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Differential benefits of steroid therapies in adults following major burn injury

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Multi-organ failure;
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Burns

Abstract
Background: Major thermal injury induces a complex pathophysiological state characterized by burn shock and hypercatabolism. Steroids are used to modulate these post-injury responses. However, the effects of steroids on acute post-burn outcomes remain unclear.
Methods: In this study of 52 thermally injured adult patients (median total burn surface area 42%, 33 males and 19 females), the effects of corticosteroid and oxandrolone on mortality, multi-organ failure (MOF), and sepsis were assessed individually. Clinical data were collected at days 1, 3, 7, and 14 post-injury.

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Results: Twenty-two (42%) and 34 (65%) burns patients received corticosteroids and oxandrolone within the same cohort, respectively. Following separate analysis for each steroid, corticosteroid use was associated with increased odds of in-hospital mortality (OR 3.25, 95% CI: 1.32–8•00), MOF (OR 2.36, 95% CI: 1.00–1.55), and sepsis (OR 5.95, 95% CI: 2.53–14.00). Days alive (HR 0.32, 95% CI: 0.18–0.60) and sepsis-free days (HR 0.54, 95% CI: 0.37–0.80) were lower among corticosteroid-treated patients. Oxandrolone use was associated with reduced odds of 28-day mortality (OR 0.11, 95% CI: 0.04–0.30), in-hospital mortality (OR 0.19, 95% CI: 0.08–0.43), and sepsis (OR 0.24, 95% CI: 0.08–0.69). Days alive, at 28 days (HR 6.42, 95% CI: 2.77–14.9) and in-hospital (HR 3.30, 95% CI: 1.93–5.63), were higher among the oxandrolone-treated group. However, oxandrolone was associated with increased MOF odds (OR 7.90, 95% CI: 2.89–21.60) and reduced MOF-free days (HR 0.23, 95% CI: 0.11–0.50).

Conclusion: Steroid therapies following major thermal injury may significantly affect patient prognosis. Oxandrolone was associated with better outcomes except for MOF. Adverse effects of corticosteroids and oxandrolone should be considered when managing burn patients.

Introduction

Patients with ≥ 20% total burn surface area (TBSA) injury are potentially predisposed to significant morbidity and mortality.[1] Severe thermal injury triggers a genomic storm resulting in profound, persistent, and simultaneous systemic inflammatory and compensatory anti-inflammatory responses.[2] Consequently, this induces hypovolemic shock, immunosuppression, and hypermetabolism.

Despite advancements in trauma medicine, most burn mortalities occur acutely following injury.[3] Thus, acute burn care requires improvements to mitigate death rates. Potential avenues include medications used by other specialties such as critical care, as well as those already employed in post-acute burn management such as steroids. Corticosteroids and oxandrolone, a testosterone analog, are assessed in this study.

Corticosteroid use in critically ill patients is endorsed by the surviving sepsis campaign guidelines to address treatment-refractory septic shock.[4] Corticosteroids ameliorate vasoplegia and shock duration, restoring hemodynamic stability. Similar positive findings were reported in burns patients.[5] However, the broader effects of corticosteroid therapy on acute patient outcomes following burn injury remain unclear.

Oxandrolone is used to attenuate post-burn hypermetabolic responses, improve lean body mass, and aid in weight restoration following injury.[6,7] Oxandrolone's influence on acute outcomes following severe thermal injury also remains to be fully elucidated. One study reported improved survival in oxandrolone-treated burns patients, with no associations with multi-organ dysfunction observed.[8]

Our study examines, retrospectively, the impact of corticosteroids' and oxandrolone's effects on acute outcomes following severe thermal injury. The study's hypothesis was that corticosteroid use, secondary to their immunosuppressive properties, would be associated with increased risk of sepsis and mortality in burns patients. In contrast, we hypothesized that oxandrolone use following severe thermal injury would be associated with improved survival.

Methods

Patient enrollment and procedures

This was a retrospective analysis of adult burns patients (16-99 years, ≥20% TBSA) recruited into the Scientific Investigations Following Thermal Injury (SIFTI) study who presented to a UK tertiary burn center within 24 h of injury, between January 2013 and October 2015. Exclusion criteria included deep electrical or chemical burn injury, associated trauma with injury severity score (ISS) >25, decision not to treat, cardiac failure (ejection fraction <20%), active malignancy, prolonged glucocorticoid therapy, and multiple limb amputations (>1). Informed consent was obtained before enrollment or if patients lacked capacity, a consent was sought from a legal, personal, or nominated consultee until patients regained capacity to consent themselves.

