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A Systematic Review and Meta-Analysis of Extracorporeal Membrane Oxygenation in Patients with Burns

Yu-Jen Chiu, M.D.
Yu-Chen Huang, M.D.
Tai-Wei Chen, M.D.
Yih-An King, M.D.
Hsu Ma, M.D., Ph.D.

Taipei, Taiwan

PATIENT SAFETY

Background: Severely burned patients are at high risk for cardiopulmonary failure. Promising studies have stimulated interest in using extracorporeal membrane oxygenation as a potential therapy for burn patients with refractory cardiac and/or respiratory failure. However, the findings from previous studies vary.

Methods: In this study, the authors conducted a systematic review and meta-analysis using standardized mortality ratios to elucidate the benefits associated with the use of extracorporeal membrane oxygenation in patients with burn and/or inhalation injuries. A literature search was performed, and clinical outcomes in the selected studies were compared.

Results: The meta-analysis found that the observed mortality was significantly higher than the predicted mortality in patients receiving extracorporeal membrane oxygenation (standardized mortality ratio, 2.07; 95 percent CI, 1.04 to 4.14). However, the subgroup of burn patients with inhalation injuries had lower mortality rates compared to their predicted mortality rates (standardized mortality ratio, 0.95; 95 percent CI, 0.52 to 1.73). Other subgroup analyses reported no benefits from extracorporeal membrane oxygenation; however, these results were not statistically significant. Interestingly, the pooled standardized mortality ratio values decreased as the selected patients' revised Baux scores increased ($R = -0.92$), indicating that the potential benefits from the treatment increased as the severity of patients with burns increased.

Conclusions: The authors' meta-analysis revealed that burn patients receiving extracorporeal membrane oxygenation treatment were at a higher risk of death. However, select patients, including those with inhalation injuries and those with revised Baux scores over 90, would benefit from the treatment. The authors suggest that burn patients with inhalation injuries or with revised Baux scores exceeding 90 should be considered for the treatment and early transfer to an extracorporeal membrane oxygenation center. (*Plast. Reconstr. Surg.* 149: 1181e, 2022.)

From the Divisions of Plastic and Reconstructive Surgery and Cardiovascular Surgery, Department of Surgery, Taipei Veterans General Hospital; Department of Surgery, School of Medicine, and Institute of Clinical Medicine, National Yang Ming Chiao Tung University; Department of Dermatology and Research Center of Big Data and Meta-Analysis, Wan Fang Hospital, and Department of Dermatology, School of Medicine, College of Medicine, Taipei Medical University; Department of Dermatology, Taipei Medical University-Shuang Ho Hospital; and Department of Surgery, National Defense Medical Center.

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Severely burned patients, particularly those whose injuries are 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 with refractory respiratory failure is one of the most dominant causes of death in patients with burns.[2,4] Acute respiratory distress

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syndrome 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 acute respiratory distress syndrome, which uses a lung-protective strategy to avoid superimposing additional damage on the already-injured pulmonary alveoli to let the "lung rest." However, such ventilation is unable to provide lifesaving respiratory support when a critical volume of the alveolar unit has failed.[7] Extracorporeal membrane oxygenation 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 extracorporeal membrane oxygenation are venoarterial extracorporeal membrane oxygenation and venovenous extracorporeal membrane oxygenation. Venoarterial extracorporeal membrane oxygenation support is required for cardiac and/or respiratory failure; venovenous extracorporeal membrane oxygenation 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 unfavorable outcomes in extracorporeal membrane oxygenation–treated groups.[9] In recent years, extracorporeal membrane oxygenation has become more reliable with improvements in equipment, and increased practitioners' experience has led to extracorporeal membrane oxygenation becoming an alternative tool to treat patients with severe cardiac and pulmonary dysfunctions.[10–12] These promising studies have stimulated interest in using extracorporeal membrane oxygenation 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 extracorporeal membrane oxygenation in the context of burns and/or smoke inhalation.[13–22] Asmussen et al. in 2013 performed a systematic review of extracorporeal membrane oxygenation treatment for burn and smoke inhalation injuries. Because of the insufficient patient numbers from the available literature, along with limited evidence, the role of extracorporeal membrane oxygenation 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.[3,23–34] Randomized controlled trials of extracorporeal membrane oxygenation compared to conventional therapy might be the solution. However, burn patients with cardiac and/or respiratory failure are rare, making it difficult to perform randomized 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 indicate the mortality in a cohort relative to the mortality in a reference population. A meta-analysis of standardized mortality ratios investigated the all-cause and cause-specific standardized mortality ratios, eliminating the effect of differing patient characteristics in the two compared populations, and thus provides a better picture of the changes in survival.[35,36] Because most of the available literature on burn patients being treated with extracorporeal membrane oxygenation 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 standardized mortality ratios. This was performed to elucidate the benefits associated with the use of extracorporeal membrane oxygenation in patients with burn and/or inhalation injuries.

