SOUTHERN SURGICAL ASSOCIATION ARTICLE

Contemporary Burn Survival

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BACKGROUND: The standard of burn treatment today reflects major advances. We sought to quantitate the impact of these advances on burn survival via age-stratified mortality ratios compared with other reported mortality analyses in burns.

STUDY DESIGN: Age, percent of the total body surface area (TBSA) burned, presence of inhalation injury, length of stay, and survival status were recorded at admission and at discharge for all new burn admissions between 1989 and 2017. The expected mortality probability was calculated using historical multiple regression techniques and compared with observed data. We developed a prediction model for our observed data.

RESULTS: Between 1989 and 2017, there were 10,384 consecutive new burn admissions, with 355 mortalities (median age, 13 years; median percent TBSA burn, 11%). We saw a significant decrease in our observed mortality data compared to historical predictions ($p < 0.0001$), and a 2% reduction per year in mortality during the 3 decades. The prediction model of mortality for the data is as follows: $Pr(dying) = e^x/(1 + e^x)$ where $x = -6.44 - 0.12\ age + 0.0042\ age^2 - 0.0000283\ age^3 + 0.0499\ TBSA + 1.21\ Inhalation\ Injury + 0.015\ third\ degree\ TBSA$.

CONCLUSIONS: The reduction in mortality over time may be attributed to successful changes in standard of care protocols in the burn center that improved the outlook for burned individuals, including protocols for management of inhalation injury, nutrition, resuscitation, and early excision and grafting. (J Am Coll Surg 2018;■:1−11. © 2018 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

Mortality from burns is determined by age, sex, burn size, and the presence or absence of inhalation injury. Severe burn injuries also produce a profound hypermetabolic stress response, which is characterized by excessive glucose production, protein catabolism, and an influx of oxidants.[1-3] The stress response to burn causes a severe loss of lean body mass and muscle wasting.[4,5] Infection that occurs during the hospital course, immunologic compromise,[6] and growth delays in both muscle and bone[7] contribute to morbidity, mortality, and prolonged recovery.

The association between percent total body surface area (TBSA) burned and survival was first noted in 1902.[8] Beginning in 1949, age-stratified probit modeling was used to evaluate changes in the standard of burn care, although other methods have been occasionally used.[9] Probit analysis converts a sigmoid dose-response curve into linear form and allows the evaluation of burn size in terms of mortality and other binary outcomes data.[10-12] Bull, Squire, and Fisher[13-15] are credited with the first application of probit analysis for the quantitative assessment of advancements in burn care, and 3 analyses were separately published spanning the years 1942 to 1970. They selected the age categories of 0 to 14, 15 to 44, 45 to 64, and ≥65 years; for each, they reported the percent TBSA burned that resulted in 50%

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Table 1. Historical Comparison of Percent Total Body Surface Area Burn Resulting in 50% Mortality (Lethal Area$_{50}$)

		0–14 y		15–44 y		45–64 y		≥65 y	
Year	**First author (country)**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1949	Bull (UK)	342	51	311	43	95	23	46	9
1954	Bull (UK)	1,366	49	967	46	330	27	144	10
1956	Schwartz (US)	–	__	480	65	–	__	–	__
1957	Barnes (US)	217	39	221	65	219	39	128	26
1964	Pruitt (US)	238	49	806	56	56*	29*	__	__
1971	Bull (UK)	962	64	565	56	246	40	149	17
1980	Cureri (US)	232	63	413	63	178	38	114	23
1987	Herndon (US)	875	95	612	76	132	46	52	19

*≥50 years.

mortality (LA$_{50}$).[13-15] Barnes[16] reported data from Massachusetts General Hospital in 1957. Schwartz and colleagues,[17] and later Pruitt and associates,[18] reported similar numbers for the Brooke Army Medical Center; additional reports of burn LA$_{50}$ have used the 4 age categories established by Bull, Squire, and Fisher (Table 1). In 1980, Currerri and coworkers[19] predicted age-adjusted mortality in 937 burned patients (79% survival, median age of 29 years, median burn size of 18% TBSA) using a logistic regression formula to describe the standard of care at the time. Predicted mortality based on TBSA burn and age was used as the primary metric of progress in burn care in their model. There was an apparent decrease in mortality beginning in 1987, particularly in younger individuals, which may have been attributed to the implementation of standardized protocols. To further explore mortality, we analyzed data from 1989 and onward.

The specific objectives of our study were to determine a regression model of mortality in all pediatric and adult burned patients who were admitted to Shriners Hospitals for Children–Galveston (SHC) or the Blocker Burn Unit (BBU) in Galveston, from 1989 to 2017. All patients were treated according to standardized protocols of care at 1 burn center, including protocols for inhalation injury, nutrition, resuscitation strategies, and early excision and grafting. This retrospective chart and database review was approved by the University of Texas Medical Branch Institutional Review Board (Protocol No. 14-036 and 17-0036). The datasets analyzed during this study are available from the corresponding author on reasonable request.