Burn patients received similar treatments based on local protocols, inclusive of modified Parkland formula. When suspected, inhalation injury was diagnosed using bronchoscopy. Surgical management/episodes involved excision and grafting of deep dermal and full-thickness burns within 7 days of injury. Patients with deep burns and unsuitable for surgical excision were treated with daily topical application of silver sulfadiazine/cerium nitrate until medically optimized. Other patient requirements such as musculoskeletal, nutritional, and pharmacological needs were addressed during daily joint multi-disciplinary rounds that include dietitians and physiotherapists. Furthermore, weekly multidisciplinary meetings were held with relevant specialties to ensure adherence to management protocols and minimize treatment variability.

Data collection and definitions

Data including patient demographics, burn injury characteristics, physiological status, and clinical outcomes were prospectively recorded using case-report forms. The data were collected over 2 weeks at different timepoints: the day of thermal injury (D01), day 3 (D03), day 7 (D07), and

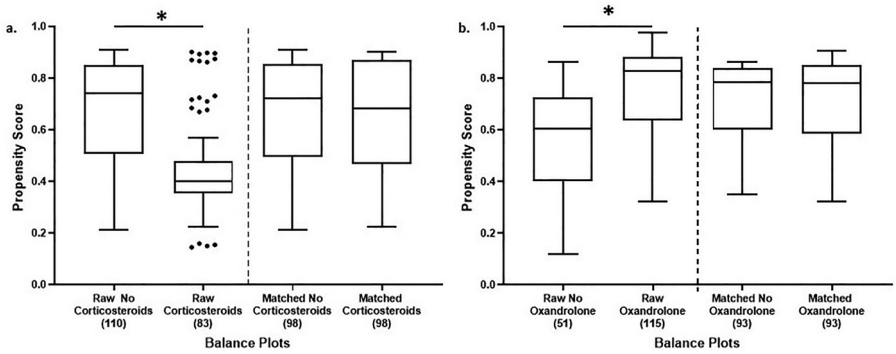

Fig. 1 Propensity score balance plots matching treatment and no-treatment groups. Burns patient demographics, injury severity characteristics, and timepoints were matched using PSM analysis. (a) Propensity scores boxplot of corticosteroid and no-corticosteroid groups before and after matching. (b) Propensity scores boxplot of oxandrolone and no-oxandrolone groups before and after matching. Propensity scores of both cohorts were compared using Mann–Whitney test; * $p < 0.05$.

day 14 (D14) post-burn injury. Recorded parameters and outcomes included sepsis, multi-organ failure (MOF), organ dysfunction, and mortality.

Sepsis in burn patients was defined using the 2007 American Burn Association criteria. MOF was defined using the Denver2 score as previously published.[9-11] Organ dysfunction was quantified using composite and individual organs SOFA scoring system.[12,13] Mortality was assessed as two categories: twenty-eight-day from initial injury and in-hospital mortality during the entire inpatient episode.

Treatments

Corticosteroids used to manage treatment-refractory shock included hydrocortisone (a loading dose of 100 mg followed by 50 mg four times daily maintenance, $n = 19$), dexamethasone (6–8 mg once or twice daily, $n = 2$), and fludrocortisone (100 μg once daily, $n = 1$). Oxandrolone was administered, usually at day 5, to attenuate the post-burn hypermetabolic response at a dose of 5–10 mg twice daily enterally as per local protocol. These treatments were discontinued when deemed appropriate clinically and/or on patient discharge.

Statistical analysis

All statistical analyses were performed using Prism® version 7 (GraphPad Software Inc., California, USA) and IBM SPSS® Statistics version 25 (IBM Corp, New York, USA). Propensity score matching analysis was performed using extension bundle Propensity Sore Matching version 3.0.4 for IBM SPSS® Statistics version 25 (IBM Corp, New York, USA), Python version 3.4 for IBM SPSS® Statistics version 25 (IBM Corp, New York, USA), and R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Patients were grouped according to administered treatments and labeled as "medication" or "no medication". Each treatment was assessed individually to evaluate their respective effects on clinical outcomes. Propensity scores were calculated via logistic regression and were matched to age, gender, TBSA, presence of inhalation injury, revised Baux score, and timepoints. This approach was performed to balance the differences in co-variates between the treated and non-treated groups. The matching ratio of 1:1 using the nearest neighbor matching algorithm with replacement and maximum caliper distance of 0.2 was set. Thus, allowing multiple datapoints between both cohorts can be matched when applicable. This analysis was performed to explore the clinical rationale of starting or delaying steroid therapy as well as compare outcomes of both groups.

