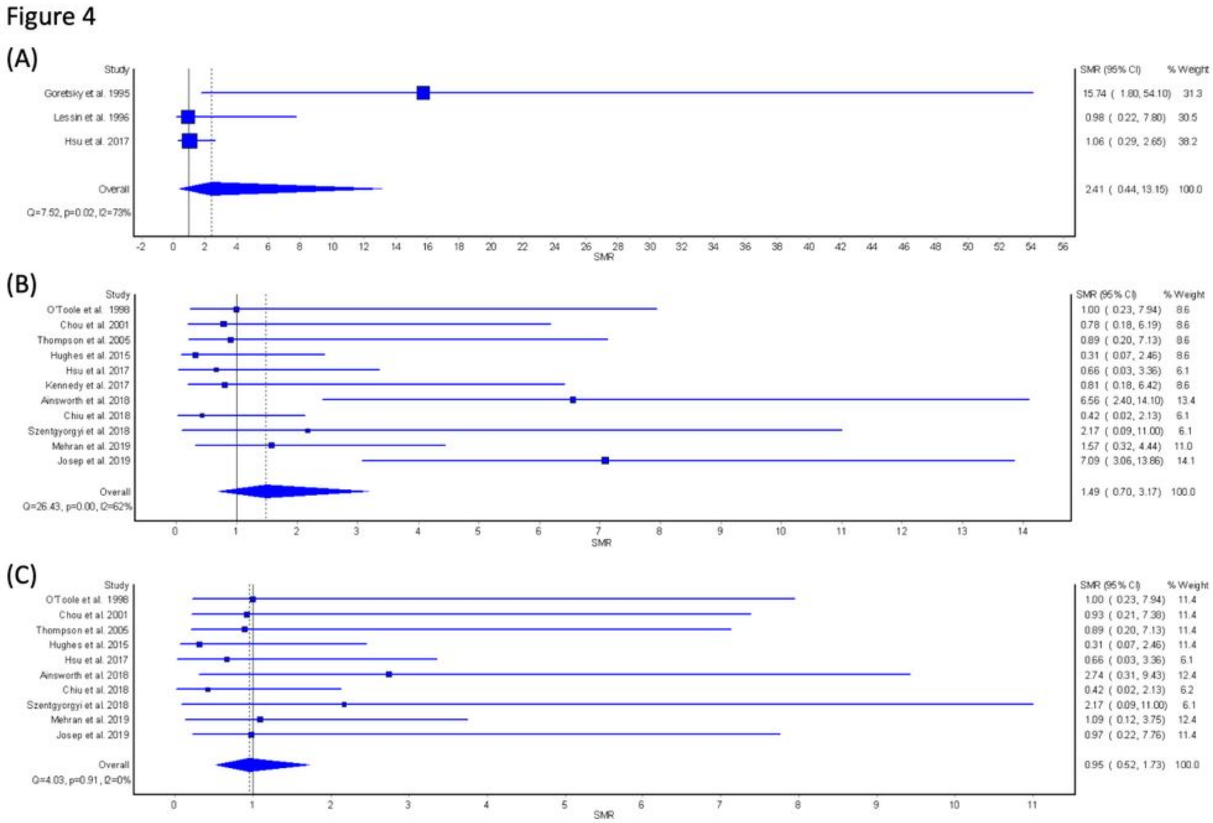

Figure 4

In V-A setting group, and V-V setting group, did not report benefits from ECMO (A) and (B); in the burn patients with inhalation injuries subgroup, all patients receiving V-V ECMO had a lower mortality than their predicted mortality, with a pooled SMR of 0.95 (95% CI: 0.52-1.73) (C). CI: confidence interval

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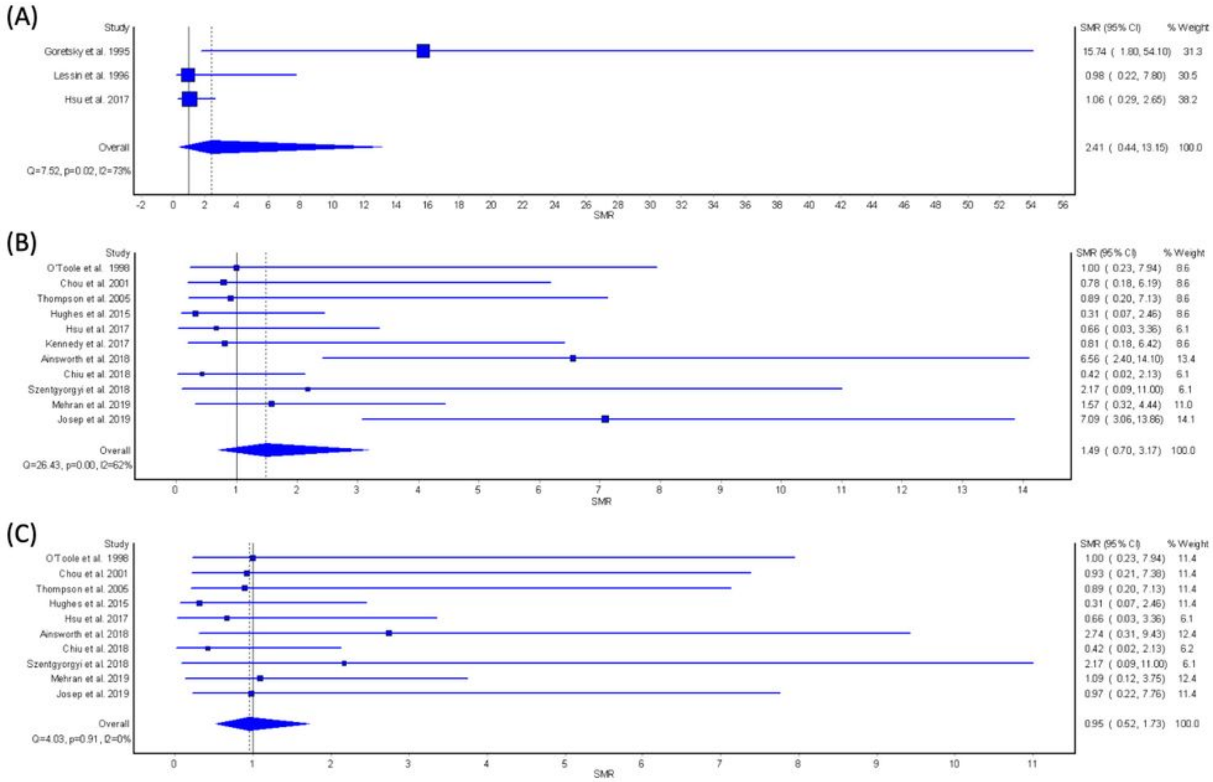