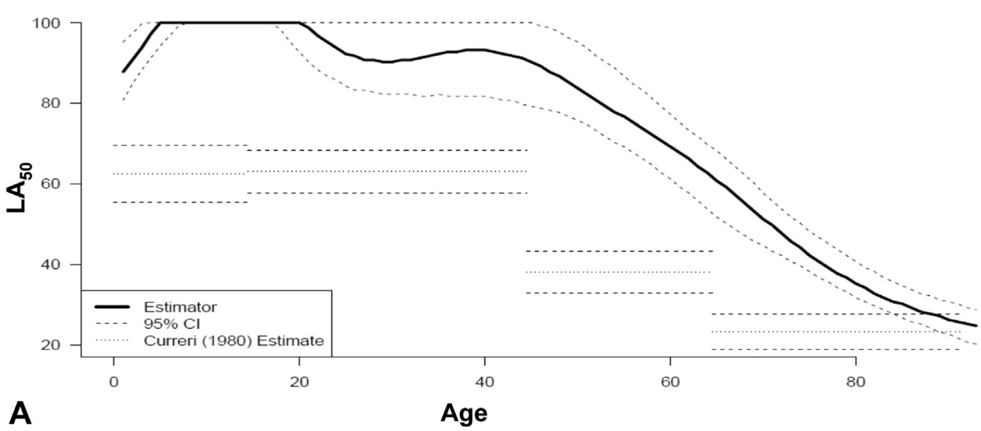


Figure 1. (A) The LA$_{50}$ (% total body surface area resulting in 50% mortality) function of the nonlinear prediction model (solid line) with 95% CI (dashed lines) compared with Currerri and colleagues'[19] model (dotted lines). (B-D) shows a comparison of (B) Curreri,[19] (C) Shirani,[20] and (D) revised Baux[21] prediction of probability of mortality (small dotted line at 45 degrees) vs observed rate of mortality (solid line) along with standard errors, overall and divided by age groups. (Ba) The Curreri predicted and true survival rates overall and among different age groups: (Bb) 0 to 14 years, (Bc) 15 to 44 years, (Bd) 45 to 64 years, (Be) >65 years, from 1989 to 2017. Similar comparisons are illustrated with (Ca-e) Shirani and (Da-e) the revised Baux analysis. In both historical cases, the predicted fit falls below the line of agreement, indicating that these models predicted a greater number of mortalities than we observed in our dataset.