Data were checked for normality using the Shapiro–Wilk test. Normally distributed data were reported as mean and standard deviation (SD), while non-normal data were presented as median and inter-quartile range (IQR). Continuous variables were compared using independent t or Mann-Whitney tests depending on the normality of data. Categorical variables were assessed using a chi-square test. Relative risk (RR) was examined using univariate analyses of categorical variables. Multivariate regression analysis was performed to account for variables that may influence outcomes. Multivariate cox regression analysis was performed to assess the proportional hazard ratio (HR) of outcomes in burns patients. Area under the curve (AUC)/receiver operating characteristics (ROC) curve analysis was performed to assess the model's predictive strength. Significance was set at $p < 0.05$.

Ethical approval

Ethical approval for the SIFTI study was granted by the National Research Ethics Service Committee East Midlands, UK (Reference 12/EM/0432). The SIFTI study assessed the endocrine, immune, inflammatory, and metabolic responses post-major burn injury over a 12-month. Enrolled patients were followed-up at various timepoints where their blood samples and clinical data are taken prospectively until death, the end of study period, or refusal to continue.

Results

Patient demographics

Fifty-two patients with major burn injuries were enrolled into the study. Participants had a median TBSA of 42% and

Table 1 Demographics of burn patients enrolled in the study.

	Total ($n = 52$)
Age	41 (33–55)
Gender (M/F)	33/19
% TBSA	42 (25–53)
Inhalation Injury (Y/N)	31/21
Revised Baux Score	98 (75–113)
Corticosteroids (Y/N)	22/30
Oxandrolone (Y/N)	34/18
28 Day Mortality (Y/N)	10/42
Mortality (Y/N)	18/34
MOF (Y/N)	18/34
Sepsis (Y/N)	34/18

Continuous variables are shown as median values with interquartile range. Data prior to PSM. Abbreviations: MOF, multi-organ failure; TBSA, total burn surface area.

revised Baux score of 98. Thirty-one (60%) patients were diagnosed with inhalation injury. Forty-nine (94%) patients were managed surgically, of which 37% (18 patients) had total burn excision ± reconstruction within 7 days of thermal injury. Eighteen (35%) burns patients did not survive their injuries. Eighteen (35%) participants developed MOF at median day 3 (IQR, 2–5) post-thermal injury. Thirty-four (65%) burns patients were diagnosed with sepsis at median day 5 (IQR, 4–7) following injury. Twenty-two (42%) patients received corticosteroids while 34 (65%) patients received oxandrolone (Table 1).

To assess the effects of each steroid, separate analyses were performed for corticosteroids and oxandrolone. Patient demographics and injury characteristics were significantly different between steroid and no-steroid groups (Supplementary Table 1). The matching process using co-variates previously stated is described below.

Across the four study timepoints, 110 and 83 datapoints were collected from burn patients not given and those given corticosteroids, respectively. Of these, 98 and 41 datapoints were matched, respectively. Standardized mean differences (SMD) of co-variates pre- and post-matching were assessed for co-variate balance. Median SMD of pre-matched co-variates was −0.278 with some co-variates exceeding 1.0. Median SMD of co-variates post-matching was 0.041 with all co-variates within 0.130 range with exception of one count being 0.375. Furthermore, propensity score comparison between both groups was not significant post-matching ($p = 0.793$).

Across the four study timepoints, 51 and 115 datapoints were collected from thermally injured patients not managed and those managed with oxandrolone, respectively. Of these, 32 and 93 datapoints were matched respectively. Median SMD of pre-matched co-variates was 0.124 with some co-variates exceeding 1.0. Median SMD of co-variates post-matching was 0.02 with all co-variates within 0.2 range. Furthermore, propensity score comparison between both groups was not significantly different post-matching (p 0.570). PSM analysis indicates robust matching (Figure 1).

