Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study

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Summary

Background Patient survival after severe burn injury is largely determined by burn size. Modern developments in burn care have greatly improved survival and outcomes. However, no large analysis of outcomes in paediatric burn patients with present treatment regimens exists. This study was designed to identify the burn size associated with significant increases in morbidity and mortality in paediatric patients.

Methods We undertook a single-centre prospective observational cohort study using clinical data for paediatric patients with burns of at least 30% of their total body surface area (TBSA). Patients were stratified by burn size in 10% increments, ranging from 30% to 100% TBSA, with a secondary assignment made according to the outcome of a receiver operating characteristic (ROC) analysis. Statistical analysis was done with Student’s t test, χ² test, logistic regression, and ROC analysis, as appropriate, with significance set at p<0.05.

Findings 952 severely burned paediatric patients were admitted to the centre between 1998 and 2008. All groups were comparable in age (mean 7.3 [SD 5.3] years, ranging from 6.1 [5.1] years in the 30–39% TBSA group to 9.6 [5.4] years in the 90–100% TBSA group) and sex distribution (628 [66%] boys, ranging from 59% [73/123] in the 60–69% TBSA group to 82% [42/51] in the 90–100% TBSA group). Patients were stratified by burn size (increasing from 3% [five of 180] in the 30–39% TBSA group to 82% [42/51] in the 90–100% TBSA group). 123 (13%) patients died (increasing from 3% [five of 180] in the 30–39% TBSA group to 26% [13] in the 90–100% TBSA group; p<0.0001). 154 (16%) developed multiorgan failure (increasing from 6% [ten] in the 30–39% TBSA group to 55% [28/51] in the 90–100% TBSA group; p<0.0001), 89 (9%) had sepsis (increasing from 2% [three] in the 30–39% TBSA group to 26% [13] in the 90–100% TBSA group; p<0.0001), and 123 (13%) patients died (increasing from 3% [five of 180] in the 30–39% TBSA group to 82% [42/51] in the 90–100% TBSA group; p<0.0001).

Interpretation We established that, in a modern paediatric burn care setting, a burn size of roughly 60% TBSA is a crucial threshold for postburn morbidity and mortality. On the basis of these findings, we recommend that paediatric patients with greater than 60% TBSA burns be immediately transferred to a specialised burn centre. Furthermore, at the burn centre, patients should be treated with increased vigilance and improved therapies, in view of the increased risk of poor outcome associated with this burn size.


Introduction Prediction of survival and outcomes has always been an important goal in the treatment of thermally injured patients. In the 1980s and early 1990s, clinical predictions and decisions were based mainly on burn size.

1,2 In 1998, Ryan and colleagues assessed improvements in burn care in a large population of 1665 patients treated between 1990 and 1996, and developed a prediction model for individual patient risk and mortality; and (3) to correlate patient outcomes with biochemical markers and measures of organ dysfunction. This
investigation was intended to provide a rationale for clinical decisions based on survival, expected complication rates, and outcome after burn injury.

**Methods**

**Patients and procedures**

The study was approved by the institutional review board of the University of Texas Medical Branch (Galveston, TX, USA). Informed consent was obtained from each patient, parent, or child’s legal guardian. All acutely burned patients arriving at our burn centre were included in this analysis to be consistent with a previously published trial and to compare the outcomes from the previous study to our study.4

Thermally injured children admitted to the burn unit with burns of 30% of their TBSA or greater were enrolled. Patients were resuscitated according to the Galveston formula with 5000 mL/m² TBSA burned plus 2000 mL/m² TBSA lactated Ringer’s solution, given in increments during the first 24 h as necessary. Within 48 h of admission, all patients underwent total burn wound excision, and their wounds were covered with autograft. Any remaining open wound areas were covered with homograft. Admission and treatment criteria were based on the guidelines published by the American Burn Association.6 All patients received similar nutritional treatment according to a standardised protocol. Intake was calculated as 1500 kcal/m² body surface plus 1500 kcal/m² area burned.7 Patient demographic and injury characteristics, hospital course, morbidity, and mortality were recorded. Sepsis was defined according to the modified American College of Chest Physicians/Society of Critical Care Medicine criteria.9 Multimorgan failure was assessed according to DENVER2 score.10 We further established the time between operations, judging this measure to be reflective of donor site healing and, therefore, an estimate of wound healing and rep epithelisation. Patient data were obtained prospectively and were processed and analysed with Microsoft Access and Excel (2010 versions).

