Revista do Instituto de Medicina Tropical de São Paulo

PREDICTIVE FACTORS OF MORTALITY IN BURN PATIENTS

Jefferson Lessa Soares de MACEDO(1) & João Barberino SANTOS(2)

SUMMARY

Burn mortality statistics may be misleading unless they account properly for the many factors that can influence outcome. Such estimates are useful for patients and others making medical and financial decisions concerning their care. This study aimed to define the clinical, microbiological and laboratorial predictors of mortality with a view to focus on better burn care. Data were collected using independent variables, which were analyzed sequentially and cumulatively, employing univariate statistics and a pooled, cross-sectional, multivariate logistic regression to establish which variables better predict the probability of mortality. Survivors and non-survivors among burn patients were compared to define the predictive factors of mortality. Mortality rate was 5.0%. Higher age, larger burn area, presence of fungi in the wound, shorter length of stay and the presence of multi-resistant bacteria in the wound significantly predicted increased mortality. The authors conclude that those patients who are most apt to die are those with age > 50 years, with limited skin donor sites and those with multi-resistant bacteria and fungi in the wound.

KEYWORDS: Burns; Infection; Mortality; Survival.

INTRODUCTION

Burn injury is very common and affects approximately one per cent of the general population every year. The vast majority of burn injuries are minor although painful. In contrast, a small number of individuals receive massive, deep burns that are accompanied by permanent disfigurement or death[9].

Traditionally, burn area and patient´s age have been employed as the primary predictors of mortality after thermal injury. Other factors identified during the course of hospitalization also may help to predict accurately those patients who are likely to die[18]. Thus, it seems unlikely that mathematical models based solely on these two, or on any other two indices of burn mortality, can fully describe this complex problem.

Recently developed multifactorial models of burn mortality rates omit microbiological aspects of burn wounds from their calculations[18]. In the present study, we analyzed these and other factors to determine predictors of mortality in burn patients. We compared initial presentation characteristics, and microbiological and laboratory tests during the course of hospitalization in surviving and non-surviving burn patients.

MATERIALS AND METHODS

The study population consisted of 278 burn patients consecutively admitted to the Burn Unit of the Hospital Regional da Asa Norte, Brasília, Brazil, between February 2004 and February 2005. Data were obtained at admission and were recorded prospectively during the hospital course. The patients were followed until discharge or death.

Survivors were compared to non-survivors to determine what factors might predict a high risk of mortality. More than 90% of the patients were admitted to the hospital within 48 hours of burn with an equal distribution between survivors and non-survivors. Patients readmitted for reconstructive or other care of the same burn, and patients transferred elsewhere for acute care, were excluded.

The variables chosen to predict mortality during the hospital course included age, gender, presence of inhalation injury, total burn area, development of infection, flame injuries, surgical intervention (skin grafting), self-damage, need for blood transfusion, presence of multi-resistant bacteria in wound, presence of fungi in wound, serum albumin level ≤ 2.0 mg/dL, platelet count $< 100,000/mm^3$, and length of hospitalization.

Burn area was estimated from age-appropriate diagrams by one of the attending physicians. The total body surface area burned (TBSAB) was calculated from LUND & BOWDER's chart, adding percentages of dermal and subdermal burns[8].

Since 1980, patients having partial skin thickness burns covering less than 25% of the body surface area, were not generally admitted to the Burns Unit if they were adults, or less than 10% if they were

(1) Hospital Regional da Asa Norte, Secretaria de Saúde do Distrito Federal, SMHN, AE 1, Bloco A, 70000-000, Brasília, DF, Brasil.
(2) Núcleo de Medicina Tropical, Universidade de Brasília, Brasília, DF, Brasil.
Correspondence to: Jefferson Lessa Soares de Macedo, SQS 213 Bloco 'H' Apto. 104, Asa Sul, 70292-080 Brasília, DF, Brasil. E-mail: jlsmacedo@yahoo.com.br

children. Patients with full skin thickness burns of small extent (≤ 5% of body surface area), were also treated as outpatients until the wound was ready for excision and grafting by members of the plastic surgery team.