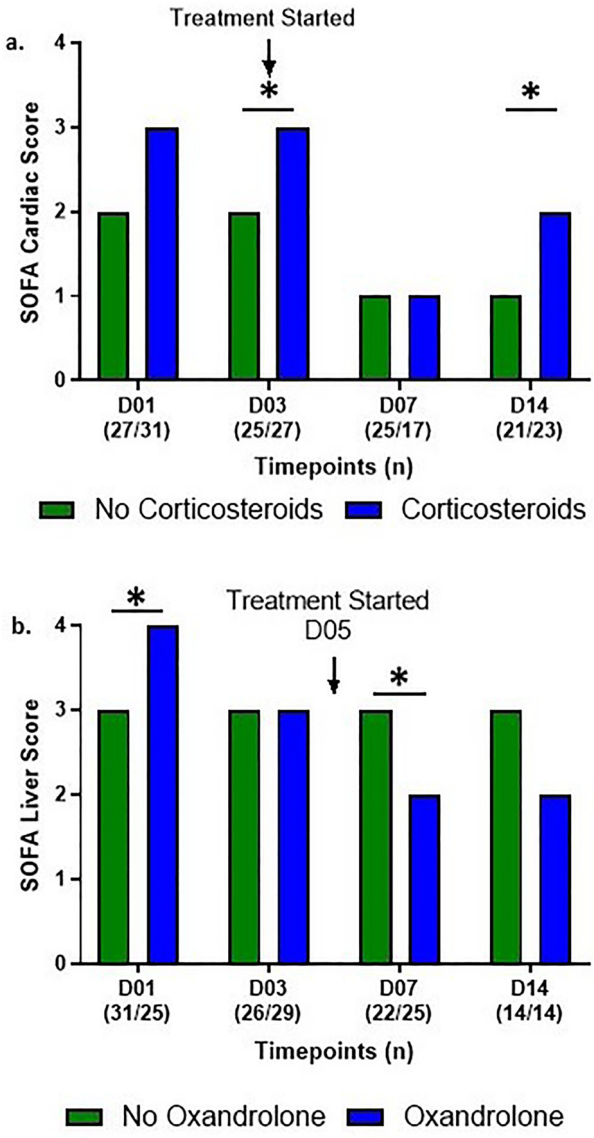

Fig. 2 SOFA organ scores of PSM-matched treatment and no-treatment groups.
Extent of organ dysfunction of burns patients was examined at D01, D03, D07, and D14 post-injury. (a) SOFA cardiac scores of corticosteroid and no-corticosteroid cohorts. (b) SOFA liver scores of oxandrolone and no-oxandrolone cohorts. SOFA organ scores of both groups were compared at each timepoint using Mann–Whitney test; $^*p < 0.05$. SOFA, sequential organ failure assessment.

Initiation of steroid treatment

Corticosteroid therapy was started at median day 3 (IQR, 2–14) following burn injury for a median total duration of 5 (IQR, 2–12) days. At day 3 post-injury, corticosteroid cohort had significantly higher SOFA cardiac scores compared to no-corticosteroid group, median 4 vs. 1 ($p = 0.027$). This indicates that the corticosteroid cohort was more hemodynamically unstable and vasoplegic as compared to their counterpart prior to treatment.

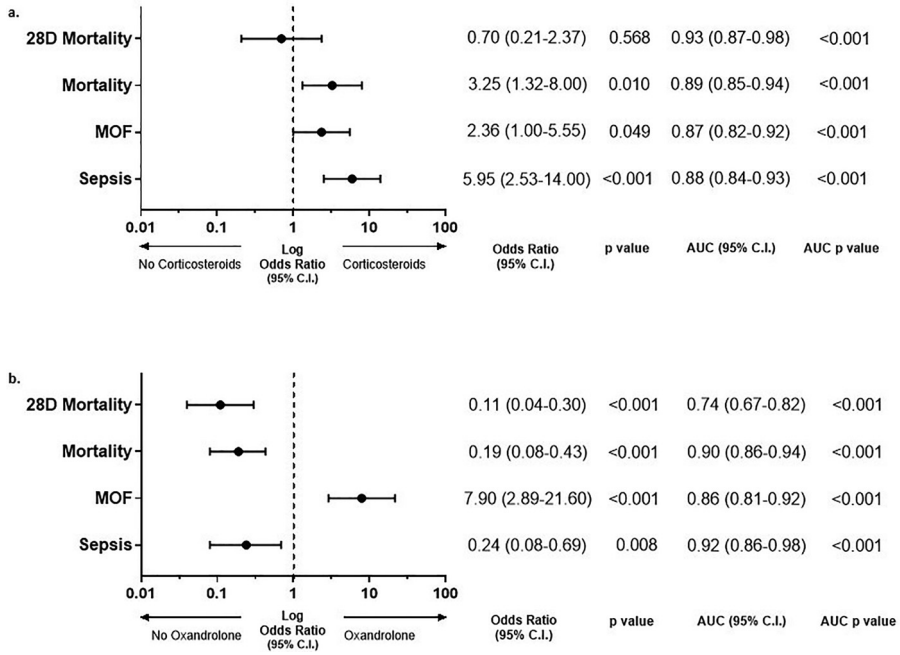

Fig. 3 Influence of corticosteroid and oxandrolone treatment on patient outcomes following severe thermal injury.
Outcomes in PSM-matched steroid and no-steroid groups were compared using logistic regression model accounting for age, gender, TBSA, inhalation injury, timepoints, relevant SOFA scores, and treatments used. (a) Effects of corticosteroids on outcomes following severe thermal injury adjusting for SOFA cardiac scores. (b) Effects of oxandrolone on outcomes following major burn injury adjusting for SOFA liver scores. Forest plots are odds ratios of outcomes with horizontal lines being 95% confidence intervals. AUC analysis was performed for each regression model. Abbreviations: 28D Mortality, 28-day mortality; AUC, area under curve; MOF, multi-organ failure; CI, confidence interval.