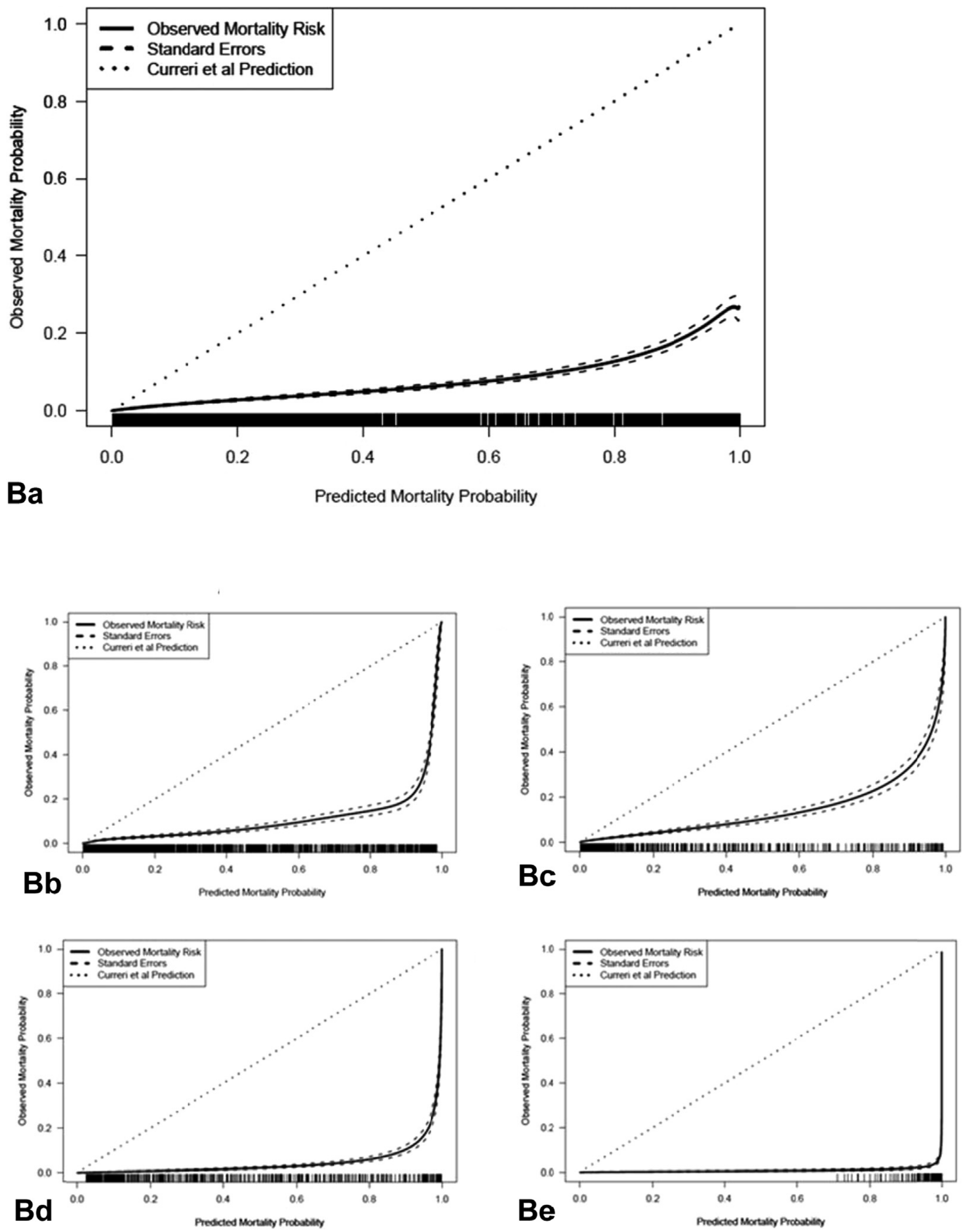
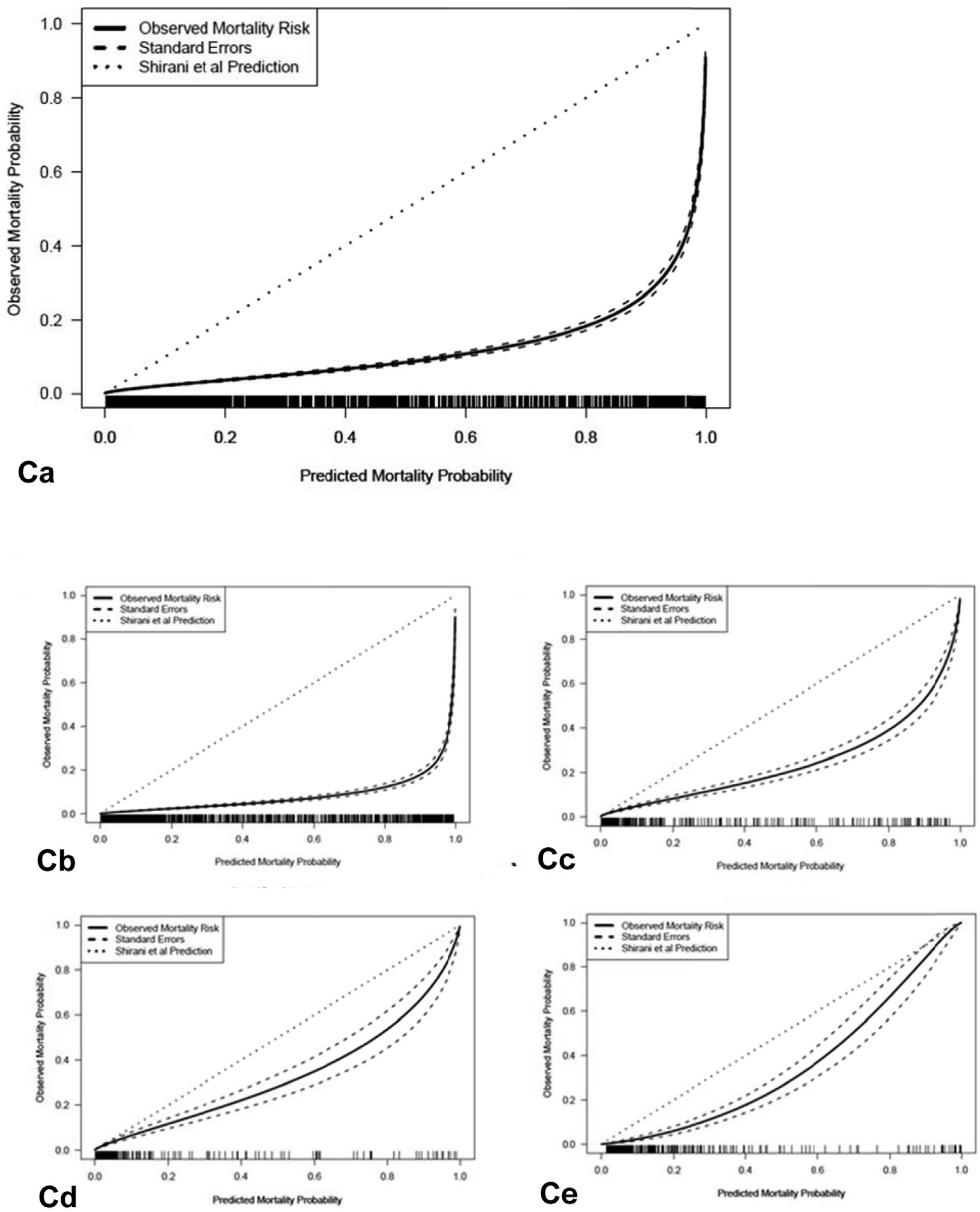