As part of our routine clinical practice, all patients underwent resting energy expenditure measurements within 1 week of hospital admission and every week thereafter during their acute hospital stay. Resting energy expenditure was measured with a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA, USA) and calculated as described by Mlcak and colleagues7 (n=696). Liver ultrasound measurements (n=405) were made with the HP Sonos 100 CF echocardiogram (Hewlett Packard Imaging Systems, Andover, MA, USA). The liver was scanned with an Eskoline B-scanner, and liver size/volume was calculated with a formula as previously described.10 Actual size was then compared with predicted size for healthy volunteers.

Blood and urine samples were obtained from every patient at admission and during the acute stay until discharge and were used for serum hormone (n=479), protein (n=713), and cytokine (n=461) analysis. Serum hormones and acute phase proteins were measured with high-performance liquid chromatography, nephelometry (BNII, Plasma Protein Analyzer, Dade/Behring/Siemens, Tarrytown, NY, USA), and ELISA techniques.

<table>
<thead>
<tr>
<th>TBSA, burn (%)</th>
<th>30–39% TBSA (n=180)</th>
<th>40–49% TBSA (n=260)</th>
<th>50–59% TBSA (n=121)</th>
<th>60–69% TBSA (n=85)</th>
<th>70–79% TBSA (n=82)</th>
<th>80–89% TBSA (n=51)</th>
<th>90–100% TBSA (n=51)</th>
<th>p value</th>
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<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>628 (66%)</td>
<td>122 (68%)</td>
<td>167 (64%)</td>
<td>112 (65%)</td>
<td>73 (59%)</td>
<td>61 (72%)</td>
<td>51 (62%)</td>
<td>42 (82%)</td>
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<tr>
<td>Female</td>
<td>324 (34%)</td>
<td>58 (32%)</td>
<td>93 (36%)</td>
<td>59 (35%)</td>
<td>50 (41%)</td>
<td>24 (28%)</td>
<td>31 (38%)</td>
<td>9 (18%)</td>
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<td>Ethnic origin</td>
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<td>Afro-American</td>
<td>73 (8%)</td>
<td>18 (10%)</td>
<td>24 (9%)</td>
<td>7 (4%)</td>
<td>10 (8%)</td>
<td>6 (7%)</td>
<td>4 (5%)</td>
<td>4 (8%)</td>
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<tr>
<td>White</td>
<td>154 (16%)</td>
<td>48 (27%)</td>
<td>32 (12%)</td>
<td>24 (14%)</td>
<td>15 (11%)</td>
<td>10 (12%)</td>
<td>12 (15%)</td>
<td>15 (29%)</td>
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<td>Hispanic</td>
<td>697 (73%)</td>
<td>106 (59%)</td>
<td>200 (77%)</td>
<td>136 (82%)</td>
<td>96 (78%)</td>
<td>67 (79%)</td>
<td>61 (74%)</td>
<td>31 (61%)</td>
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<td>Other</td>
<td>28 (3%)</td>
<td>8 (4%)</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
<td>3 (1%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Type of burn</td>
<td></td>
<td></td>
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<tr>
<td>Flame</td>
<td>637 (67%)</td>
<td>109 (61%)</td>
<td>167 (64%)</td>
<td>116 (68%)</td>
<td>85 (69%)</td>
<td>64 (75%)</td>
<td>66 (83%)</td>
<td>28 (55%)</td>
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<td>Scald</td>
<td>215 (23%)</td>
<td>59 (33%)</td>
<td>69 (27%)</td>
<td>39 (23%)</td>
<td>24 (20%)</td>
<td>13 (15%)</td>
<td>5 (6%)</td>
<td>6 (12%)</td>
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<tr>
<td>Other</td>
<td>100 (11%)</td>
<td>12 (7%)</td>
<td>24 (9%)</td>
<td>16 (9%)</td>
<td>14 (11%)</td>
<td>8 (9%)</td>
<td>9 (11%)</td>
<td>17 (33%)</td>
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<td>Age at admission (years)</td>
<td>7 (5–3)</td>
<td>6 (5–1)</td>
<td>7 (5–2)</td>
<td>7 (5–1)</td>
<td>7 (5–1)</td>
<td>8 (5–9)</td>
<td>8 (4–6)</td>
<td>9 (5–4) &lt;0.0001</td>
</tr>
<tr>
<td>Inhalation injury</td>
<td>32 (34%)</td>
<td>28 (16%)</td>
<td>85 (33%)</td>
<td>50 (29%)</td>
<td>55 (45%)</td>
<td>38 (45%)</td>
<td>38 (46%)</td>
<td>27 (33%) &lt;0.0001</td>
</tr>
<tr>
<td>TBSA, burn (%)</td>
<td>55% (18)</td>
<td>34% (3)</td>
<td>44% (3)</td>
<td>54% (3)</td>
<td>64% (3)</td>
<td>73% (3)</td>
<td>83% (3)</td>
<td>95% (3)</td>
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<tr>
<td>TBSA, third-degree burn (%)</td>
<td>38% (27)</td>
<td>17% (14)</td>
<td>27% (17)</td>
<td>36% (20)</td>
<td>47% (22)</td>
<td>56% (25)</td>
<td>69% (26)</td>
<td>76% (34) &lt;0.0001</td>
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<tr>
<td>Burn to admission (days)</td>
<td>3 (6–4)</td>
<td>3 (7–4)</td>
<td>4 (4–4)</td>
<td>3 (9–4)</td>
<td>8 (2–3)</td>
<td>2 (6–2)</td>
<td>3 (0–4)</td>
<td>2 (5–4) 0.0002</td>
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<tr>
<td>Admission to excision (days)</td>
<td>1.0 (1.6)</td>
<td>1.2 (1.5)</td>
<td>1.0 (1.7)</td>
<td>0.9 (1.4)</td>
<td>0.8 (1.1)</td>
<td>0.9 (1.2)</td>
<td>0.9 (1.5)</td>
<td>0.9 (2.2) 0.07</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or p value. TBSA=total body surface area.