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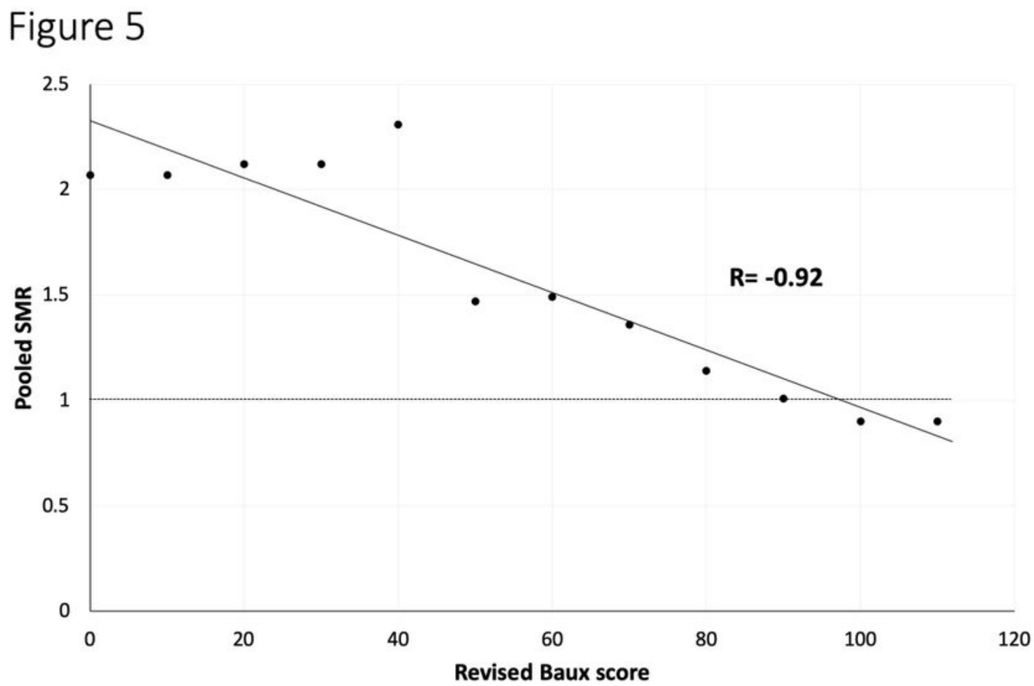
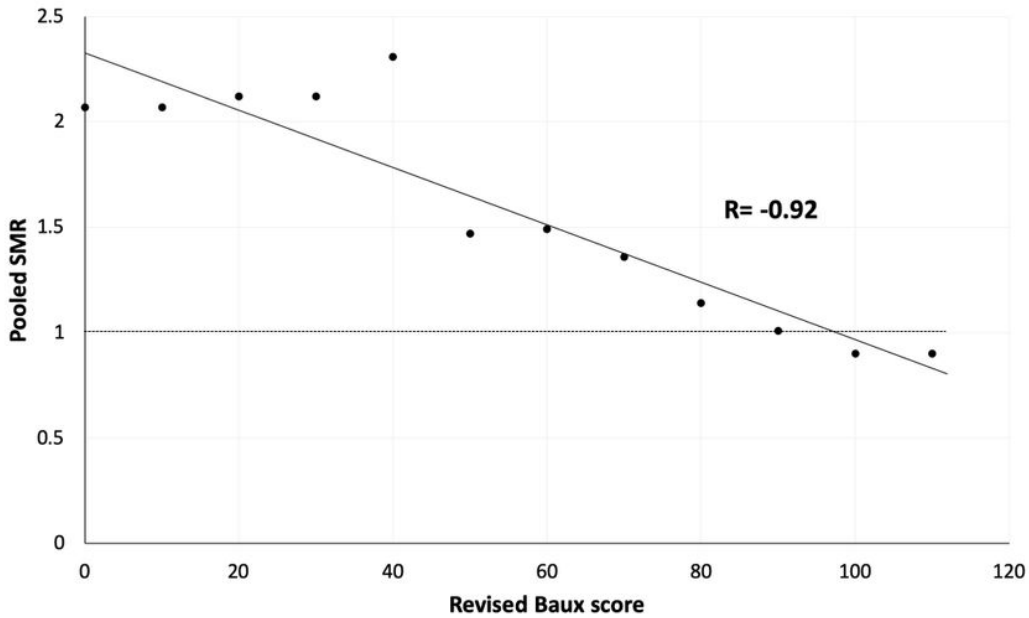


Figure 5

The pooled SMR decreased as the patients' revised Baux scores increased, with a high correlation (R= -0.92). The pooled SMR would cross over 1 when the patient's revised Baux exceeded approximately 90, indicating that the potential benefits from ECMO treatment increased as the severity of patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

Figure 5



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