PATIENTS AND 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) children or adults

with a diagnosis of a thermal burn and/or smoke inhalation requiring extracorporeal membrane oxygenation as determined by a physician; (2) an identified group of patients who received extracorporeal membrane oxygenation as part of their therapeutic regimen; and (3) refer to disease severity in patients treated with extracorporeal membrane oxygenation 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 standardized mortality ratios. 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.[37] Revised Baux scores were calculated as age (years) + total body surface area (percent) + (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 inclusion criteria independently: study type, sample size, inclusion dates, treatment regimen, age, sex, country, burn type, total body surface area burned, presence of inhalation injury or acute respiratory distress syndrome, extracorporeal membrane oxygenation settings, mortality status, mortality rate, revised Baux score, and revised Baux score–based standardized mortality ratio with 95 percent confidence interval. 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We calculated the pooled crude mortality rate of patients receiving extracorporeal membrane oxygenation. The results were expressed as the overall odds ratio with associated 95 percent confidence interval. 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. Standardized mortality ratio was defined as the ratio of observed mortality to expected mortality, and the accompanying 95 percent confidence interval was based on the methods used by Ury and Wiggins.[36] We produced a pooled standardized mortality ratio for extracorporeal membrane oxygenation treatment, with the results expressed as overall standardized mortality ratios and associated 95 percent confidence intervals. Subgroup analyses of different extracorporeal membrane oxygenation settings and pediatric patients were also performed.

Heterogeneity across studies was evaluated using the chi-square 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 presence of publication bias.[38] When the mortality rate was 0, we added 0.5 to both the observed deaths and expected deaths and used the adjusted standardized mortality ratios in our analysis.

RESULTS

Study Selection

The abstraction process is detailed in Figure 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 eight case series) eligible for final review and analysis; these articles are summarized in Table 1. In the standardized mortality ratio quantitative analysis, nine records were removed because of incomplete and undetailed data.

Outcomes

The overall pooled mortality rate of burn patients receiving extracorporeal membrane oxygenation was 48.0 percent (95 percent CI, 0.405 to 0.556). The pooled mortality rate in the