Oxandrolone therapy was started at median day 5 (IQR, 4–8) following burn injury for a median total duration of 19 (IQR, 15–43) days. At day 3 post-injury, burns patients who were subsequently started on oxandrolone therapy had similar SOFA liver scores compared to the no-oxandrolone group, median 3 vs. 3 ($p = 0.744$). Following administration of oxandrolone, treated burns patients exhibited significantly lower SOFA liver scores compared to their counterpart at D07 post-injury, median 2 vs. 4 ($p<0.001$). At day 14 post-injury, both groups had a median SOFA liver score of 2 ($p = 0.265$). This indicates that the oxandrolone may have been omitted in burns patients due to liver dysfunction. SOFA organ scores of steroid and no-steroid cohorts are summarized longitudinally in Figure 2.

Effects of corticosteroids and oxandrolone on clinical outcomes following severe thermal injury

Corticosteroid therapy had significant associations with outcomes following severe thermal injury (Figure 3a). On regression analysis, corticosteroid use in burns patients was independently associated with increased odds of in-hospital mortality (OR 3.25, 95% CI: 1.32–8.00), MOF (OR 2.36, 95% CI: 1.00–5.55), and sepsis (OR 5.95, 95% CI: 2.53–14.00).

During hospital admission, death occurred in 11 of 22 (50%) corticosteroid-treated burns patients and in 7 of 30 (23%) not treated with corticosteroids (p 0.046). Furthermore, MOF and sepsis were diagnosed in 12 of 22 (55%) and 19 of 22 (86%) corticosteroid-treated patients compared to 6 of 30 (20%) and 15 of 30 (50%) not managed with corticosteroids ($p = 0.01$ and $p = 0.006$), respectively. Following matching, corticosteroid use in burns patients was associated with poorer outcomes as follows. The RR and HR of death were 1.89 (95% CI: 0.83–4.28) and 3.13 (95% CI: 1.66–5.56), respectively (Figure 4a). In addition, the RR and HR of MOF were 2.47 (95% CI: 1.14–5.35) and 1.76 (95% CI: 0.96–3.33), respectively (Figure 4b). The RR and HR of sepsis were 1.68 (95% CI: 1.09–2.57) and 1.85 (95% CI: 1.25–2.70), respectively (Figure 4c).

Oxandrolone therapy had significant associations with outcomes following severe thermal injury (Figure 3b). On regression analysis, oxandrolone use was independently associated with reduced odds of 28-day mortality (OR 0.11, 95% CI: 0.04–0.30), in-hospital mortality (OR 0.19, 95% CI: 0.08–0.43), and sepsis (OR 0.24, 95% CI: 0.08–0.69). However, oxandrolone use was independently associated with increased odds of MOF (OR 7.90, 95% CI: 2.89–21.60).

Death within 28 days following thermal injury and during hospital admission occurred in 12% (4 of 34) and 29% (10 of 34) oxandrolone-treated patients compared to 33% (6 of 18) and 44% (8 of 18) not treated with oxandrolone (p 0.06 and p 0.278), respectively. Moreover, MOF and sepsis rates were similar between both groups 38% vs. 28% (13 of 34 vs. 5 of 18, p 0.451) and 68% vs. 61% (23 of 34 vs. 11 of 18, p 0.637), respectively. Following matching, oxandrolone therapy had significant associations with outcomes post-injury. The RR and HR of 28-day mortality and in-hospital mortality were 0.17 (95% CI: 0.04–0.66) & 0.16 (95% CI: 0.07–0.36) and 0.55 (95% CI: 0.29–1.05) & 0.30 (95% CI: 0.18–0.51), respectively,

