Development and Validation of an Age-Risk Score for Mortality Predication after Thermal Injury

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Background: In burn patients, the risk of mortality typically decreases as children mature, reaches a nadir at age 21, rises linearly thereafter, and levels off in old age. We hypothesized that a single "age-risk score" (AGESCORE), incorporating a cubic functional form, can be used in predictive models for mortality after burns.

Methods: Data from 6,395 thermally injured patients admitted to a single burn center between January 1, 1950, and December 31, 1999, were used. Variables included age, total burn size, year of discharge, and survival. AGESCORE was defined as follows: $-5(\text{age}) + 14(\text{age}^2/100) - 7(\text{age}^3/10{,}000)$. Logistic regression verified the cubic functional form of the age-mortality relationship. Models using a general cubic functional form of age, and AGESCORE, were compared for lack of fit. The stability of AGESCORE was assessed over six distinct treatment eras within the 50-year period. AGESCORE was also validated using data from a different burn center.

Results: AGESCORE provided an accurate method for modeling mortality in burn patients across different age groups, burn sizes, eras, and burn centers.

Conclusion: The benefits of a standardized index of age risk include ease of comparison, reduction of bias, and increased efficiency attributable to statistical parsimony. The applicability of this approach to nonthermal trauma patients remains to be seen.

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Age is recognized as an important determinant of mortality and morbidity in trauma patients. Predictions and comparisons of mortality within or between intensive care units require adjustment for the age distributions of the patient populations involved.[1] Champion et al. have developed metrics for gauging risk caused by trauma,[2] and in this article we demonstrate a similar metric for gauging risk attributable to age. Such a metric should be simple, accurate, parsimonious, easily incorporated in prediction models, and portable across various types of studies.

Mortality after trauma is commonly modeled using regression (specifically, generalized linear models that include logistic and other regression variants), but the functional form of the age variable has also been reported in a variety of different ways, such as categorized age (implicitly, a step function),[3] a linear age function,[4] a quadratic function without a linear term,[5] a cubic age function,[6] and so on. However, the age functions in these models are highly variable.

The wide range of age-adjustment functions reported in the literature (including a priori illogical functions) highlights the need for standardization. Such a standardized age adjustment should accommodate the "bathtub-shaped" mortality function prevalent in mortality prediction models, which reflects increased risk for the very young and the very old. Moreover, a standardized age adjustment should provide biologically reasonable risk values throughout an age range, including the extremes (fitted polynomials often give poor predictions at the extremes, such as declining mortality in the extreme geriatric age group), and provide a simple, parsimonious, and easy-to-use score for linear input into equations that are specifically built to predict mortality. Finally, a standardized age variable is particularly useful in small data sets where an age adjustment is desired and the data do not provide enough information to estimate all the terms of a polynomial function. To address this need, we suggest that the risk associated with a particular age can be expressed as an age risk score or AGESCORE:

$$\text{AGESCORE} = -5\text{age} + 14(\text{age}^2/100) - 7(\text{age}^3/10{,}000) \quad (1)$$

Coefficients of AGESCORE were chosen to reflect the bathtub-shaped relationship between age and mortality over the entire age range. Namely, AGESCORE shows increased risk for infants and the elderly. Because patients older than 112 years are not anticipated, the specific coefficients (−5, 14, and −7) restrict risk from declining until 112 years. As such, the AGESCORE function seems realistic over the entire age span. The cubic character of AGESCORE is consistent with studies from a variety of other burn centers that have demonstrated higher mortality for the very young and the

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Table 1 Six Eras of Changing Burn Care Practices and Impact on Mortality

Era	
1950–1963	Invasive gram-negative burn wound infection (burn-wound sepsis) was common. The available antibiotics were ineffective and mortality was high.
1964–1968	Mafenide acetate (Sulfamylon), a topical antibacterial cream, was introduced. This effectively prevented burn-wound sepsis, resulting in a dramatic fall in mortality.
1969–1972	Organisms resistant to Sulfamylon appeared; gram-negative sepsis became more common, with a concomitant increase in mortality.
1973–1977	Silver sulfadiazine was introduced, and improved control of sepsis was gradually achieved.
1978–1983	Excision of burns was gradually introduced.
1984–1999	In 1983, the burn intensive care unit was remodeled to permit individual patient isolation, thus limiting the transfer of multiple-drug-resistant organisms among patients. A stringent set of infection-control practices (e.g., gowns, masks, gloves, frequent surveillance cultures, and cohort patient management) was implemented. Introduction of high-frequency percussive ventilation decreased the pneumonia rate in patients with inhalation injury.