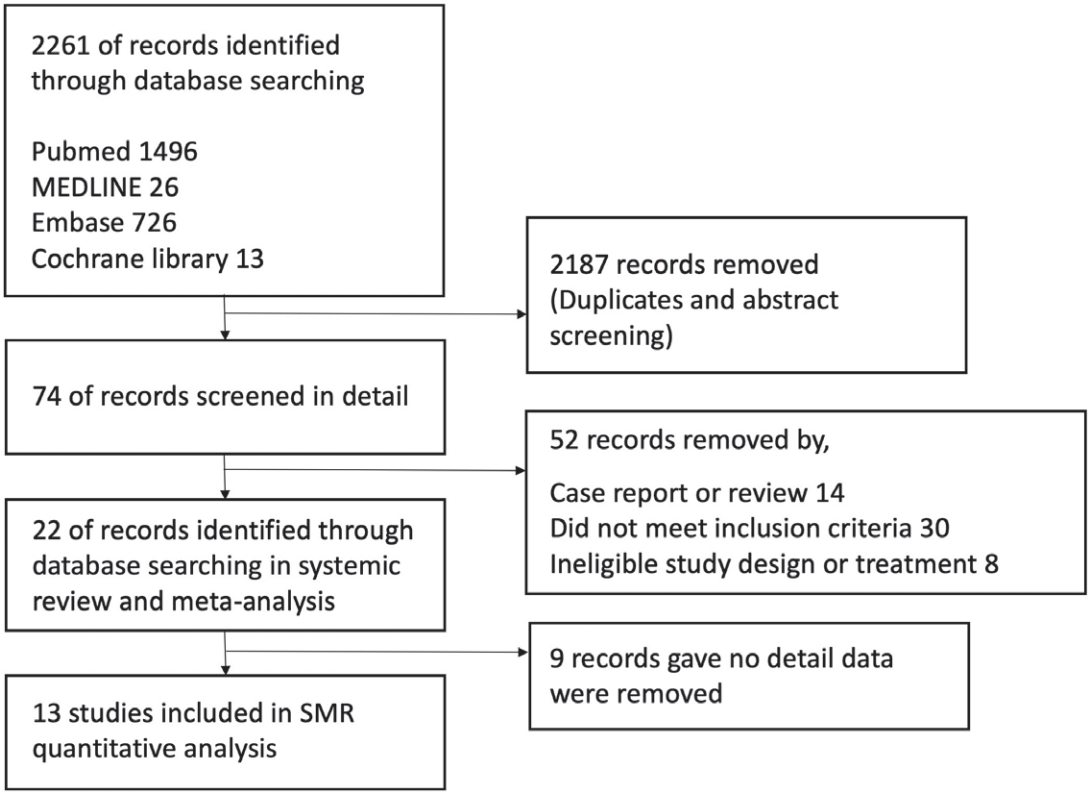

Fig. 1. Flow diagram of search strategy and study selection processes for the systematic review and meta-analysis. *SMR*, standardized mortality ratio.

pediatric subgroup was 41.4 percent (95 percent CI, 0.298 to 0.540), the mortality rate in the adult subgroup was 49.4 percent (95 percent CI, 0.375 to 0.613), the mortality rate in the venovenous subgroup was 41.8 percent (95 percent CI, 0.333 to 0.508), and the mortality rate in the venoarterial subgroup was 41.1 percent (95 percent CI, 0.219 to 0.634).

The meta-analysis found that the observed mortality was significantly higher than the predicted mortality in patients receiving extracorporeal membrane oxygenation, with a pooled standardized mortality ratio of 2.07 (95 percent CI, 1.04 to 4.14), as shown in Figure 2, *above*. However, the adult group and the pediatric group did not report benefits from extracorporeal membrane oxygenation, as shown in Figure 2, *center* and *below*. The funnel plot did not indicate any publication biases (Fig. 3). In the venoarterial group and the venovenous groups, the results did not report benefits from extracorporeal membrane oxygenation, as shown in Figure 4, *above* and *center*, in the subgroup of burn patients with inhalation injuries; all patients receiving venovenous extracorporeal membrane oxygenation had a lower mortality than their predicted mortality, with a pooled standardized mortality ratio of 0.95 (95 percent CI, 0.52 to 1.73), as shown in Figure 4, *below*. Interestingly, the pooled standardized mortality ratios decreased as patients' revised Baux scores increased, with a high correlation ($R = -0.92$), as shown in Figure 5. The pooled standardized mortality ratios were less than 1 when the selected patients' revised Baux scores exceeded approximately 90, indicating that the potential benefits from extracorporeal membrane oxygenation 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 Figure 3. A random effects model was used for all analyses because of the large heterogeneity of the sample. According to the Grades of Recommendation Assessment, Development and Evaluation classification, we judged the quality of evidence of included studies. Subcategories of bias (e.g., indication, selection, allocation, performance, attrition, or reporting bias) were not assessed.