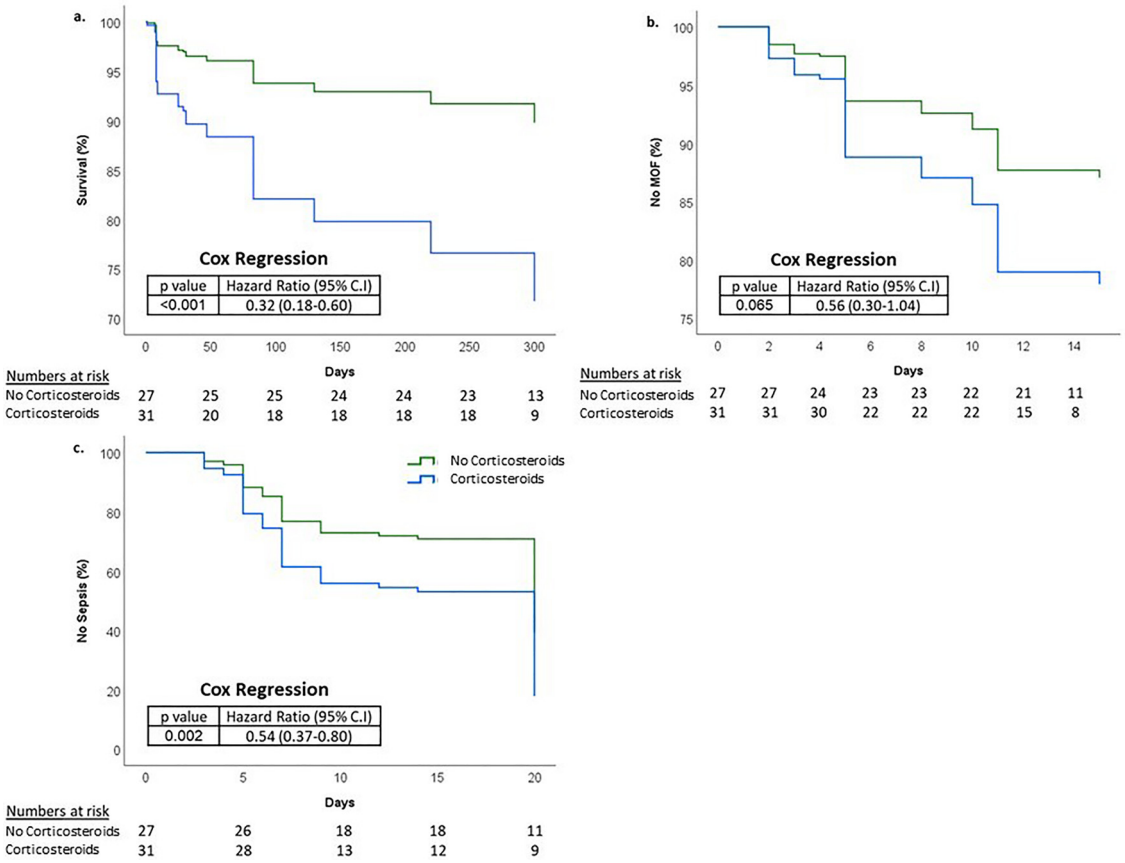

Fig. 4 Kaplan–Meier survival graphs demonstrate significant distribution differences for in-hospital mortality and sepsis among corticosteroid and no-corticosteroid burns patient groups.
Survival distribution analysis in PSM-matched corticosteroid and no-corticosteroid groups was performed using Cox regression accounting for age, gender, TBSA, inhalation injury, timepoints, SOFA cardiac score, and corticosteroid use. (a) Survival curve distributions for in-hospital mortality for both cohorts. (b) Survival (No MOF) curve distributions for MOF diagnosis for both groups. (c) Survival (No Sepsis) curve distributions for sepsis diagnosis for both cohorts. Abbreviations: MOF, multi-organ failure; CI, confidence interval.

favoring oxandrolone treatment in burns patients (Figure 5a and b). In contrast, the RR and HR of MOF were 4.96 (95% CI: 1.15–21.30) and 4.34 (95% CI: 2.00–9.09) opposing oxandrolone therapy in burns patients (Figure 5c). The RR and HR of sepsis were 0.79 (95% CI: 0.56–1.12) and 0.84 (95% CI: 0.58–1.21), respectively (Figure 5d).

Discussion

This retrospective study assessed associations between different steroid therapies, corticosteroids and oxandrolone, and patient prognosis following major burn injury. In-hospital mortality, MOF, and sepsis rates were significantly higher among corticosteroid-treated burns patients, with these individuals also exhibiting a significantly reduced number of days alive and free of sepsis. In contrast, oxandrolone was associated with improved survival and sepsis rates following burn injury, with patients exhibiting increased number of days alive. However, MOF rates and number of days free of MOF were worse among oxandrolone-treatment patients.

The clinical rationale for instigating steroid therapy involves controlling complex pathophysiological responses induced by major thermal injury, including hypovolemia and hypercatabolism. Hypovolemia involves intravascular volume depletion and translocation of proteins and fluids leading to concomitant hemoconcentration, hypoproteinemia, myocardial dysfunction, and massive edema formation.[14,15] This circulatory and fluid distribution failure results in tissue hypoperfusion. Current burn shock treatment modalities involve volume replenishment and vasopressor therapy.[16] These maybe inadequate as over 75% of reported mortalities following injury remains attributed to burn shock and the resuscitation phase.[3] Consequently, alternative treatments like corticosteroids are often used to address treatment-refractory shock.