Table 1: Patient demographic characteristics
Nephelometry is a fairly old technique that has given reliable and consistent data in our burn centre. The Bio-Plex Human Cytokine 17-Plex panel was used with the Bio-Plex Suspension Array System (Bio-Rad, Hercules, CA, USA) to profile expression of cytokines and inflammatory mediators.

Statistical analysis
For biochemical measurements, we applied the confidence interval 2Σ (CI=0.9544997) to improve reliability. Student’s t test, χ² analysis, Fischer’s exact test, and linear and multiple logistic regression analysis were used as appropriate. For the cutoff analysis, receiver operating characteristic (ROC) analysis was used. Statistical analysis was done with Microsoft Excel and Systat Software Sigmastat version 3.5 and SigmaPlot. Data are expressed as mean (SD or SEM). Significance was accepted at p<0.05.

Role of the funding source
All funding sources had no involvement in data collection, data analysis, data interpretation, and writing of the report. All authors had access to the data, vouch for its accuracy and completeness, and approved the final report before submission for publication.

Results
952 thermally injured children admitted to the burn unit with burns of 30% of their TBSA or greater were enrolled between Jan 1, 1998, and Sept 6, 2008. Burn size ranged from 30% to 100% TBSA, and most patients had burns between 40% and 50% TBSA. On the basis of burn size, we stratified patients into seven groups using 10% increments between 30% and 100% TBSA. Sex distribution, ethnic origin, and time from burn to admission were similar in all groups (table 1). Incidence of inhalation injury, sex, age, and burn-to-admission time, we showed that TBSA greater than 60% was a prediction of survival (figure 1). Using multiple logistic regression, after adjustment for inhalation injury, sex, age, and burn-to-admission time, we showed that TBSA greater than 60% was a significant predictor of mortality starting at 60% TBSA, with the Kaplan-Meier survival curve showing a significant difference in short-term and long-term survival (p=0.00131) between the groups with burns smaller than or larger than 60% TBSA. However, in patient groups with burns smaller than 60% TBSA, there were only minor increases in mortality starting at 3% and reaching up to 7%. To validate these findings, we undertook ROC analysis for mortality to establish the critical value for survival, with the threshold identified as 62% TBSA. The ROC curve validated this finding, with a fair value of A=0.81 for prediction of survival (figure 1).