Fluid replacement was provided according to a modified Parkland formula. Plasma was given from the second day on. Central venous catheters were placed in the subclavian or femoral vein at the discretion of the anesthetist. Early excision and skin grafting were performed within the first five days in the case of full thickness burns when the patient's condition permitted.

When at admission, inhalation injury was suspected for any reason (such as facial burn, stridor, exposure to heavy smoke, burned nasal vibrissae, etc.), the following variables were also analyzed: presence or absence of soot in or edema of the larynx or laryngopharynx on direct or endoscopic examination, and presence or absence of abnormal carboxyhemoglobin concentrations (≥ 5%). Patients judged clinically to require neither laryngoscopy nor arterial pH or gas analysis were coded as normal for these variables.

Microbial cultures were processed according to standard methods. Bacteriological isolation was performed at the Microbiology Laboratory of the Hospital Regional da Asa Norte, Brasília. Swabs were dipped in Stuart´s transport medium then plated on blood agar, chocolate agar, MacConkey, and Sabouraud´s dextrose agar media (Difco). After incubation for 18-48h at 37 °C, the isolates were identified using conventional protocols. Afterwards, the sensitivity to the antibiotics was accomplished by automated method (BioMérieux Vitek). Confirmation of the precision and accuracy of the procedures used to evaluate antimicrobial susceptibility was performed using ATCC (American Type Culture Collection) standard strains. When isolated *Staphylococcus aureus* oxacillin resistant, *Acinetobacter.* sp and *Pseudomonas aeruginosa* multi-resistant were confirmed by disc using an agar diffusion method according to the guidelines established by the former NCCLS, now CLSI[17].

Fungal cultures were obtained on Sabouraud dextrose agar (Difco) and on Mycogel agar (Oxoid) at 37 °C and observed daily for 20 days. Fungal characterization was performed by the germ tube test, by morphological examination, and by an automated method (Vitek YBC yeast identification system, BioMérieux Vitek, Inc., MI, USA)[3].

Infections in all patients admitted and treated for burn injury were registered prospectively, according to previously defined criteria[12]. All infections were registered, starting on the day of admittance. Any infection manifested during the management of a burn victim was followed carefully. Only burn wound infections already present at admission were excluded. Infections were grouped in three major classes: bloodstream infection (BSI), pneumonia and burn wound infection. The diagnosis of infection in the burn patient was based on clinical and laboratory parameters. The criteria for infection were based mainly on those suggested by the Centers for Disease Control, Atlanta, USA[4].

Infection was suspected when a patient showed signs of disorientation, hyperpyrexia or hypothermia, circulatory failure, petechial hemorrhage, black or dark discoloration in a previously clean appearing burn wound, early and rapid eschar separation, bleeding into the subcutaneous tissue, and increasing edema in surrounding areas or leukocytosis in white blood cell counts.

All values are expressed as mean ± standard error or as percentages. Each variable was tested for differences between survivors and non-survivors by univariate statistical methodology with significance accepted at p < 0.05 (Chi squared test, Student's t test or Mann-Whitney test where appropriate). All variables significant by univariate analysis were included in the multivariate analysis. A pooled, cross-sectional, multivariate logistic regression analysis was used to test the hypothesis that the variables employed affected the probability of mortality. This analysis was performed using the Statistical Analysis System Package (SAS, Cary, NC). The dependent variable was mortality, and the model determined the log odds of increased mortality given the independent variables. Stepwise logistic-regression analysis was performed with forward selection to evaluate predictive factors for death. This analysis resulted in a final prediction model. Additionally, the model was evaluated using receiver operating characteristic (ROC) curve analysis.

This study was approved by the Ethics Committee of the State Secretariat for Health, Brasília, Federal District.

