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

Yu-Jen Chiu
Taipei Veterans General Hospital

Yu-Chen Huang
Taipei Municipal Wan-Fang Hospital

Tai-Wei Chen
Taipei Veterans General Hospital

Yih-An King (✉ saltycat.king@gmail.com)
Taipei Medical University Shuang Ho Hospital Ministry of Health and Welfare

Hsu Ma
Taipei Veterans General Hospital

Research

Keywords: Extracorporeal membrane oxygenation, Burn, Meta-analysis, Standardized mortality ratios, revised Baux Score

DOI: https://doi.org/10.21203/rs.3.rs-125432/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
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 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 (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 \( e^{\frac{8.8163 + (0.0775 \cdot r_{Baux})}{1 + e^{8.8163 + (0.0775 \cdot r_{Baux})}}} \). 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.

Funding

This study was supported by a grant from the Taipei Veterans General hospital, Taipei, Taiwan (V106A-008 and V110B-038).

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.

Acknowledgements

nil

References

1. Zuo KJ, Medina A, Tredget EEJP, surgery r: Important developments in burn care. Plastic reconstructive surgery 2017, 139(1):120e-138e.

2. Asmussen S, Maybauer DM, Fraser JF, Jennings K, George S, Keiralla A, Maybauer MO: Extracorporeal membrane oxygenation in burn and smoke inhalation injury. Burns 2013, 39(3):429-435.

3. Soussi S, Gallais P, Kachatryan L, Benyamina M, Ferry A, Cupaciu A, Chaussard M, Maurel V, Chaouat M, Mimoun M: Extracorporeal membrane oxygenation in burn patients with refractory acute respiratory distress syndrome leads to 28% 90-day survival. Intensive care medicine 2016, 42(11):1826-1827.

4. Ma H, Tung K-Y, Tsai S-L, Neil DL, Ling Y-Y, Yen H-T, Lin K-L, Cheng Y-T, Kao S-C, Lin M-NJB: Assessment and determinants of global outcomes among 445 mass-casualty burn survivors: a 2-year retrospective cohort study in Taiwan. Burns 2020.

5. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. Jama 2008, 299(6):637-645.

6. Ziolkowski NI, Pusic AL, Fish JS, Mundy LR, She RW, Forrest CR, Hollenbeck S, Arriagada C, Calcagno M, Greenhalgh D: Psychometric Findings for the SCAR-Q Patient-Reported Outcome Measure Based on 731 Children and Adults with Surgical, Traumatic, and Burn Scars from Four Countries. Plastic Reconstructive Surgery 2020, 146(3):331e-338e.

7. Lewandowski K: Extracorporeal membrane oxygenation for severe acute respiratory failure. Critical Care 2000, 4(3):156.

8. Rilinger J, Zotzmann V, Bemtgen X, Schumacher C, Biever PM, Duerschmied D, Kaier K, Stachon P, von Zur Mühlen C, Zehender M: Prone positioning in severe ARDS requiring extracorporeal membrane oxygenation. Critical Care 2020, 24(1):1-9.

9. Morris A, Wallace C, Menlove R, Clemmer T, Orme Jr J, Weaver L, Dean N, Thomas F, East T, Pace N: Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. American journal of respiratory critical care medicine 1994, 149(2):295-305.

10. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK: Referral to an extracorporeal membrane oxygenation center and mortality among patients...
with severe 2009 influenza A (H1N1). *Jama* 2011, 306(15):1659-1668.

11. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalananey MM, Hibbert CL, Truesdale A, Clemens F, Cooper N: **Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial.** *The Lancet* 2009, 374(9698):1351-1363.

12. Goretsky MJ, Greenhalgh DG, Warden GD, Ryckman FC, Warner BW: **The use of extracorporeal life support in pediatric burn patients with respiratory failure.** *Journal of pediatric surgery* 1995, 30(4):620-623.

13. Lessin MS, El-Eid SE, Klein MD, Cullen ML: **Extracorporeal membrane oxygenation in pediatric respiratory failure secondary to smoke inhalation injury.** *Journal of pediatric surgery* 1996, 31(9):1285-1287.

14. O'Toole G, Peek G, Jaffe W, Ward D, Henderson H, Firmin R: **Extracorporeal membrane oxygenation in the treatment of inhalation injuries.** *Burns* 1998, 24(6):562-565.

15. Pierre E, Zwischenberger J, Angel C, Upp J, Cortiella J, Sankar A, Herndon D: **Extracorporeal membrane oxygenation in the treatment of respiratory failure in pediatric patients with burns.** *The Journal of burn care rehabilitation* 1998, 19(2):131-134.

16. Kane TD, Greenhalgh DG, Warden GD, Goretsky MJ, Ryckman FC, Warner BW: **Pediatric burn patients with respiratory failure: predictors of outcome with the use of extracorporeal life support.** *The Journal of burn care rehabilitation* 1999, 20(2):145-150.

17. Masiakos PT, Islam S, Doody DP, Schnitzer JJ, Ryan DP: **Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure.** *Archives of Surgery* 1999, 134(4):375-380.