Using multiple logistic regression, after adjustment for inhalation injury, sex, age, and burn-to-admission time, we showed that TBSA greater than 60% was a significant predictor of mortality.
strong predictor of mortality with an odds ratio of death that was ten times higher (p<0·0001) than that for patients below this threshold, confirming that burn size was the main factor for the estimate of survival. Inhalation injury was associated with an odds of death that was nearly three times higher (p<0·0001) than that for patients without this injury. Age and time from burn to admission were not associated with mortality differences in this patient population during the hospital stay (table 3).

Inhalation injury contributes to mortality, and in each burn group examined, patients with inhalation injury had a significantly higher mortality than did patients without this injury (webappendix pp 1–2). An ROC cutoff analysis for burn size with inhalation injury was not done because most patients with inhalation injury had a significantly larger burn size, skewing the data to a higher threshold than a lower, which would be an observational error.

Blood glucose (p<0·0001) and insulin concentrations (p=0·036) were significantly increased in the group with large burns during the whole study period, with a slight normalisation by day 60 (figure 2). Analysis of resting energy expenditure showed significantly higher values at discharge than at admission in each group. These values significantly (p=0·043) increased with burn size (figure 2), reflecting caloric needs after burn injury. Liver size normalised for age, expressed as percentage of predicted value, increased from admission to discharge with increasing burn size (p=0·05). Although only a slight increase in liver size was noted in patients with burns up to 59% TBSA, a massive and significant increase occurred between admission and discharge for patients with larger burns (figure 2).

Figure 1: Kaplan-Meier survival curve (A) and cutoff determination (B) with sensitivity and specificity validated by ROC analysis (C)

TBSA=total burn surface area. ROC=receiver operating characteristic.
Production of liver constitutive proteins is shown in figures 2 and 3. Both burn size groups showed a decrease in all measured proteins, which began to normalise after the first week postinjury. Total protein, apolipoprotein B, apolipoprotein A1, prealbumin, and transferrin were all significantly (all \( p<0.05 \)) decreased in the larger burn group (figure 2). A change in retinol binding protein after day 10 postburn was noted, with the expression of this protein being significantly less in the smaller burn group (\( p=0.019 \)). Triglycerides were also significantly higher in the larger burn group at several timepoints (\( p=0.045 \)).

All measured cytokines (figure 3) showed major differences between the two burn size groups during the...
Figure 3: Inflammatory response and liver and kidney function

(A-J) Proinflammatory cytokines and (K) C-reactive protein. (L, M) Liver function; (N) change in liver size according to burn size; and (O) kidneys shown with organ specific markers. Error bars show SE.

monitored time period from immediately postburn up to 60 days after the injury (p<0.05). In the larger burn group, interleukin 8 (p=0.037) and interleukin 10 (p=0.039) remained significantly increased over most of the study period. Macrophage inflammatory protein 1β (days 2–28; p=0.035) and interleukin 13 (days 2–22; p=0.020) also remained significantly increased. Figure 3 shows the cytokine response grouped for important cellular response mechanisms, as well as macrophage activity, cell death, and repair mechanisms. Levels of tumour necrosis factor α (TNFα) and granulocyte colony-stimulating factor (G-CSF) were significantly and constantly increased from day 2 to day 60 (p=0.032 and p=0.036, respectively). Interferon γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) were significantly higher in patients with burns greater than 60% TBSA between days 2 and 22 (p=0.038 and p=0.010, respectively). Established markers of the inflammatory response are shown in figure 3, where we selected interleukin 6 and C-reactive protein. These showed an immediate increase after burn, with significant differences throughout the whole study period (p=0.036 and p=0.0002, respectively). The liver-synthesised C-reactive protein increased more slowly after day 1 postburn and then increased rapidly from day 8.