RESULTS

Two hundred and seventy-eight patients with burns, admitted to the Burn Unit of the Hospital Regional da Asa Norte, Brasília, Brazil, between February 2004 and February 2005, were included in the study. One hundred and sixty-seven were males and 111 were females. Mortality rate was 5.0%. The mean age of the 278 patients was 24 years (range 1-82 years), and mean total burn size area body (TBSAB) was 14% (range 1-100%). One-hundred and fifty-two (54.7%) patients had flame injuries, 96 (34.5%) were scald injuries, 25 (9%) electrical injuries and five (1.8%) chemical injuries. Inhalation injury was present in seven (2.5%) patients.

Two-hundred and forty-five patients stayed less than 72 h in the unit. The mean length of stay was 12 days (range 1-86 days). Two-hundred and thirty-four patients were admitted on the day of injury, and eight had been treated at another hospital before admission.

Fourteen (5.0%) patients died during their stay in the burn unit. The mean age of these patients was 37.9 ± 27.1 years. Mean TBSAB was 47.5 ± 28.6%. Ten patients presented signs of severe infection at the time of death. The main contributing factors to death in patients without infection were pulmonary and cardiac failure.

A comparison between surviving and non-surviving patients is provided in Table 1. Non-surviving patients were significantly older and had larger burns. Non-surviving patients also stayed longer in the unit. With regard to the cause of burn, non-survivors suffered significantly more flame injuries and self-damage. Further, non-surviving patients needed more frequently catheters and blood transfusion. In relation to laboratory findings, non-surviving patients presented more frequent anemia, hypoalbuminemia, thrombocytopenia and a lower mean number of CD4+ cells (lymphocytes). The isolation of multi-resistant bacteria or fungi in the wound was more likely in non-surviving patients. Also, non-survivors had significantly more infectious complications.

Table 1

Comparison between surviving and non-surviving patients in a burn unit (Hospital Regional da Asa Norte, Brasília, F.D.)

	Non-survivors	Survivors	p
Number of patients	14	264	
Age (years, mean, standard deviation)	37.9 ± 27.2	23.2 ± 20.0	0.007
Age > 50 years (% patients)	35.7	12.1	0.031
Female gender (% patients)	40.5	42.9	0.597
Flame injuries (% patients)	85.7	53.0	0.016
TBSAB % (mean, standard deviation)*	47.5 ± 28.6	11.7 ± 10.4	< 0.001
Self-damage (% patients)	42.9	3.4	< 0.001
Length of stay (days, mean, standard deviation)	17.2 ± 14.9	11.9 ± 9.3	0.039
Three or more catheters (% patients)	57.1	3.0	< 0.001
Necessity for transfusion (% patients)	64.3	26.9	0.008
Multi-resistant bacteria in wound (% patients)	78.6	28.0	< 0.001
Fungi in wound (% patients)	50.0	13.3	0.001
Hemoglobin ≤ 9 g/dL (% patients)	57.1	26.9	0.008
Serum albumin ≤ 2.0 g/dL (% patients)	42.9	4.5	< 0.001
Platelets ≤ 100,000 (% patients)	42.9	1.1	< 0.001
Infectious complications (% patients)	92.9	27.6	< 0.001
Number of operations (mean, standard deviation)	1.34 ± 0.47	1.13 ± 0.35	0.104
Number of CD4+ cells (mean, standard deviation)	177 ± 52	485 ± 258	0.05

* TBSAB = Total Burn Size Area Body.

Fifty-seven of 84 blood-cultured patients (67.9%) presented 72 episodes of BSI. Their mean age was 25.2 ± 23.1 years. Their mean TBSAB was 29.1 ± 22.1%, and their mean length of stay was 20.9 ± 3.9 days.

The mortality rate for patients with verified and strongly suspected BSI (21%, 12/57) was twenty times greater than for the non-septic patients (0.9%, 2/221) (p < 0.0001).