Table 1. Characteristics of Selected Trials

Reference	Country	Study Type	Mean Age (yr)	No. of Cases (Inhalation)	ECMO Setting (VV/VA)	Mortality	SMR (95% CI)
Goretsky et al., 1995[13]	United States	Retrospective	2.5	5 (1)	0/5	2	15.74 (1.8–54.1)
Lessin et al., 1996[14]	United States	Case series	1.45	2 (2)	0/2	0	0.978 (0.223–7.799)
O'Toole et al., 1998[15]	United Kingdom	Case series	1.6	2 (2)	2/0	0	0.996 (0.227–7.939)
Pierre et al., 1998[16]	United States	Retrospective	4.33	5 (3)	N/A	2	24.69 (2.82–84.83)
Kane et al., 1999[17]	United States	Retrospective	2.5	12 (4)	N/A	4	N/A
Masiakos et al., 1999[18]	United States	Retrospective	N/A	3 (N/A)	N/A	2	N/A
Chou et al., 2001[19]	Taiwan	Case series	30.3	3 (2)	2/1	1	1.589 (0.064–8.043)
Thompson et al., 2005[20]	United States	Case series	33	2 (2)	2/0	0	0.894 (0.204–7.129)
Nehra et al., 2009[21]	United States	Retrospective	4.45	10 (N/A)	N/A	7	N/A
Askegard-Giesmann et al., 2010[22]	United States	Retrospective	N/A	36 (6)	17/19	17	N/A
Hughes et al., 2015[23]	United States	Case series	30	3 (3)	3/0	0	0.308 (0.07–2.457)
Soussi et al., 2016[3]	France	Retrospective	51	11 (6)	3/8	10	N/A
Burke et al., 2017[23]	United States	Retrospective	N/A	58 (14)	44/14	33	N/A
Hsu et al., 2017[24]	Taiwan	Retrospective	43.3	6 (6)	2/4	5	0.946 (0.306–2.172)
Nosanov et al., 2017[26]	United States	Retrospective	38.9	30 (8)	N/A	16	N/A
Kennedy et al., 2017[27]	United States	Case series	46	2 (0)	2/0	0	N/A
Ainsworth et al., 2018[28]	United States	Retrospective	36	12 (4)	12/0	6	0.805 (0.184–6.418)
Chiu et al., 2018[29]	Taiwan	Case series	21.8	5 (5)	4/1	2	6.557 (2.404–14.098)
Szentgyorgyi et al., 2018[30]	United Kingdom	Retrospective	34.4	5 (5)	5/0	1	0.644 (0.073–2.215)
Eldredge et al., 2019[31]	United States	Retrospective	5.9	8 (3)	8/0	1	N/A
Dadras et al., 2019[32]	Germany	Case series	46	8 (7)	7/1	3	2.173 (0.087–10.999)
Marcus et al., 2019[33]	United States	Retrospective	34	17 (2)	17/0	8	7.086 (3.062–13.86)

ECMO, extracorporeal membrane oxygenation; VV, venovenous; VA, venoarterial; SMR, standardized mortality ratio; N/A, not available.

DISCUSSION

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

Standardized mortality ratios based on generic mortality prediction models have been widely applied to predict deaths in the general population.[39] Various mathematical models have been developed and widely used to predict mortality as an outcome of burn injuries.[40] They are associated with several factors, including age, total body surface area burned, inhalation injuries, and so on.[41] Many prediction models such as the revised Baux score,[42] Abbreviated Burn Severity Index,[43] Total Burn Surface Index,[44] Taiwan burn score,[45] and that reported by the Belgian Outcome of Burn Injury Study Group[46] are well-known systems that fulfill the published methodologic standards for composite model construction and validation.[41] Several studies have reported that the revised Baux score system is more accurate for predicting survival not only in adult patients but also in pediatric patients.[41,42,47–52] Moreover, this model is simple to calculate and has good calibration and discriminatory power. As a result, our standardized mortality ratio calculations were based on the revised Baux score system when conducting the analyses in this study.

In recent decades, extracorporeal membrane oxygenation has become an essential tool in the care of patients with severe cardiac and pulmonary dysfunctions that are refractory to conventional management.[10,11,53] The indications for and use of extracorporeal membrane oxygenation as a treatment option have progressed strikingly. In addition, in the burn field, plastic surgeons and