Corticosteroid use for resuscitation-refractory septic shock is endorsed by the surviving sepsis campaign.[4] Recently, randomized controlled trials reported multiple benefits related to corticosteroid therapy in critical illness including lower 90-day mortality, shorter ventilation times, and quicker shock resolution.[17,18] Published data reported diminished fluid and vasopressor requirements in corticosteroid-treated patients following major thermal

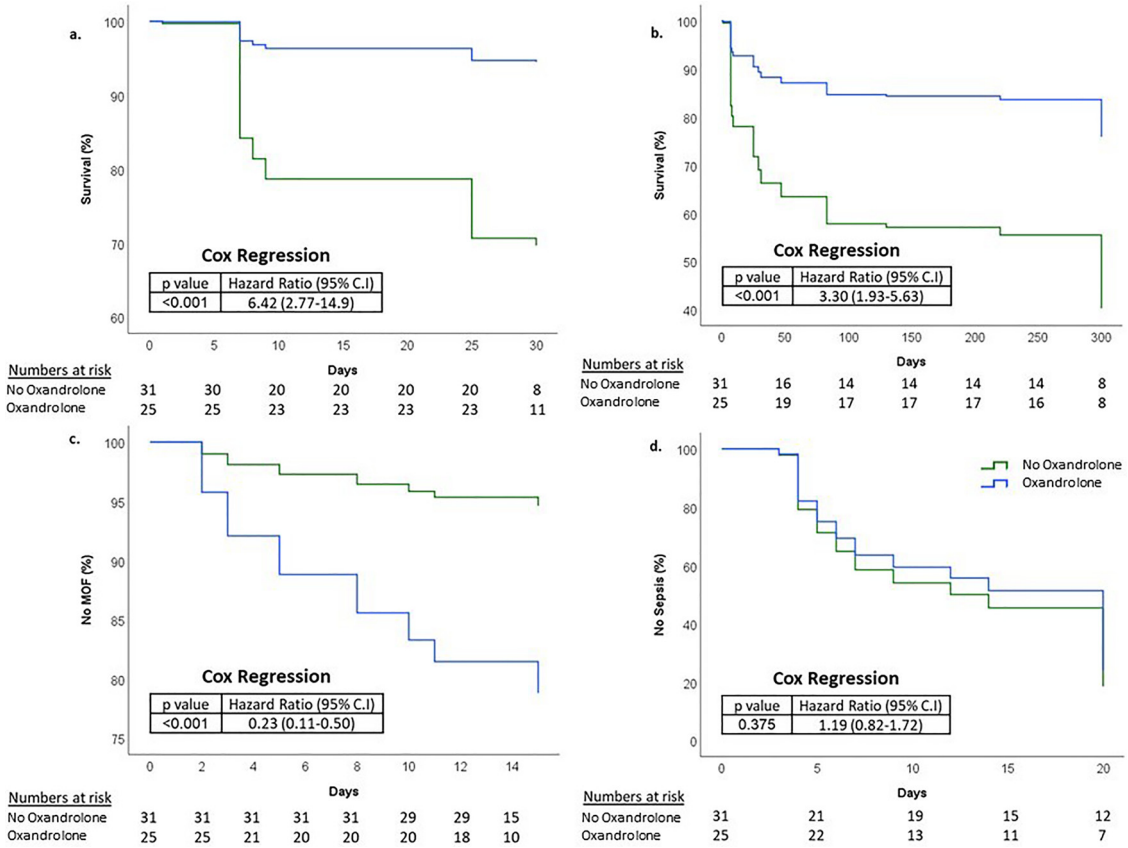

Fig. 5 Kaplan–Meier survival graphs demonstrate significant differences in 28-mortality, in-hospital mortality, and MOF distributions among oxandrolone and no-oxandrolone burns patient groups.
Survival distribution analysis in PSM-matched oxandrolone and no-oxandrolone groups was performed using Cox regression accounting for age, gender, TBSA, inhalation injury, timepoints, SOFA liver score, and oxandrolone use. (a) Survival curve distributions for 28-day mortality for both cohorts. (b) Survival curve distributions for in-hospital mortality for both groups. (c) Survival (No MOF) curve distributions for MOF diagnosis for both cohorts. (d) Survival (No Sepsis) curve distributions for sepsis diagnosis for both groups. Abbreviations: MOF, multi-organ failure; CI, confidence interval.

injury.[5,19,20] These findings could be attributed to reduced capillary leakage as indicated by significant reductions in proteinuria observed in corticosteroid-treated burns patients.[19] Additionally, de Leeuw et al. observed improvements in organ dysfunction indicated by Denver2 and SOFA scores reductions following hydrocortisone administration.[19] This potentially explains the reduced mortality rates observed in catecholamine-dependent septic burns patients treated with hydrocortisone.[21] However, other studies reported no improvement in mortality or sepsis rates among the general burns patient population.[5,19,22] Limitations of these studies include small-moderate sample sizes, lack of or varying definitions of outcomes (including sepsis), and univariate statistical methodology. Due to this, widespread clinical translation proved difficult.