elderly.[7–10] Using AGESCORE,[1] mortality prediction models are then given by:

$$f(p) = b_o + b_1(\text{AGESCORE}) + b_2(\text{factor } 2) + b_3\ (\text{factor } 3) \tag{2}$$

where f(p) is the "link function," relating the mortality parameter p[a] to the linear equation, and b_0, b_1, b_2, and b_3 are coefficients to be estimated from the data. Models using the AGESCORE transformation (e.g., Equation 2 above) are parsimonious because logistic mortality models can be fit that are linear in the transformed age variable, whereas the cubic character of the age variable is maintained. The reduction of model dimensionality resolves problems of multicolinearity and statistical imprecision because the linear, quadratic, and cubic age terms are subsumed by the AGESCORE transformation (and thus do not have to be explicitly included as regressor variables). Moreover, comparisons of risk factors (in addition to age) between sites are facilitated because AGESCORE provides a standardized adjustment.

In this article, we verify the cubic functional specification of age risk and validate AGESCORE. Although our model applies primarily to burn patients, where "factor 2" is the percentage of body surface area having second- or third-degree burns (% burn), we suggest that AGESCORE[1] may be more widely applicable when predicting mortality and/or morbidity caused by other forms of trauma.

PATIENTS AND METHODS

Patients

Data for 10,564 burn patients admitted to the U.S. Army Institute of Surgical Research (USAISR, the U.S. Army Burn Center) in San Antonio, Texas, between January 1, 1950, and December 31, 1999, were considered for analysis (fully validated data were not available for more recent years). From this population, patients having flame or scald burns and admitted to the USAISR on or before postburn day 2 were selected. Applying these criteria yielded a study population of 6,395 patients consecutively admitted to the USAISR for burn care. For each patient, percentage burn, age (years), postburn day of hospital admission, and discharge or death were recorded. Reliable data indicating the presence or absence of inhalation injury were not available before 1976, so inhalation injury was not included as a risk factor in our model. The average age of patients entering the facility was 27.3 years (SD, 19.5 years) with an average burn size of 31.2% (SD, 24.5%) of the total body surface area. Twenty-four percent of the patients died as a result of burn injury or associated complications. Recognizing that infection is the leading cause of death in burn patients, the 50-year study period was divided into six discrete eras on the basis of changing infection control and other practices, and their impact on mortality (Table 1). Figure 1 illustrates the changes in baseline mortality rates over the entire 1950 to 1999 time interval. It can be seen that the treatment regimens described in Table 1 initially improved survival after the intervention but that there was a tendency for mortality to rise later, suggesting the development of resistance to antibiotics and similar factors.

Statistical Analysis

Development of AGESCORE

AGESCORE (Equation 1) was selected by first fitting the model (Equation 2) using AGESCORE and percentage burn as regressor variables. A constrained maximum likelihood estimation algorithm was used to solve for AGESCORE coefficients that maximized the log likelihood of Equation 2. The coefficients were selected such that:

$$\frac{d}{dx} f(x) = 0 \tag{3}$$

when age = 112. The constrained maximum likelihood estimates (−5, 14, and −7) were chosen by the algorithm. This

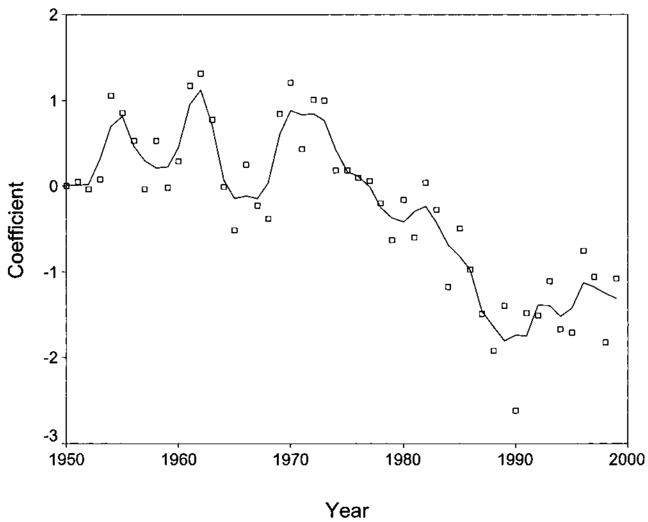

Fig. 1. *Logit mortality over time. The* y *values (log odds ratios) are coefficients for each year obtained by logistic regression analysis of the whole data set, using burn size and the cubic of age, and using year as a categorical variable. This generates a coefficient for each individual year, reflecting that year's contribution to the logistic equation in comparison with that of 1950. These "year" coefficients reflect changes in the logistic equation predicting mortality, corrected for age and burn size. Higher values reflect higher age- and burn size-corrected mortality for that year. The graph shows a gradual decrease in age- and burn size-corrected mortality risk over time. Note that there were peaks in mortality in 1960–63 and 1969–73, both periods in which sepsis was more frequent. (The line is a LOESS—a nonparametric local regression technique—fit to the coefficients.)*