18. Chou NK, Chen YS, Ko WJ, Huang SC, Chao A, Jan GJ, Lin FY, Wang SS, Chu SH: **Application of extracorporeal membrane oxygenation in adult burn patients.** *Artificial Organs* 2001, 25(8):622-626.

19. Thompson JT, Molnar JA, Hines MH, Chang MC, Pranikoff T: **Successful management of adult smoke inhalation with extracorporeal membrane oxygenation.** *The Journal of burn care rehabilitation* 2005, 26(1):62-66.

20. Nehra D, Goldstein AM, Doody DP, Ryan DP, Chang Y, Masiakos PT: **Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure: the Massachusetts General Hospital experience from 1990 to 2008.** *Archives of surgery* 2009, 144(5):427-432.

21. Askegard-Giesmann JR, Besner GE, Fabia R, Caniano DA, Preston T, Kenney BD: **Extracorporeal membrane oxygenation as a lifesaving modality in the treatment of pediatric patients with burns and respiratory failure.** *Journal of pediatric surgery* 2010, 45(6):1330-1335.

22. Hughes W, Guy TS, Shiose A, Hughes L: **Lessons learned from the use of ECMO in three adult burn patients with smoke inhalation.** *Annals of Burns and Fire Disasters* 2015, XXVIII.

23. Burke CR, Chan T, McMullan DM: **Extracorporeal life support use in adult burn patients.** *Journal of Burn Care Research* 2017, 38(3):174-178.

24. Hsu P-S, Tsai Y-T, Lin C-Y, Chen S-G, Dai N-T, Chen C-J, Chen J-L, Tsai C-S: **Benefit of extracorporeal membrane oxygenation in major burns after stun grenade explosion: experience from a single military medical center.** *Burns* 2017, 43(3):674-680.
25. Nosanov LB, McLawhorn MM, Vigiola Cruz M, Chen JH, Shupp JW: A National Perspective on ECMO utilization use in patients with burn injury. *Journal of Burn Care Research* 2017, 39(1):10-14.

26. Kennedy JD, Thayer W, Beuno R, Kohorst K, Kumar AB: ECMO in major burn patients: feasibility and considerations when multiple modes of mechanical ventilation fail. *Burns trauma* 2017, 5(1).

27. Ainsworth CR, Dellavolpe J, Chung KK, Cancio LC, Mason P: Revisiting extracorporeal membrane oxygenation for ARDS in burns: a case series and review of the literature. *Burns* 2018, 44(6):1433-1438.

28. Chiu Y-J, Ma H, Liao W-C, Shih Y-C, Chen M-C, Shih C-C, Chen T-W, Perng C-K: Extracorporeal membrane oxygenation support may be a lifesaving modality in patients with burn and severe acute respiratory distress syndrome: Experience of Formosa Water Park dust explosion disaster in Taiwan. *Burns* 2018, 44(1):118-123.

29. Szentgyorgyi L, Shepherd C, Dunn KW, Fawcett P, Barker JM, Exton P, Maybauer MO: Extracorporeal membrane oxygenation in severe respiratory failure resulting from burns and smoke inhalation injury. *Burns* 2018, 44(5):1091-1099.

30. Eldredge RS, Zhai Y, Cochran A: Effectiveness of ECMO for burn-related acute respiratory distress syndrome. *Burns* 2019, 45(2):317-321.

31. Dadras M, Wagner JM, Wallner C, Huber J, Buchwald D, Strauch J, Harati K, Kapalschinski N, Behr B, Lehnhardt MJB et al.: Extracorporeal membrane oxygenation for acute respiratory distress syndrome in burn patients: a case series and literature update. *Burns Trauma* 2019, 7.

32. Marcus JE, Piper LC, Ainsworth CR, Sams VG, Batchinsky A, Okulicz JF, Barsoumian AE: Infections in patients with burn injuries receiving extracorporeal membrane oxygenation. *Burns* 2019, 45(8):1880-1887.

33. Ulm K: Simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *American journal of epidemiology* 1990, 131(2):373-375.

34. Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS: Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. *Journal of Neurology, Neurosurgery Psychiatry* 2016, 87(3):324-331.

35. Osler T, Glance LG, Hosmer DW: Simplified estimates of the probability of death after burn injuries: extending and updating the baux score. *Journal of Trauma Acute Care Surgery* 2010, 68(3):690-697.

36. Chiu Y-J, Perng C-K, Ma H: Fractional CO 2 laser contributes to the treatment of non-segmental vitiligo as an adjunct therapy: a systemic review and meta-analysis. *Lasers in Medical Science* 2018, 33(7):1549-1556.

37. Steinvall I, Elmasry M, Fredrikson M, Sjoberg F: Standardised mortality ratio based on the sum of age and percentage total body surface area burned is an adequate quality indicator in burn care: an exploratory review. *Burns* 2016, 42(1):28-40.

38. Hussain A, Choukairi F, Dunn K: Predicting survival in thermal injury: a systematic review of methodology of composite prediction models. *Burns* 2013, 39(5):835-850.