In regard to other infectious complications, 18 patients developed pneumonia and seven of 18 patients died from pneumonia. Forty-nine patients had burn wound infections.

All independent variables except gender and number of surgical operations were significant by univariate analysis and significantly influenced mortality rate. When these variables were combined using the logistic regression, the significant independent variables that remained were TBSAB, age > 50 years, length of stay, and isolation of fungi or multi-resistant bacteria in the wound. The log odds of high mortality is expressed by the following equation fitted from the data, where (p) is the conditional probability of mortality, and fungi or multi-resistant bacteria is 0 or 1 corresponding to the absence or presence of these micro-organisms in the wound, respectively.

Logito (p) = -6.78 + 0.10*TBSAB%* + 2.41*Fungi* + 2.83*Age > 50* - 0.09*Length of Stay* + 2.15 *Multi-resistant bacteria*

This model predicts that the probability of death increases with larger TBSA burned, age > 50 years, presence of fungi or multi-resistant bacteria in the wound, and shorter length of stay (Tables 1 and 2).

The causes of death were sepsis related complications in ten

Table 2

The set of five independent factors that best discriminated between survivors and non-survivors as determined by a stepwise discriminant analysis, and their relationship to survival

Predictive factor	Odds Ratio (CI 95%)*	p
Age > 50 years	16.90 (2.71-105.91)	0.003
TBSAB %	1.10 (1.06-1.15)	< 0.001
Length of stay	0.91 (0.84-0.99)	0.037
Multi-resistant bacteria in wound	8.54 (1.12-65.01)	0.038
Fungi in wound	11.16 (1.85-67.39)	0.009

* CI denotes confidence interval

patients, wound infections in two, and pneumonia in two patients.

Figure 1 presents the ROC curve for this logistic regression model. ROC analysis graphically represents the sensitivity and specificity of the model in predicting mortality. The area under the curve was 96.9% (95% confidence interval was 94.2 to 99.6%).

DISCUSSION

There is no doubt that the traditional factors of burn size and patient age are important determinants of mortality rate in burned patients, but so are many other factors. Initially, BULL & SQUIRE[2] defined their prediction of mortality after burn based on age and burn area. Nearly 50 years later, the importance of other factors such as pre-admission shock[6], inhalation injury[19,21], sepsis[10,15] and thrombocytopenia[7] have been identified. Over time, various reports have shown progressive

Table 3
The effect of added predictive factors on the probability of a fatal outcome using multifactorial probit analysis

		Hypothetical cases and predictive factors present*			
Age > 50 years	TBSAB %	Fungi in wound	Multi-resistant bacteria in wound	Length of stay	Probability (%) of mortality (CI 95%)
-	2	-	-	29	0.01 (0 - 0.32)
+	13	-	+	14	14 (2.6 - 50.5)
-	25	+	+	11	30.9 (9.7 - 64.9)
-	50	-	+	6	40.9 (10.8 - 79.9)
-	100	-	-	3	92.9 (36.5 -99.7)

* A minus sign indicates that the predictive factor is not present; a plus sign indicates that the predictive factor is present.
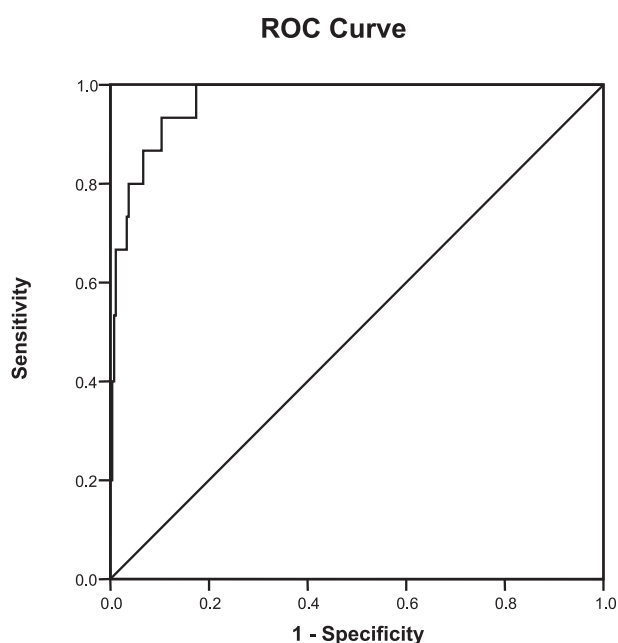
ROC Curve