integer triplet was individually evaluated for good statistical fit and for sensible graphical appearance over a range of age values extending into the centenarian range. Coefficients (−5, 14, and −7) were ultimately settled on because they fit the above constraint, are sensible from a subject matter point of view, and provide a good fit to the actual age-mortality relationship.

Exploring the Functional Form of Age

Logistic regression was then used to validate the cubic functional form of the age-mortality relationship. First, an estimate of the true relationship between age and mortality, free of any particular functional specification, was obtained. This was performed by using indicator variables for 27 age categories, each of which had roughly equivalent numbers of patients. This categorized age variable is denoted as AGECAT, and the unrestricted model is given by:

$$f(p) = a_i + b_1\,(\%\ \text{burn}) \tag{4}$$

To obtain valid χ^2 statistics for comparing Equation 4 with the general cubic function (given below in Equation 5), values of AGECAT were entered into the logistic regression model. A test for lack of fit was then obtained by comparing the deviance (defined as $-2 \times$ [model log likelihood]) of Equation 4 with that of the general cubic model:

$$f(p) = b_o + b_1(\text{AGECAT}) + b_2(\text{AGECAT}^2/100) + b_3(\text{AGECAT}^3/10000) + b_4(\%\ \text{burn}) \tag{5}$$

This analysis was repeated using a general quadratic function to determine whether the higher order cubic polynomial is needed:

$$f(p) = b_0 + b_1(\text{AGECAT}) + b^2(\text{AGECAT}^2/100) + b_3(\%\ \text{burn}) \tag{6}$$

Table 2 **Exploring the Functional Form of Age**

Compared Models	χ^2	*df*	*p* Value	Conclusion
4 and 5	28.7	23	0.1921	Good fit
4 and 5	65.8	24	<0.0001	Poor fit

Model 4, unconstrained or "true" model. Model 5, general cubic model. Model 6, general quadratic model.

Validation of AGESCORE

To assess the fit of AGESCORE, deviance tests were performed comparing Equation 2 with the general cubic function:

$$f(p) = b_0 + b_1(\text{age}) + b_2(\text{age}^2/100) + b_3\,(\text{age}^3/10{,}000) + b_4(\%\ \text{burn}) \tag{7}$$

in which age is entered as a continuous variable. The estimated Equations 2 and 7 were compared for groups of patients entering the burn facility during various treatment regimens to assess the stability of AGESCORE over time. Finally, a deviance test was performed to compare Equations 2 and 7 for the entire data from years 1950 to 1999.

RESULTS

Exploring the Functional Form of Age

Table 2 summarizes the results of deviance tests for comparing the unconstrained or true relationship (Equation 4) with the general cubic model (Equation 5) and the general quadratic model (Equation 6). It is clear that the cubic model (Equation 5) provides an appropriate fit, whereas the quadratic model does not. In other words, the additional information gained by including the cubic term improves goodness of fit.

Validation of AGESCORE

Table 3 summarizes the χ^2 tests for the AGESCORE model (Equation 2) versus the general cubic model (Equation 7) during various treatment eras. It shows that mortality predictions using AGESCORE are similar to those predictions obtained from the general cubic across all subsets of data. Note that for the time period of 1950 to 1963 there is

Table 3 **Comparing the AGESCORE Model with the General Cubic Model for Various Treatment Eras**