Figure 1. (Continued)

We also compared our dataset with prediction models from groups including Curreri and colleagues[19]; Shirani and associates[20]; and the revised Baux score from the National Burn Repository.[21] We found that percentage of TBSA burned, patient age, and the presence of inhalation injury are primary determinants of mortality and that improvements in standardized protocols of burn care have resulted in a lower mortality compared with referenced prediction models from earlier periods.



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METHODS

Subject demographics and injury characteristics

A total of 10,384 patients were admitted to Shriners Hospitals for Children—Galveston and Blocker Burn Unit between January 1989 and July 2017. All subjects, regardless of age or TBSA burned, were included in our analysis. Patients admitted for nonburns (toxic epidermal necrolysis, Stevens-Johnson syndrome, inhalation injury without burn, aggressive bacterial infections, reconstructive surgery only) were excluded from this study. Patient age, sex, percent TBSA burned, percent of TBSA with third-degree burns, length of stay, and presence of inhalation injury were recorded at the time of admission for patients. Age-appropriate diagrams were used to determine burn size.[22] Survival status at the time of hospital discharge had been recorded. All subjects received our

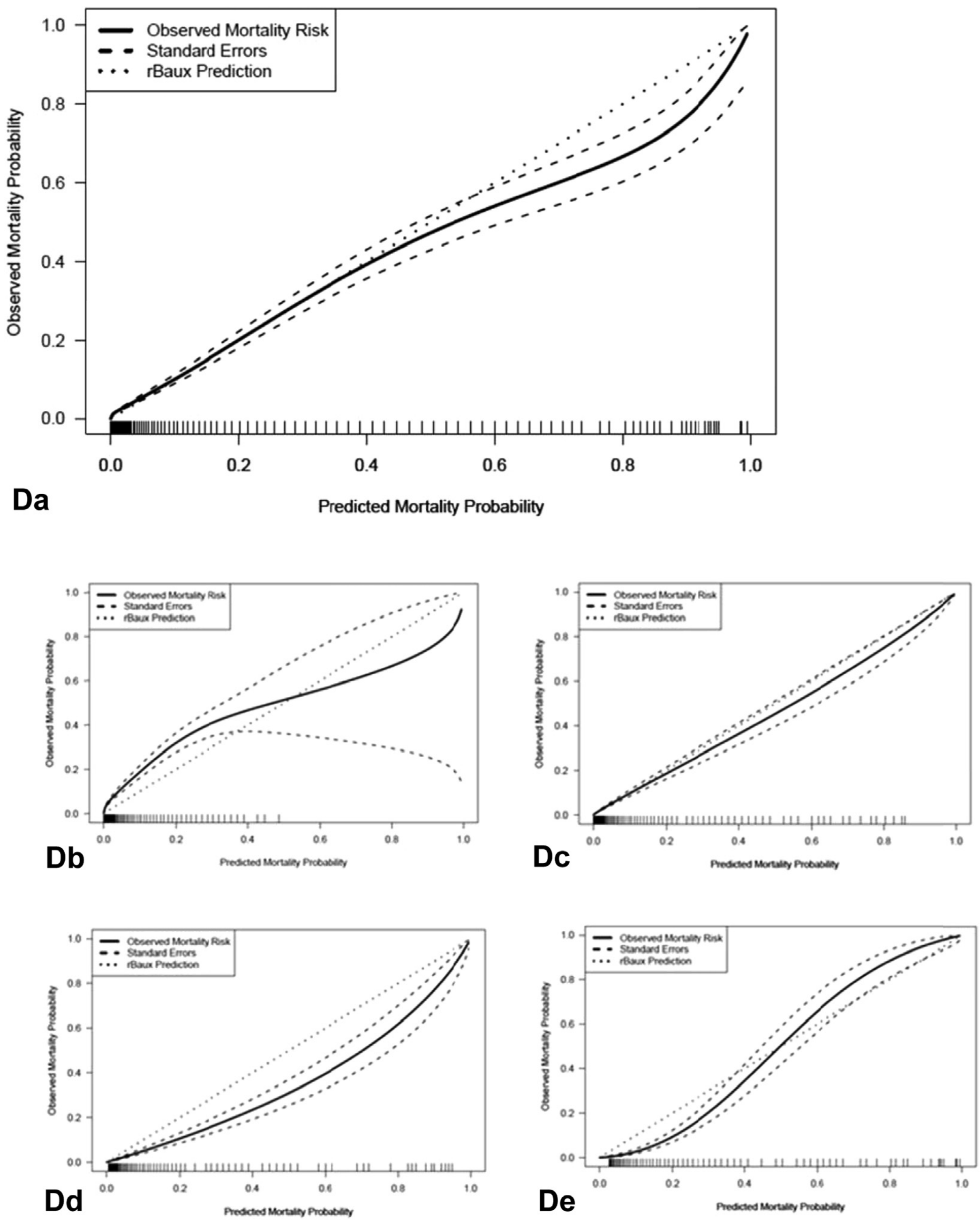

Figure 1. (Continued)

standard of care for wound treatment and nutrition as described previously.[23,24]

The Institutional Review Board of the University of Texas Medical Branch (Galveston, TX) and the Shriners Hospitals for Children's Office for Clinical Research approved this study. Individual patient consents were not required for this retrospective review.

Inhalation injury diagnosis

The presence or absence of inhalation injury was confirmed by bronchoscopy in patients suspected to have inhalation injury. Presence was diagnosed by positive findings including edema, erythema, hemorrhage and bronchorrhea, mucosal blisters and erosion, and deposits of soot.

Table 2. Demographics

Parameter	Value
n	10,384
Age, y, mean ± SE (median, IQR)	21 ± 0.21 (13, 3–35)
Male, %	69
TBSA burned, median, mean ± SE (median, IQR)*	20 ± 0.21 (11, 4–30)
TBSA third-degree burned, mean ± SE (median, IQR)†	13 ± 0.27 (1, 0–17)
Presence of inhalation injury, %	12.2
Length of stay, d, mean ± SE (median, IQR)	12 ± 0.20 (5, 2–14)
Burn to admission, d, median, IQR	1, 0–3
Mortality, %	3.4

*TBSA burned, percent total body surface area burned.
†TBSA third-degree burn, percent of total body surface area with third-degree burns.
IQR, interquartile range; TBSA, total body surface area.

Statistical modeling