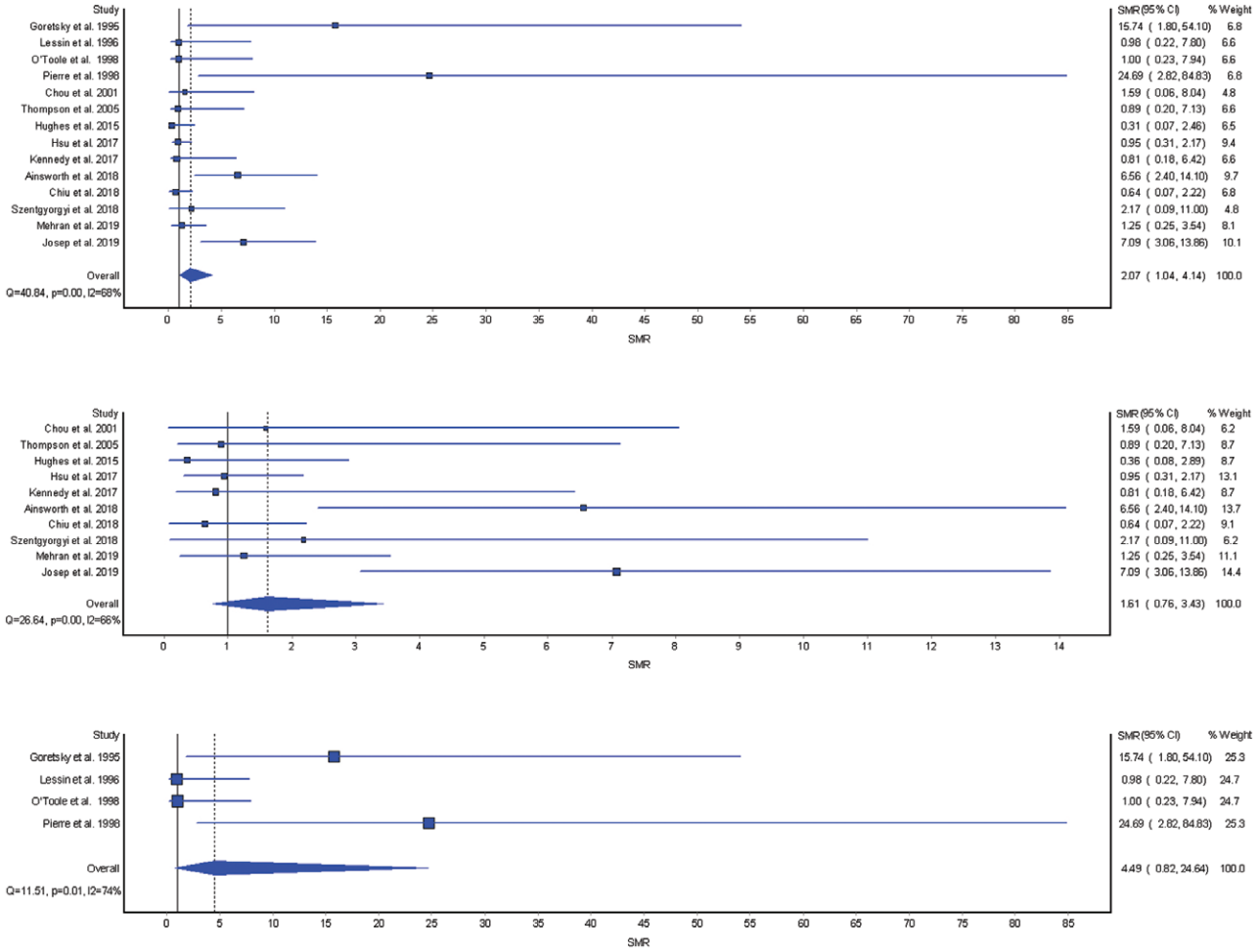

Fig. 2. For all studies that provided the revised Baux scores of patients, logistic regression calculations between the revised Baux scores and predicted mortality rates were performed. A pooled standardized mortality ratio for extracorporeal membrane oxygenation treatment, with the results expressed as overall standardized mortality ratios and associated 95 percent confidence intervals, is shown. The observed mortality was significantly higher than the predicted mortality in patients receiving extracorporeal membrane oxygenation, with a pooled standardized mortality ratio of 2.07 (95 percent CI, 1.04 to 4.14) (*above*). Adult (*center*) and pediatric (*below*) groups did not report benefits from extracorporeal membrane oxygenation. *SMR*, standardized mortality ratio.