Treatment Era	χ^2	*p* Value
1950–1963	7.046	0.0246
1964–1968	3.745	0.1537
1969–1972	4.297	0.1167
1973–1977	1.185	0.5529
1978–1984	1.475	0.4783
1985–1999	0.662	0.7182
1950–1999	7.878	0.0194

some indication of lack of fit when using AGESCORE. It is worth noting that during this time period the general cubic produces a curious leveling off in mortality predictions around age 66 and a decrease in mortality predictions shortly thereafter. However, AGESCORE produces rising mortality predictions for the elderly, which are more sensible for this increasingly aged group. Though the goal of the AGESCORE transformation is not necessarily to provide superior predictions to the general cubic (rather, we suggest that AGESCORE is at least as good as the general cubic in terms of modeling the relationship between age and mortality), in this specific circumstance AGESCORE outperforms the general cubic despite the significant lack of fit between the two models. The average mortality prediction for patients 66 years or older given by AGESCORE (81% mortality) more closely matches observed mortality (78% mortality) than those predictions of the general cubic (63% mortality). Table 2 also shows some lack of fit for the AGESCORE model compared with the general cubic when estimating these models for the entire 50-year data set (χ^2 = 7.878, $df = 2$, $p = 0.0194$). Figure 2 plots the estimated general cubic versus AGESCORE models for the entire data set (1950–1999). The AGESCORE model agrees well with the cubic model. However, it must be noted from Figure 2 that the AGESCORE model appears to underpredict mortality for infants and young children when compared with the general cubic. Figure 3 displays the contributions of the various age categories to the χ^2 lack of fit statistic (larger values indicate poorer fit). It can be seen that the bulk of deviance between the AGESCORE and general cubic models stems from the 2-year-old category. Specifically, 80% of the χ^2 likelihood ratio statistic is derived from the 2-year-old age group, which represents 230 observations or 3.6% of the entire data set. Despite the disagreement between the two models for young children, it can be seen from Figure 3 that the two functions generally appear to agree very well (e.g., contributions to the χ^2 lack of fit statistic hovers around zero for the remainder of age categories). Little information is lost when the AGESCORE variable is used instead of a full estimated cubic age function.

Finally, the AGESCORE variable was empirically validated on an external database. The Timothy J. Harnar Burn Center, Texas Tech University, Lubbock, Texas, provided us with all recent entries to their current burn registry database, spanning February 10, 2001, until the present. There were 743 patients with measurable burn sizes, with average age 31.2 years and average burn size of 11.6% (SD, 15.2%), and with 5.6% mortality. The logistic regression prediction model using AGESCORE and percentage burn was compared with the same model with a general cubic in age and percentage burn, using the likelihood ratio test. The results were χ^2 (df = 2) = 3.15 (p = 0.207), implying that lack of fit of the AGESCORE variable is insignificant.

DISCUSSION

AGESCORE (Equation 1) provides a standardized approach to incorporating age into burn mortality prediction models and simplifies comparisons of various patient populations. Discrepancies between the various age functions re-

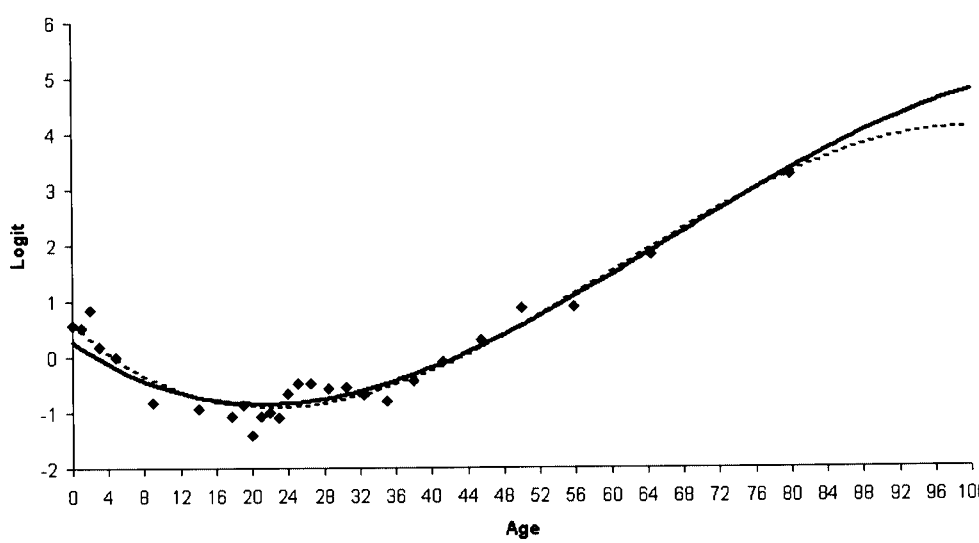

Fig. 2. *The years 1950 to 1999: General cubic (*dashed line*) versus AGESCORE (*solid line*) superimposed over the unconstrained, categorically defined age function at 50% burn.*

Fig. 3. *Contributions of age categories to χ^2 lack of fit statistic.*

ported in the literature can be dramatic. For example, in Figure 4, we fit categorized, linear, quadratic, and cubic models to the current data set. The linear and quadratic models are deficient in that minimum mortality is predicted for infants. The categorized model more appropriately reveals higher risk in young patients. However, the categorized approach is deficient in that there is no unique way to define the group boundaries.