The LA_{50} curve was produced by fitting a generalized nonlinear logistic model on age and TBSA burn.[25] The curve corresponds to those values of TBSA burn by age for which 50% survival is expected. The confidence interval was generated by calibrating bootstrap confidence intervals on the fitted probability of mortality. To compare predicted mortality against actual mortality, a generalized smoothing spline was fit. The actual mortality risk estimate and standard errors were produced for each value of predicted mortality risk from the formulas of Curreri and colleagues,[19] Shirani and coauthors,[20] and Osler and associates.[21] The odds ratio was estimated by comparing the predicted mortality odds against the mortality odds of our cohort. The linear prediction model was constructed to minimize the Bayesian Information Criterion. Sensitivity, specificity, and accuracy were estimated using bootstrap smoothed cross-validation.[26] Year-to-year mortality odds reduction was estimated based on a generalized additive model, adjusting for age, sex, TBSA burned, TBSA with third-degree burns, inhalation injury, and length of stay. The model for length of stay was calculated based on a parametric (exponential) time-to-event model, with death as the censoring mechanism.

With the exception of third-degree TBSA burn (for which values were missing), less than 10% of subjects had missing predictor or response values, so subjects with missing values were ignored. A sensitivity comparison was done to compare models with third-degree TBSA burn (and subjects with missing values ignored) against a fit model without third-degree TBSA burn; models were similar enough to conclude that the model with third-degree TBSA burn was not biased. All calculations were done in R (version 3.4.0).

RESULTS

Figure 1A illustrates the LA_{50} of our prediction model (solid line) with 95% confidence intervals (CI, large dotted lines) compared with Curerri and colleagues'[19] probit model (small dotted lines). Figure 1B illustrates the Curreri and associates[19] predicted and true survival rates overall (a) and among different age groups (0 to 14 years [b], 15 to 44 years [c], 45 to 64 years [d], and older than 65 years [e]) compared with our data from 1989 to 2017 (Table 2; 10,029 survivors and 355 nonsurvivors [3.4% mortality]). The expected reciprocal odds ratio of mortality is 9.5 overall, 10.3 for 0 to 14 years, 4.7 for 15 to 44 years, 40 for 45 to 64 years, and 3030 for older than 65 years. Because the uncertainty in the Curreri and colleagues[19] estimator is unknown, precise inference is not possible. On average, the Curreri and colleagues[19] model overestimated the true mortality rate by an average of 12.4 standard errors (SE, overall), 6.0 SE for 0 to 14 years, 5.3 SE for 15 to 44 years, 11.9 SE for 45 to 64 years, and 31.8 SE for greater than 65 years; in these cases, the comparisons are significantly different ($p < 0.05$). Table 3 illustrates observed survival among all age-stratified groups of 10,384 burn patients from Shriners Hospitals—Galveston from 1989 to 2017 compared with the Curerri and coauthors[19] model of expected mortality (via the sum predicted mortality probability).