Fig. 1 - Receiver operating characteristic (ROC) curve analysis of the logistic regression model predictive for mortality.

improvement in mortality with advances in burn care[1,5,16]. Treatment in specialized burn centers has influenced survival after burns. New and innovative techniques such as early excision and grafting, institution of appropriate nutritional support, aggressive therapy for respiratory injury, and prompt recognition and treatment of burn-related infections have played major roles in burn survival.

The mortality rate in our study of burn patients is consistent with those reported in other studies[2,5,10,18]. Mortality rate among the patients who survived for two weeks was 1.8%, which was substantially lower than the overall rate of 5.0%. A shorter duration of hospitalization was associated with death. However, this finding must be viewed with caution since probably it is not a predictor of mortality but rather a consequence of the outcome.

Estimation of which patients might be expected to die, even with modern critical care techniques and burn wound management, is important because aggressive support should not be removed from a patient who is fully able to survive and lead a productive life.

Other studies examining the relationship between age and mortality have shown a marked increase in mortality in children younger than 2 years old compared to those older than two years of age[22]. However, this was not confirmed in our study because the children with massive burn areas were referred to another hospital. Patient age >50 years old was highly significant by univariate analysis, and was corroborated by multivariate analysis. Increasing age was one of the variables that remained significant throughout the development of the cumulative model, and is in keeping with larger studies[16,22].

Burn area is also a highly significant variable affecting mortality, even in this limited patient group. The increasing severity of injury through more skin loss exposes the largest burns to more surgical operations and more complications, thus increasing mortality rate. With increasing burn area, the degree of skin loss renders the available donor skin area very small, and multiple operations using the same area as a donor site will be required to cover the entire, large wound area. In the multivariate logistic regression analysis, the most significant contributor to mortality was burn area.

Inhalation injury is a strong predictor of mortality[16,19,21]. However, we could not confirm this owing to the small number of patients in our group with inhalation injury. Further, this also may be because of multiple improvements in the clinical management of smoke inhalation injury during the current period, or that the mortality rate for large burn areas is high, and the effect of inhalation injury identified in smaller burns is masked by the increased risk of mortality in the case of large burns. In patients with burns covering extensive areas of the body surface, the co-morbid effect of inhalation injury is largely obscured by that of the burn injury *per se*. However, another factor may be the current inability to quantify inhalation injury. That is, the diagnosis of inhalation injury is simply "yes" or "no", and there has been no way to determine the severity of inhalation injury. Another explanation may be the protective effect offered by massive cutaneous injury and the subsequent immunodeficient state on development of lung injury. In animal studies, it has been shown that receiving a burn before smoke inhalation injury reduces lung damage compared to animals receiving the burn after smoke injury[14].

Historically, the development of infectious complications in burns has been a significant cause of mortality[12,15]. During the course of

hospitalization, the development of infectious complications, especially sepsis, is a harbinger of a poor outcome[10,20]. The mortality rate for patients with sepsis (21%, 12/57) was twenty times greater than for non-septic patients (0.9%, 2/221) (p < 0.0001).

In this study, the development of infectious complications was significantly different between survivors and non-survivors by univariate analysis; however, we could not confirm the same difference using multivariate statistics. This finding does not diminish the importance of infectious complications in the burn patient, because we have shown that it does occur more often in non-survivors, and should be avoided vigorously if possible and combated aggressively when encountered[13].