AGESCORE's use of a single variable to represent the age function would ease mortality comparisons between centers. By contrast, comparisons using separate terms for age, age^2, and age^3 require extensive graphical analysis, because the intercept terms reflect different (sometimes biased) quantities in those models. When AGESCORE is used, one can evaluate the contributions of various risk factors (including age) across studies simply by comparing coefficients.

The general cubic model, although reasonable, is not without drawbacks. These include the following. (A) Comparisons across sites are difficult because the coefficients of the linear, quadratic, and cubic terms would all differ even if all mortality data were reported as general cubic functions. (B) Parameter estimates have less precision (especially in smaller data sets) when more variables (age, age^2, and age^3) are included. (C) polynomials often yield poor results when used at or outside the boundaries of the range of the predictor variable (e.g., predicting similar relative risks to a hypothetical 111-year-old patient and an 85-year-old patient). (D) The general cubic age adjustment function complicates the mod-

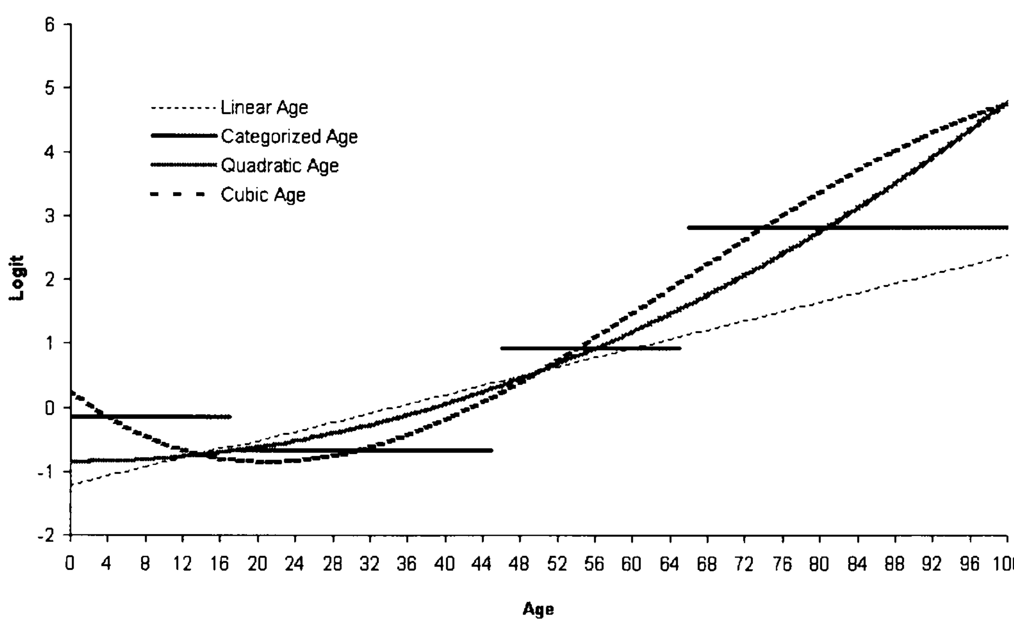

Fig. 4. *Estimated logit mortality at 50% burn using the USAISR data with categorized, linear, quadratic (no linear term), and cubic age adjustment functions.*

eling process. For example, to investigate the interaction between age and burn severity, one might have to consider cross-product terms between percentage burn and each of the linear, quadratic, and cubic terms.

Using AGESCORE rather than the general cubic lessens these problems. Problem A is lessened because comparisons between institutions involve fewer coefficients. Problem B is solved because there is only one age variable (AGESCORE) in the model, rather than three. Problem C is solved because the age function does not decline until age 112. Finally, problem D is lessened because general interaction effects may be explored conveniently using a simple linear-by-linear interaction term.

CONCLUSION

AGESCORE may benefit researchers who wish to use an externally validated measure in their mortality prediction models. Benefits include standardization, biologically reasonable functional form, parsimony, and in some cases, improved predictions. AGESCORE was validated using data from burn patients; one must be aware of possible sources of lack of fit in other applications. Assessment of lack of fit may be performed using the deviance tests described in this article or using a variety of other techniques (e.g., Hosmer and Lemeshow).[11] Of course, any significant lack-of-fit test should be accompanied by appropriate graphs to assess magnitudes of deviation, as statistical significance does not necessarily imply biological significance.

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