intensivists have tried to use extracorporeal membrane oxygenation 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 extracorporeal membrane oxygenation treatment in burn patients were reported. Several case series and retrospective studies have been reported recently. However, the findings are still varied. Retrospective data from the Extracorporeal Life Support Organization international registry reported 58 adult burn patients from 1999 to 2015 with a hospital mortality rate of 57 percent.[24] Soussi et al. in 2016 reported a 91 percent in-hospital mortality rate in 11 burn patients receiving extracorporeal membrane oxygenation therapy, suggesting that extracorporeal membrane oxygenation treatment for burn patients is not advisable.[3] However, in the past few years, several observational studies have revealed favorable outcomes from the use of extracorporeal membrane oxygenation.[24,26–32] In this study, our meta-analysis revealed a pooled standardized mortality ratio of 2.07, suggesting a two-fold higher mortality rate compared to the predicted mortality rate in patients receiving extracorporeal membrane oxygenation therapy. Based on the results, extracorporeal membrane oxygenation is not recommended as a routine therapy for patients with burns.

In contrast, the substantial growth of patients treated with extracorporeal membrane oxygenation raises ethical issues regarding patient selection and when extracorporeal membrane oxygenation support should be halted.[54] There

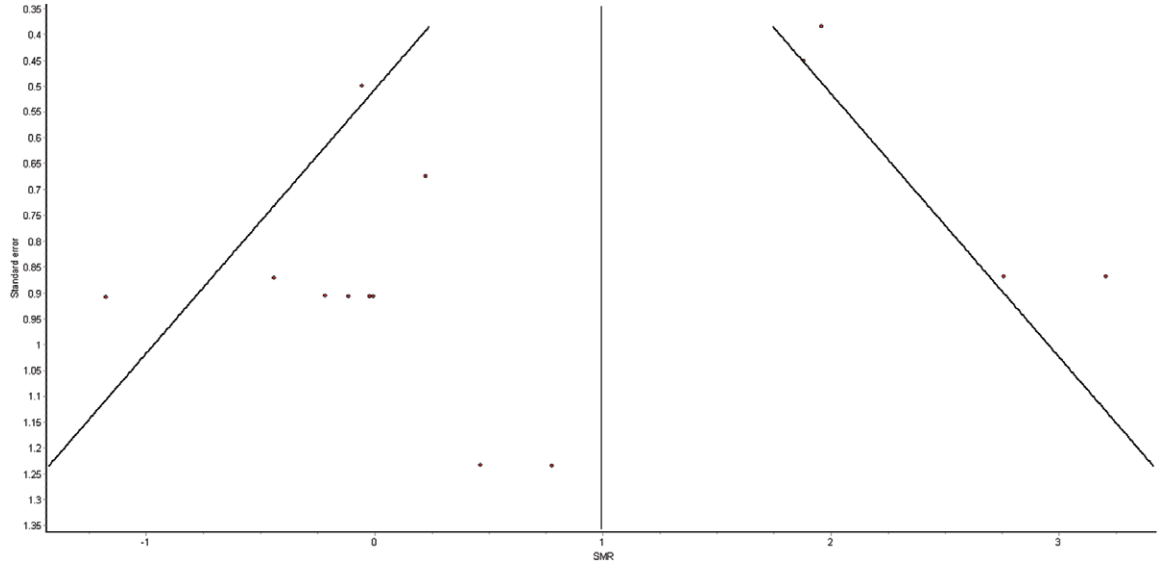

Fig. 3. Funnel plot of pooled studies. *SMR*, standardized mortality ratio.