Regarding laboratory findings, non-surviving patients presented more frequent anemia, hypoalbuminemia, thrombocytopenia and a lower mean number of CD4+ cells (lymphocytes). The lower hematocrit in the non-survivors represents blood loss from operations and hemolysis, although confirmatory measurements of blood hemochromogens were not performed in these patients. Thrombocytopenia and hypoalbuminemia are clear harbingers of multi-organ failure in burn patients that often lead to mortality not only in burn patients, but also in all other disease and injury processes[20]. These variables should emphasize their proper use and interpretation as indicators of organ dysfunction. In this study, the development of anemia, hypoalbuminemia, thrombocytopenia and lower mean number of CD4+ cells (lymphocytes) was significantly different between survivors and nonsurvivors by univariate analysis; however, the same difference was not confirmed using multivariate statistics.

An analysis of mortality using univariate statistics in these patients can be misleading because of interactions between the variables. Multivariate logistic regression can be used to examine the relationship among independent variables in determining survival in burn patients, and the equation presented can be used to calculate the risk of mortality in such patients. In an example of a 51-year-old patient with 13% TBSA and hospitalized for 14 days and showing multi-resistant bacteria in the wound, the predicted probability of death by our equation is 14%. This model includes not only demographic variables, but also variables obtained throughout the hospital course. Thus, knowledge of the fungal and bacterial flora of burn wounds, their prevalence, and bacterial resistance, is of crucial importance for fast and reliable therapeutic decisions, decreasing mortality rate. The spectrum of infectious agents varies from time to time and from place to place. Thus, it is desirable to undertake periodic reviews of the bacterial and fungal flora of burn wounds so that preventive strategies can be modified as necessary[11].

Microbiological surveillance of burn patients when performed routinely helps in learning about the types of microrganisms and facilitates the choice of antibiotics. Each individual burn unit varies in its baseline population of micro-organisms over time, and generalizations from one unit may have little applicability to others.

We constructed an ROC curve from the data collected during the study period. The closer the curve to the vertical y-axis, the better the ability of the logistic model to discern true positives from false positives. Thus, the larger the area under the ROC curve, the better the test performs. In this study, the area under the ROC curve was 96.9%, indicating that this logistic regression model exhibits a notable discriminative power for predicting mortality.

An analysis of mortality using multivariate logistic regression identifies those factors that significantly contribute to a poor outcome and informs where to focus further clinical and research activities. The resultant five-factor model significantly improved estimation of the probability of a fatal outcome when compared to probit analysis based on the traditional factors of age and total burn area.

One advantage of objective estimates of the probability of death is that they help in understanding the relative influences of specific prognostic elements. No previous study has reported on microbiological aspects as contributors to mortality rate. This study emphasizes the marked degree to which microbiological aspects contribute to mortality.

RESUMO

Fatores preditivos de mortalidade em queimaduras

As estatísticas de mortalidade em queimaduras podem ser incompletas se não levarem em consideração vários fatores que podem influenciar o óbito. Tradicionalmente, apenas a extensão da queimadura e a idade do paciente têm sido usadas como preditores de mortalidade em vítimas de queimaduras. Estas estimativas são úteis na assistência aos pacientes, interferindo em decisões médicas e financeiras no cuidado desses doentes. O objetivo desse estudo foi definir os preditores clínicos, microbiológicos e laboratoriais de mortalidade em pacientes queimados. Os autores realizaram uma análise univariada e multivariada de várias variáveis independentes para determinar os fatores preditivos de mortalidade em queimados. A taxa de mortalidade foi de 5,0%. A idade mais avançada, a extensão das queimaduras, a presença de fungo na ferida queimada e a presença de bactéria multiresistente na ferida foram os fatores que mais aumentaram significativamente a mortalidade em pacientes queimados. Os autores concluem que os pacientes com maior probabilidade de óbito são os pacientes com idade superior a 50 anos, com queimaduras extensas, presença de fungo e bactéria multiresistente na ferida.

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