Liver and renal function were monitored by aspartate transaminase, total bilirubin, blood urea nitrogen, and serum creatinine (figure 3). Blood urea nitrogen remained increased during the first 60 days (p=0.00066), with significantly higher values being recorded during the observational period in the larger burns group than in patients with smaller burns. Serum creatinine was significantly increased up to day 28 (p=0.015) and then remained similar in both groups. Representative of liver impairment, total bilirubin was significantly (p=0.013) increased in the larger burns group during the whole study period, and aspartate transaminase remained increased for the first 34 days (p=0.042).

Discussion

Building on previous studies, this study identified the critical burn size determining major complications and survival with state-of-the-art, modern burn care. In this study we accumulated a large patient population, which we used to assess the crucial threshold for survival and to corroborate with biochemical markers. We noted that mortality was nearly equal in patients with burns up to 60% TBSA, but for those with larger burns, the mortality rate increased substantially. Important to note are the relatively low mortality rates in even the most extensively burned patients (55% for ≥90% TBSA), which in our opinion were attributable to an improved and aggressive treatment regimen.

As a cofactor contributing to mortality besides the extent of the burn, inhalation injury was examined. The presence or absence of inhalation injury affects outcomes, and our data suggest that inhalation injury worsens postburn morbidity and mortality. We did not do an ROC cutoff analysis for patients with burns and presence of inhalation injury because of the uneven distribution of these patients. Patients with inhalation injury had larger burns than did patients without inhalation injury, which would skew the data towards larger burns. We recommend that the treating physician keeps in mind that the presence of inhalation injury significantly affects postburn outcomes. Of interest, patient’s age and the time from injury to admission to a specialised burn centre did not significantly contribute to in-hospital mortality.

We noted that mortality peaked within the first 20 days after admission and showed a prolonged increase related to burn size. In accordance with these findings, the incidence of sepsis and multiorgan failure combined with maximum DENVER2 score and infections correlated with burn size. For burns up to 49% TBSA, the incidence of these complications remained at 6–12% for multiorgan failure and 2–6% for sepsis, but increased up to 27–45% for multiorgan failure and 15–26% for sepsis in the group with burns greater than 60% TBSA. As expected, the number of necessary surgeries during the acute stay increased with the size of burn. These results are reflected by important organ-specific clinical measures as well as metabolic and inflammatory responses. We showed that insulin resistance worsened with increased burn size, with higher blood glucose concentrations being present in the extensively burned group despite higher serum insulin concentrations. Changes in glucose metabolism were associated with changes in lipid metabolism. Serum triglyceride concentrations rose significantly, and these increases persisted significantly longer with a larger burn size. These metabolic changes were also reflected in metabolic rate determined by resting energy expenditure. Patients with larger burns had profoundly higher metabolic rates and demands for a prolonged period of time than did those with smaller burns. Metabolic demands are reflected in organ function. The larger the burn, the worse the liver structure and function, with profoundly depleted constitutive proteins and dramatic hepatomegaly, which is most likely due to oedema formation early after burn and hepatic lipid infiltration later in hospital course. Our data also showed a profound effect on kidney and pulmonary function most likely due to the massive protein catabolism and wasting postburn. The aforementioned data all suggest that severely burned patients undergo a massive hypermetabolic response affecting all organs and contributing to postburn morbidity and mortality.

The hypermetabolic state can be at least partly attributed to the inflammatory response. Inflammatory mediators G-CSF, interleukin 8, and interleukin 10 showed an immediate increase with a decrease over time in both populations; however, the greater than 60% TBSA burn group had significantly higher levels of these factors than did the smaller burn group. Interleukin 8 targets a fairly
wide range of cells including primary neutrophil granulocytes, mast cells, macrophages, endothelial cells, and keratinocytes. Several studies have shown that interleukin 8 causes localised inflammation leading to oxidative stress. This effect would correlate with the tremendous difference between groups during the whole study period, reflecting post-traumatic tissue inflammation, which is seen clinically after burn injury. The anti-inflammatory cytokine interleukin 10 shows a similar pattern to that for interleukin 8. A key cytokine for inducing inflammatory processes is TNFα, the expression of which is characteristic and can be clearly attributed to the effects of burn size. Whereas the group with smaller burns had significantly lower concentrations and a slight decrease over time, data from extensively burned patients showed a prolonged increase in this cytokine. The complex signalling pathway leads to several effects throughout the bodies of injured patients. TNFα induces production of acute phase proteins including C-reactive protein in the liver; expression of interleukin 6, phagocytosis in macrophages, and migration of neutrophil granulocytes in infected or damaged tissues. TNFα also affects hormone regulatory processes, especially hypothalamic thermoregulation and insulin sensitivity, all present in severely burned patients.