Our observed mortality data were compared in a similar manner to other notable burn mortality prediction models including Shirani and colleagues' model,[20] which accounts

Table 3. Observed and Expected Survival in Overall and Age-Stratified Groups: Comparison with Curreri and Colleagues[19]

		Age group			
Parameter	**Total**	**0–14 y**	**15–44 y**	**45–64 y**	**≥65 y**
SHC/BBU, n	10,384	5,524	3,154	1,267	439
Observed (actual) mortality at SHC/BBU, n	355	133	93	57	72
Expected mortality per Curreri's model, n	1,342	684	223	153	282
Fold mortality reduction, reciprocal odds ratio	4.2	5.7	2.7	2.9	9.2
95% CI	(3.7–4.7)	(4.7–6.9)	(2.1–3.5)	(2.1–4)	(6.7–12.6)
p Value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

SHC/BBU, Shriners Hospitals for Children—Galveston/Blocker Burn Unit.

Table 4. Comparison of Models: Shirani and Colleagues[20]

Parameter	Total	Age group 0–14 y	15–44 y	45–64 y	≥65 y
SHC/BBU, n	10,384	5,524	3,154	1,267	439
Observed (actual) mortality at SHC/BBU, n	355	133	93	57	72
Expected mortality per Shirani's model, n	1,058	729	156	68	104
Fold mortality reduction, reciprocal odds ratio	3.2	6.2	1.7	1.2	1.6
95% CI	(2.8–3.6)	(5.1–7.4)	(1.3–2.2)	(0.8–17)	(1.1–2.2)
p Value	<0.0001*	<0.0001*	<0.0001*	0.3	0.007*

*Significant.
SHC/BBU, Shriners Hospitals for Children–Galveston/Blocker Burn Unit.

for the presence of inhalation injury and pneumonia, in addition to TBSA burn and age (Table 4; Fig. 1C) and the revised Baux score,[21] which is an updated version of the original Baux score that is calculated by adding patient age, TBSA burn, and 17 points for the presence of inhalation injury (Table 5, Fig. 1D). Figure 1C illustrates the Shirani and associates[20] predicted and true survival rates overall (a) and among different age groups (0 to 14 years [b], 15 to 44 years [c], 45 to 64 years [d], and greater than 65 years [e]), from 1989 to 2017. Table 4 illustrates that significantly lower mortality was observed overall and in all age groups, except 45 to 64 years, compared with the Shirani model prediction. Figure 1D illustrates significant differences between the revised Baux predicted and true survival rates overall (a) and among different age groups (0 to 14 years [b], 15 to 44 years [c], 45 to 64 years [d], and older than 65 years [e]), from 1989 to 2017. Table 5 shows that there were significant differences between our observed data and the revised Baux prediction. However, the dataset used to generate the revised Baux was from 2000 to 2007; our dataset includes patients from 1989 to 2017.

Of the nonsurvivors, 45% had concomitant inhalation injury ($p < 0.0001$). We present a prediction model with 97% accuracy (sensitivity, 9%; specificity, 99.9%; Fig. 2). The following terms were included in the polynomial model: age, TBSA burned, presence of inhalation injury, and third-degree TBSA burned (Table 6). The prediction model of mortality for the data is as follows: $\text{logit}(P(\text{mortality})) = -6.44 - 0.12\ \text{age} + 0.0042\ \text{age}^2 - 0.0000283\ \text{age}^3 + 0.0499\ \text{TBSA} + 1.21\ \text{Inhalation Injury} + 0.015\ \text{third-degree TBSA}$.

Additionally, we illustrate that the relative odds of death decreased only slightly over the 3-decade span from 1989 to 2017 ($p < 0.0001$). Year-by-year reduction in the odds of mortality is 2.12% ($p = 0.03$), with adjustments for sex, age, and TBSA burn. Probability of death increased as age increased ($p < 0.0001$), as TBSA burned increased ($p < 0.0001$), as length of stay increased ($p < 0.0001$), and with the presence of inhalation injury ($p < 0.0001$). Mortality for male patients was lower, with a 60% decreased odds of mortality compared with that for female patients (95% CI 44% to 81%, $p < 0.05$).