39. Prasad A, Thode Jr HC, Singer AJ: Predictive value of quick SOFA and revised Baux scores in burn patients. *Burns* 2020, 46(2):347-351.
40. Berndtson AE, Sen S, Greenhalgh DG, Palmieri TL: Estimating severity of burn in children: Pediatric Risk of Mortality (PRISM) score versus Abbreviated Burn Severity Index (ABSI). Burns 2013, 39(6):1048-1053.
41. Bhatia A, Mukherjee B: Predicting survival in burned patients. Burns 1992, 18(5):368-372.
42. Chen C-C, Chen L-C, Wen B-S, Liu S-H, Ma H: Objective estimates of the probability of death in acute burn injury: a proposed Taiwan burn score. Journal of trauma acute care surgery 2012, 73(6):1583-1589.
43. Group BOiBIS: Development and validation of a model for prediction of mortality in patients with acute burn injury. The British journal of surgery 2009, 96(1):111.
44. Halgas B, Bay C, Foster K: A comparison of injury scoring systems in predicting bum mortality. Annals of burns fire disasters 2018, 31(2):89.
45. Woods JF, Quinlan C, Shelley O: Predicting mortality in severe burns—what is the score?: evaluation and comparison of 4 mortality prediction scores in an Irish population. Plastic Reconstructive Surgery Global Open 2016, 4(1).
46. Tsurumi A, Que Y-A, Yan S, Tompkins RG, Rahme LG, Ryan CM: Do standard bum mortality formulae work on a population of severely burned children and adults? Burns 2015, 41(5):935-945.
47. Dokter J, Meijs J, Oen IM, van Baar ME, van der Vlies CH, Boxma H: External validation of the revised Baux score for the prediction of mortality in patients with acute burn injury. Journal of trauma acute care surgery 2014, 76(3):840-845.
48. Wibbenmeyer LA, Amelon MJ, Morgan LJ, Robinson BK, Chang PX, Lewis II R, Kealey GP: Predicting survival in an elderly burn patient population. Burns 2001, 27(6):583-590.
49. Lumenta D, Hautier A, Desouches C, Gouvernet J, Giorgi R, Manelli J-C, Magalon G: Mortality and morbidity among elderly people with burns—evaluation of data on admission. Burns 2008, 34(7):965-974.
50. Cho HJ, Heinsar S, Jeong IS, Shekar K, Bassi GL, Jung JS, Suen JY, Fraser JF: ECMO use in COVID-19: lessons from past respiratory virus outbreaks—a narrative review. Critical Care 2020, 24(1):1-8.
51. Ahuja A, Shekar K: Patient selection for VV ECMO: have we found the crystal ball? Journal of thoracic disease 2018, 10(Suppl 17):S1979.
52. Makdisi G, Wang l-w: Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. Journal of thoracic disease 2015, 7(7):E166.

Tables

Table 1 Characteristics of selected trials
| Study (year)            | Country | Study type  | Age (Mean) | Case number (Inhalation) | ECMO setting (VV/VA) | Mortality | SMR (95% CI) |
|------------------------|---------|-------------|------------|--------------------------|----------------------|-----------|--------------|
| Goretsky et al. 1995 [12] | USA     | Retrospective | 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     | Retrospective | 4.33       | 5(3)                     | N/A                  | 2         | 24.69(2.82-84.83) |
| Kane et al. 1999 [16]   | USA     | Retrospective | 2.5        | 12(4)                    | N/A                  | 4         | N/A           |
| Masiakos et al. 1999 [17]| USA     | Retrospective | 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     | Retrospective | 4.45       | 10(N/A)                  | N/A                  | 7         | N/A           |
| Askegard-Giesmann et al. 2010 [21] | USA | Retrospective | 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  | Retrospective | 51         | 11(6)                    | 3/8                  | 10        | N/A           |
| Burke et al. 2017 [23]   | USA     | 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 [25] | USA     | Retrospective | 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           |
| Study                        | Country | Study Design | N   | Cases | Mortality | SMR       |
|------------------------------|---------|--------------|-----|-------|-----------|-----------|
| Ainsworth et al. 2018 [27]  | USA     | Retrospective | 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      | Retrospective | 34.4| 5(5)  | 5/0       | 1         |
|                              |         |              |     |       |           | 0.644 (0.073-2.215) |
| Eldredge et al. 2019 [30]   | USA     | Retrospective | 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     | Retrospective | 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**

2261 of records identified through database searching

Pubmed 1496
MEDLINE 26
Embase 726
Cochrane library 13

2187 records removed (Duplicates and abstract screening)

74 of records screened in detail

52 records removed by,
Case report or review 14
Did not meet inclusion criteria 30
Ineligible study design or treatment 8

22 of records identified through database searching in systemic review and meta-analysis

9 records gave no detail data were removed

13 studies included in SMR quantitative analysis
Flow diagram of search strategy and study selection processes for the systemic review and meta-analysis

Figure 1

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

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.

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.
Figure 3

Funnel plot of pooled studies
Funnel plot of pooled studies

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
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
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

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.