The importance of biomarkers examined in this study was that they showed trajectories differentiating survivors from non-survivors matched for burn size. These novel trajectories are of great interest because we can clearly identify molecules that are changed according to burn size, and the next step would be to propensity match patients and establish differences in these trajectories. The propensity matching would further eliminate the amount of fluid resuscitation or outside factors that could cause an artificial iatrogenic modulation of these biomarkers. However, in this study, we showed that biomarker profiles are profoundly different between the different burn sizes, particularly during later timepoints, suggesting that these differences are not dependent on fluid or resuscitation but endogenous synthesis and expression.

Besides the injury-driven inflammatory response, the incidence of clinically relevant infections increased with burned area. The loss of the dermal barrier, profoundly increased metabolism, and an impaired immune system lead to a higher incidence of burn wound and nosocomial infections increasing with burn size. The effect of these processes on important organ functions such as renal and liver function was assessed by monitoring routine laboratory measures. Blood urea nitrogen and serum creatinine concentrations were significantly increased in the larger burns group. Comparing both measures, we noted similar results as for the inflammatory markers. Differences in serum creatinine disappeared after day 28 postburn, whereas blood urea nitrogen remained significantly different. As an explanation for these findings, we propose that metabolic breakdown and protein degradation related to burn size lead to a significantly greater increase in nitrogen load in this burn group. The effect on the liver as a pivotal organ for metabolic homeostasis is reflected in concentrations of the enzyme aspartate transaminase and total bilirubin. Bilirubin is an established measure for monitoring liver function and was significantly increased in the larger burn group. The initial increase during the first 2 days after injury might be accounted for by the breakdown of damaged red blood cells and the transfusion of red blood cells given during the burn wound excision and grafting procedures. Aspartate transaminase is a non-liver-specific marker that can also be found in red blood cells, heart, pancreas, kidneys, and muscle. Therefore, it might not specifically reflect liver damage. The tremendous increase seen during the first week in patients with burns greater than 60% TBSA might be accounted for by severe tissue damage to the skin after burn injury.

A limiting factor, which might be seen as advantageous by some in view of the endpoints used in this study, was that patients admitted to our hospital received maximum treatment irrespective of the severity of the burn injury (no do not resuscitate orders were written). This treatment regimen does not necessarily apply to all burn patients at all centres. Another limitation, yet a potential advantage, is that this study is a single-site study and did not include outcomes from other hospitals. The threshold of around 60% TBSA, therefore, might or might not apply to other burn centres. However, the use of data
from a single centre eliminates the differences that arise from multiple study sites due to homogeneous treatment protocols. In summary, the results of this study verify the clinically expected increased incidence of mortality and major changes in morbidity with increasing burn size, with a major divergence noted at around 60% TBSA burn size (panel). We show that the incidence of comorbidities increases with burn size and show a major increase over the calculated threshold. Moreover, this finding depends on a series of metabolic changes and clinically important organ monitoring measures, which were also shown to follow this pattern.

The relevance of this work is that we have established that, in a modern paediatric burn care setting, a burn size of roughly 60% TBSA is a crucial threshold for postburn morbidity and mortality. On the basis of these findings, we recommend that paediatric patients with greater than 60% TBSA burns be immediately transferred to a specialised burn centre. Furthermore, at the burn centre, patients should be treated with increased vigilance and improved therapies, recognising the increased risk for poor outcome associated with this burn size.

**Contributors**

MGJ, DNH, and RK planned the study and were responsible for the design, coordination, and drafting of the report. AMAM, FNW, and CCF participated in the study design and helped to draft the report. RK and FNW did the statistical analysis. DNH, MGJ, and CCF obtained funding.

**Conflicts of interest**

We declare that we have no conflicts of interest.

**Acknowledgments**

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**References**