Lastly, we present a prediction model of length of stay. The following terms were included in the polynomial model: age, TBSA burned, presence of inhalation injury, and third-degree TBSA burn (Table 7). The prediction model of length of stay for the data is as follows: $E(\hat{u}) = (\beta_0 + \beta_1\text{age} + \beta_2\text{TBSA} + \beta_3(\text{inhalation injury} = \text{“yes”}) + \beta_4\text{TBSA } 3^{\text{rd}})^{-1}$. Each percent increase of TBSA burn increases length of stay by 3.03%. Given that the average length of stay for survivors is 11.7 days, the average increase was 0.36 days per percent TBSA burn.

DISCUSSION

In 1980, Curreri and colleagues[19] reported improved survival after burn. In 1987, Herndon and associates[27]

Table 5. Comparison of Models: Revised Baux Score

Parameter	Total	Age group 0–14 y	15–44 y	45–64 y	≥65 y
SHC/BBU, n	10,384	5,524	3,154	1,267	439
Observed (actual) mortality at SHC/BBU, n	355	133	93	57	72
Expected mortality per revised Baux, n	412	112	114	89	97
Fold mortality reduction, reciprocal odds ratio	1.2	0.8	1.2	1.6	1.4
95% CI	(1.01–1.3)	(0.7–1.1)	(0.9–1.6)	(1.1–2.3)	(1–2)
p Value	0.04*	0.18	0.14	0.007*	0.03*

*Significant.
SHC/BBU, Shriners Hospitals for Children–Galveston/Blocker Burn Unit.

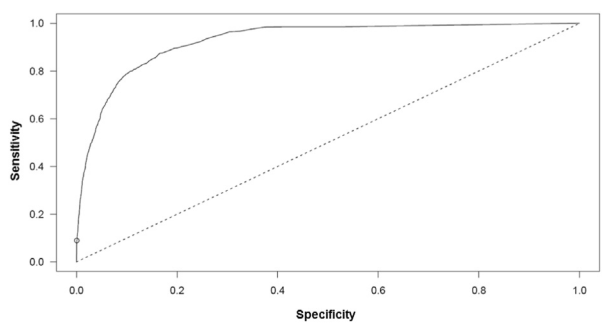

Figure 2. The receiver operating characteristic (ROC) curve for a nonlinear prediction model for 10,384 burn patients. The area underneath the ROC curve was calculated as 0.93.

reported survival of a large cohort of children with burns covering more than 70% of the TBSA. In 2003, the same group reported greater than 50% survival in a cohort of children with burns covering over 88% of the TBSA.[28]

Metrics that summarize field-specific improvements are warranted, and they can be used to determine whether care is improving universally and to evaluate how mortality at individual institutions compares with that at other institutions. Here, we present a generalized regression model based on a large consecutive patient cohort, which illustrates the substantial increase in survival of burns. Overall, our data suggest that treatment by standard protocols, relative to other published datasets, may have contributed to decreases in mortality. Other variables include changes in public health and infrastructural changes allowing for more rapid transport of the critically ill. We compared our results with Curerri and colleagues'[19] logistic prediction model (Table 3) because it reflected burn care in 1980 at an appropriate comparison time point; our results directly connect to their landmark probit studies in both mathematical and qualitative manners. Other notable burn mortality prediction models include Pruitt and associates'[18] and Shirani and coworkers'[20] models, which are based on TBSA burn and/or the presence of inhalation injury and pneumonia, and the revised Baux score.[21] The revised Baux score is an updated version of the original Baux score, which is

Table 6. Linear Logistic Prediction Model Coefficients for Mortality in Burn Patients

Coefficient	Estimate	Standard error	p Value
Intercept	−6.44	0.272	<0.0001
Age	−0.12	0.0274	<0.0001
Age squared	0.0042	0.000884	<0.0001
Age cubed	-2.83×10^{-5}	7.45×10^{-6}	0.00015
TBSA burn	0.0499	0.00585	<0.0001
Inhalation injury	1.21	0.192	<0.0001
TBSA burn third	0.015	0.00482	0.002

TBSA, total body surface area.

Table 7. Linear Logistic Prediction Model Coefficients for Length of Stay in Burn Patients

Coefficient	Estimate	Standard error	p Value
Intercept	1.13	0.0247	<0.0001
Age	0.0106	0.000679	<0.0001
TBSA burn	0.0342	0.00114	<0.0001
Inhalation injury	0.309	0.0384	<0.0001
TBSA burn third	0.0103	0.00124	<0.0001

TBSA, total body surface area.

calculated by adding patient age, TBSA burn, and 17 points for the presence of inhalation injury. Comparisons of Shirani and colleagues'[20] model and the revised Baux score model are included in Tables 4 and 5. It is widely recognized that the revised Baux score underestimates mortality in the first decade of life.