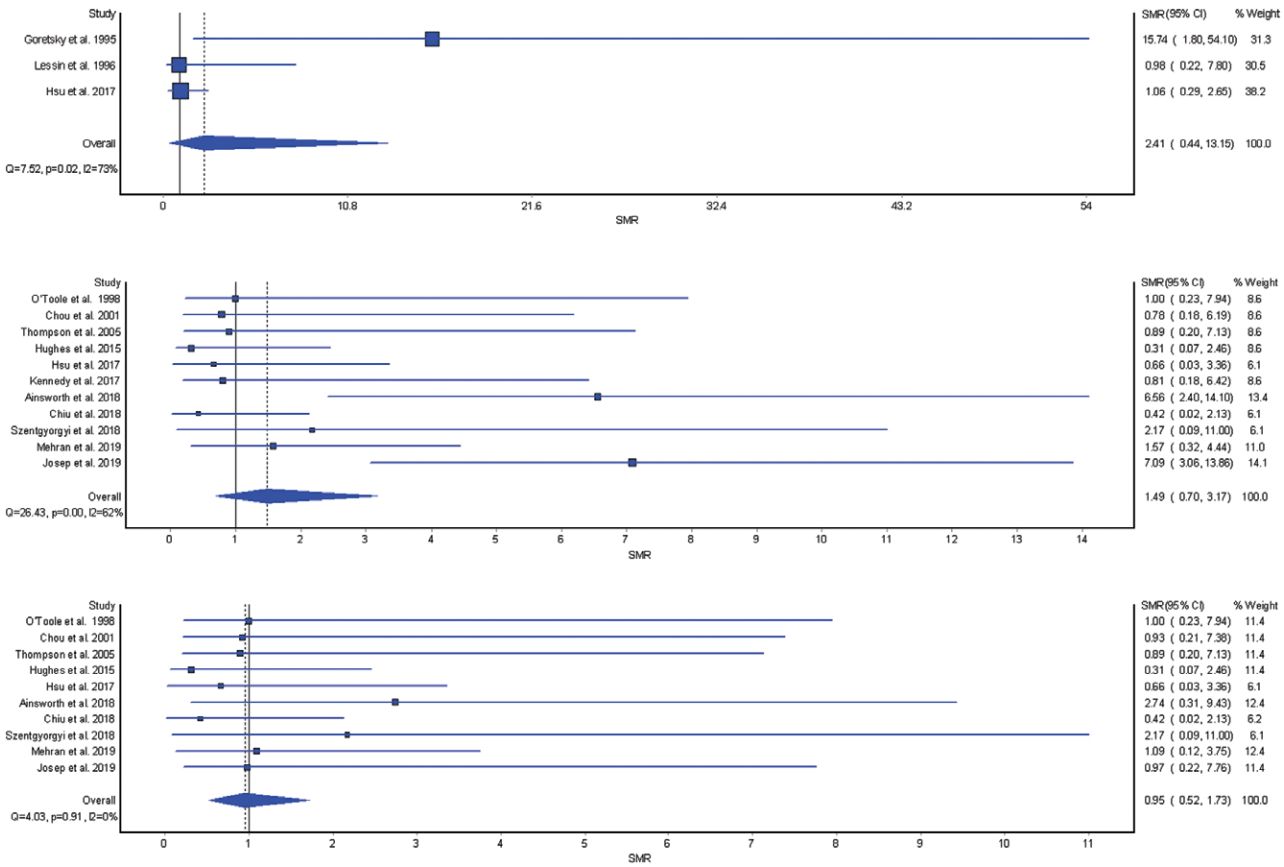

Fig. 4. In the venoarterial group and the venovenous group, benefits from extracorporeal membrane oxygenation (*above*) and (*center*) were not reported; in the burn patients with inhalation injuries subgroup, all patients receiving venovenous extracorporeal membrane oxygenation had a lower mortality than their predicted mortality, with a pooled standardized mortality ratio of 0.95 (95 percent CI, 0.52 to 1.73) (*below*). *SMR*, standardized mortality ratio.