In agreement with other reports,[19,21] we found that corticosteroid use resulted in hemodynamic stabilization with significant reductions in SOFA cardiac scores and median score 4 at D03 vs. 0 at D07 ($p<0.001$). Despite this, increased odds of mortality, MOF, and sepsis were observed among corticosteroid-treated burn patients, independent of patient demographics, injury severity, and SOFA cardiac scores. These findings could be attributed to the immune-modulatory effects of corticosteroids increasing infection and sepsis risk. Transcriptomic analysis of circulating leukocytes isolated from burns patients have provided some insight into the potential mechanisms of these observed outcomes.[23] For example, the hemodynamic improvements could be attributed to quicker resolution of nitric oxide-mediated signal transduction pathways among hydrocortisone-treated burns patients.[23] Importantly, hydrocortisone enhanced the adaptive and innate immunosuppressive states in these patients,[23] reminiscent of the immune dysfunction associated with poor outcomes following severe thermal injury such as sepsis and secondary septic shock.[9,24] Therefore, clinical caution should be exercised when prescribing corticosteroids to manage treatment-refractory burn shock.

Following burn resuscitation, hypermetabolism management following injury remains challenging. Post-burn hypercatabolism involves persistent and prolonged increased energy expenditure; cardiac dysfunction and lean body mass loss; worsening patient morbidity and mortality.[1,25,26] Oxandrolone became a mainstay of burn treatment due to its reported anabolic effects in burns patients, including weight loss amelioration, successful weight restora-

tion, reduced wound healing times, and hospital length of stay.[6,7,27] Studies examining oxandrolone effects on acute outcomes in adults following thermal injury remain limited. Pham et al. concluded improved survival rates among oxandrolone-treated burns patients.[8] Similarly, oxandrolone was independently associated with improved 28-day survival, in-hospital survival, and sepsis rates in this study. The mechanisms underlying these observations remain to be fully elucidated.

Our data do, however, suggest that oxandrolone use in burns patients is not without risk as it was independently associated with MOF. However, this finding should be cautiously interpreted due to the MOF OR large 95% CI. Additionally, oxandrolone therapy was started at median day 5 post-burn injury while the MOF was diagnosed at median day 3 post-burn injury. To date, no significant associations between oxandrolone and MOF were reported.[8,28] However, oxandrolone has been associated with increased ventilator days and reintubation rates.[28] Although the mechanisms behind these observations are unclear, one possibility is enhanced collagen deposition and fibrosis as reported in an oxandrolone-treated rodent wound healing model.[29] Consequently, progressive fibrosis may exacerbate adult respiratory distress syndrome leading to poor outcomes.[30] This hypothesis requires testing.

The strengths of this study include prospective data collection, clear outcome definitions, and robust statistical analysis. Furthermore, the no interference approach with clinical decisions by the research team ensured that the data collected remains pragmatic and reflective of patient management in a tertiary burn center. An important limitation of this analysis is the examination of a critically ill subpopulation following major burn injury, those who did not respond to standard treatment regimens and therefore are liable to poor outcomes. Other study limitations include moderate sample size, its observational nature, and retrospective analysis, thereby restricting the use of some clinical scores, such as APACHE, and further analysis on patients who may have benefited from both steroids. Hence, any potential influence both steroids may have had on clinical outcomes remains unassessed and unclear. Additionally, some outcomes may have occurred prior to steroid initiation potentially affecting analysis. Despite these limitations, our observations and conclusions are supported by the published literature. Therefore, clinical teams should consider this study's findings when managing patients following major burn injury. Randomized controlled trials are needed to confirm our observations and determine the mechanisms driving the different outcomes in steroid treatment.

In conclusion, this study reports the effects of two different steroid therapies following severe thermal injury. Despite amelioration of vasoplegia, corticosteroids were independently associated with poor outcomes in burns patients, including mortality, MOF, and sepsis. In contrast, oxandrolone administration following thermal injury was independently associated with improved survival and lower odds of sepsis development, but increased risk of MOF.

Declaration of Competing Interest

The authors declare no competing interests.

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Ethical approval

Ethical approval for the SIFTI study was granted by the National Research Ethics Service Committee East Midlands, UK (Reference 12/EM/0432).

Author's contributions

KA, NM, JML, YW, and TT were responsible for the conception and design of this study. KA, PT, and JH contributed to data collection. KA, AA, and BT conducted the statistical analyses. All authors contributed to data interpretation and manuscript preparation. All authors critically reviewed and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.04.007.

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