Substantial advances in acute burn care occurred between 1980 and 1989, including early excision and grafting,[23,27,29] early and standardized resuscitation,[30-32] modulation of the hypermetabolic response,[33-39] goal-directed nutrition and reversal of systemic catabolism,[40,41] prevention and support of organ failure syndromes,[42,43] and standardization of critical care.[43,44] Incorporation of these advances into the standard of burn care may have contributed to the reduction of postburn mortality observed. Additionally, all protocols were supervised by the last author, Dr Herndon, consistently from 1989 to 2017 at our burn center.

Because age is included as a predictive variable, our models may be used to compare historically expected and observed mortality and length of stay across groups from different age cohorts. In clinical practice, the models can be used to gauge expected mortality and length of stay in an adjusted manner; therefore, they allow for an individual prediction of mortality and length of stay at the time of admission for a burn patient treated with the current protocols. Furthermore, our model allows continuous analysis of the relationship between expected and observed mortality, as well as length of stay, in individual institutions.

Inhalation injury remains a contributor to morbidity and mortality in burn patients.[45,46] At our site, approximately 65% of all nonsurvivor pediatric burn patients had inhalation injury. The trauma caused by smoke inhalation injury in burn patients commonly results in an exaggerated inflammatory cascade and acute respiratory distress syndrome.[47] The impact of inhalation injury is confounded by its difficulty of diagnosis and its spectrum of severity. However, the overall contribution of inhalation injury to mortality has decreased. The effects of inhalation injury are seen most in patients with burns covering 40% to 60% of the TBSA and between 18 and 60 years of age. Our findings show that individually, percent TBSA burned and age are more powerful determinants of mortality than inhalation injury, and become dominant at extremes of age and in the largest of burns (Table 6).

Limitations of our study include the unavailability of post-discharge follow-up information, including mortality, for all subjects. More importantly, it has been increasingly argued that using mortality as an endpoint to assess advances in burn care is losing validity because of the reduction in burn-related deaths.[48] This reduced mortality poses a statistical problem owing to difficulty in devising interventions or achieving adequate enrollment to further affect this percentage positively. However, the 3- to 5-fold reduction, which we demonstrate in this analysis relative to 1980, leaves the actual absolute percentage of mortality at an all-time low. Therefore, it is imperative that new metrics are established in a standardized manner over long periods to maintain the ability to quantify improvements in care and to define future research trajectories. In the future, long-term metrics that transcend survival, such as restoration of growth in children,[33] mental and functional status, quality of life, or quality-adjusted life years, will likely gain even more traction as powerful endpoints.[49-54] Second, our model has greater statistical power owing to patient number. We note that the median age of our cohort was 13 years (mean 21 ± 0.21 years), with a median TBSA burn of 11% (mean 20% ± 0.21%) and that the cohort of Cururerri and associates[19] had a median age of 29 years with 18% TBSA burn, the cohort of Shirani and colleagues[20] had an average age of 33 ± 20 years with 37% ± 22% TBSA burn, and the cohort for revised Baux score[21] had a mean age of 31 years, with an average TBSA burn of 9.7%. Third, the retrospective nature of this study precludes inferences that could have been made in a prospective approach, which could have compared expected and actual mortality patient by patient. This concern is moderated by the inclusion of the entire cohort of burn admissions during this study period. Our present model is not able to directly assess the effectiveness of specific interventions or protocol changes. Last, several historically important prognostic models that were developed to predict mortality after burns were developed before widespread understanding of the importance of internal and external validation, and therefore have an unknown generalizability.[55] Because historically important models have unknown generalizability, their results are difficult to interpret when applied to modern data.[56] Models that lack generalizability may give erroneously high or low estimates of mortality for reasons unrelated to changes in the quality of care. The various prediction models that have been developed, including our own, can best be validated against observed datasets that are either not widely available or suffer from variability. We also note that third-degree burn size reporting varies through hospital course because of progression of disease and interobserver differences.

Future directions of our work include the inclusion of additional determinants such as resuscitation fluid, weight and BMI, comorbidities at admission, and the effect of infections such as pneumonia and sepsis during the hospital course. Also, stratifying the severity of inhalation injury rather than including a binary outcome of either presence or absence will more accurately describe its role in mortality. Lastly, the sexually dimorphic response to burn injuries observed in this large dataset encourages further study that may improve survival outcomes, particularly in female patients.

CONCLUSIONS

Advances in burn care have significantly increased survival and raised the standard of care. Additional endpoints must be established to assess future advancements that focus on function and quality of life.

Author Contributions

Study conception and design: Capek, Sousse, Voigt, Finnerty, Jennings, Herndon
Acquisition of data: Capek, Sousse, Hundeshagen, Voigt
Analysis and interpretation of data: Capek, Sousse, Suman, Finnerty, Jennings, Herndon
Drafting of manuscript: Capek, Sousse, Hundeshagen, Finnerty, Jennings, Herndon
Critical revision: Capek, Sousse, Hundeshagen, Finnerty, Herndon

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