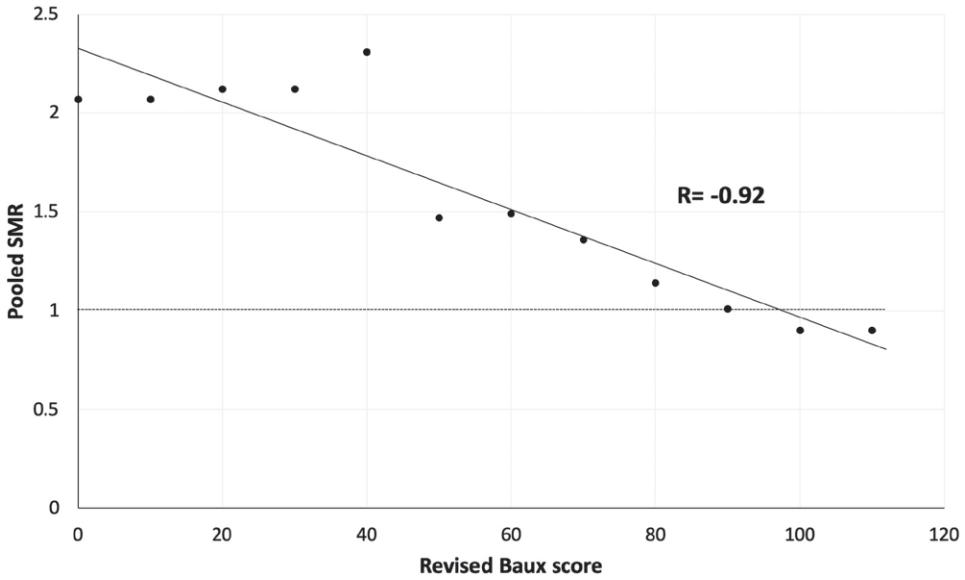

Fig. 5. The pooled standardized mortality ratio decreased as the patients' revised Baux scores increased, with a high correlation ($R = -0.92$). The pooled standardized mortality ratio would cross over 1 when the patient's revised Baux exceeded approximately 90, indicating that the potential benefits from extracorporeal membrane oxygenation treatment increased as the severity of injury in patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

is an increasing amount of studies demonstrating that careful patient selection is important to obtain the best results.[54,55] Moreover, resource use should be justified to minimize the economic burden on the health system.[55] In this study, different patient groups were analyzed to determine the benefits from extracorporeal membrane oxygenation treatment. The results showed that the observed mortality in burn patients with inhalation injuries was lower than their predicted mortality, considering that the pooled standardized mortality ratio was 0.95. Other subgroup analyses, including an adult group, a pediatric group, a venovenous group, and a venoarterial group, found that extracorporeal membrane oxygenation treatment was not beneficial. It is also worth mentioning that the pooled standardized mortality ratio decreased as the patients' revised Baux scores increased, with a high correlation ($R = -0.92$), as shown in Figure 5. The pooled standardized mortality ratio would cross over 1 when the patient's revised Baux score exceeded approximately 90, indicating that the potential benefits from extracorporeal membrane oxygenation treatment increased as the severity of injury in patients with burns increased, especially when the patients' revised Baux scores exceeded 90.

Another pressing issue regarding extracorporeal membrane oxygenation is patient transfer. Several studies have reported that patients with severe acute respiratory failure should be transferred to an extracorporeal membrane oxygenation center for further treatment. In burn patients, Dadras et al. and Eldredge et al. suggested early consideration of extracorporeal membrane oxygenation consultation in burn patients with severe acute respiratory distress syndrome and proposed the transfer of these patients.[31,32] 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 extracorporeal membrane oxygenation center. We believe that the potential benefits from extracorporeal membrane oxygenation 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 include in randomized trials because of ethical considerations and the rarity of the injuries with extracorporeal membrane oxygenation therapy. Second, standardized mortality ratios that are based on prediction scoring systems such as in our study may have biases, other comorbidities, and complications during hospitalization that were not evaluated as well. Last, because extracorporeal membrane oxygenation 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 extracorporeal membrane oxygenation treatment were at high risk of death. However, select patients, including those with inhalation injuries and patients with a revised Baux score exceeding 90, may benefit from extracorporeal membrane oxygenation treatment. Based on our finding, extracorporeal membrane oxygenation should not be routinely used in all burn patients. In contrast, we recommend that patients with inhalation injuries and/or with high revised Baux scores (>90) should be considered for extracorporeal membrane oxygenation treatment and early transfer to an extracorporeal membrane oxygenation center.

Hsu Ma, M.D., Ph.D.
Division of Plastic and Reconstructive Surgery
Department of Surgery
Taipei Veterans General Hospital
19/F, No. 201, Sec. 2, Shipai Road
Beitou District
Taipei 11217, Taiwan, Republic of China
sma471124@gmail.com

Yih-An King, M.D.
Department of Dermatology
Taipei Medical University-Shuang Ho Hospital
No. 291, Zhongzheng Road
Zhonghe District
New Taipei City 23561, Taiwan, Republic of China
saltycat.king@gmail.com

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