Who By Fire? Sepsis in the Adult Burn Patient: Prognostic Factors

Yoav Y. Pikkel MD[1,2], Yoav A. Levy MD[2], Yitzchack Ramon MD[1], Tal Tobias MD[1], and Assaf A. Zeltzer MD PhD FCCPlast[1,2]

[1]Department of Plastic and Reconstructive Surgery, Rambam Health Care Campus, Haifa, Israel
[2]Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

ABSTRACT **Background:** Modern medicine has improved survival rates in burn care. However, this progress has led to a new challenge of sepsis, which has become the leading cause of death in burn patients, accounting for over 50% of mortality. The diagnosis and treatment of sepsis in the burn care unit pose significant challenges due to the hypermetabolic state of the patient, which can mask septic signs and symptoms. This situation underscores the urgent need for improved strategies in sepsis management in burn patients.

Objectives: To assess the predictors of morbidity and mortality among severe burn patients.

Methods: Rambam Health Care Campus is the referral center for burn patients in northern Israel. We reviewed 5 years of patient records, noting information regarding sepsis, laboratory results, infections, and overall morbidity and mortality. In addition, a comparative cohort of burn patient records without sepsis was compared.

Results: Thirty patients had recorded sepsis. Total and direct bilirubin were associated with higher mortality ($P < 0.05$). Elevated white blood cell count and platelet count at admission were also associated with mortality ($P < 0.05$). The most prominent burn areas were the arms, head, and legs. The leading cause of injury was fire, followed by an explosion. Burns of total body surface area ≥ 40% was associated with sepsis.

Conclusions: Sepsis is a complex challenge when diagnosing and treating burn patients. Identifying specific traits and prognostic factors is crucial to adequately treat these patients. Research in burn care and sepsis management is essential.

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Burns caused by trauma are a significant burden on the healthcare system. With modern medicine, the mortality rate has declined constantly in the past decades and is currently 4.8 to 100,000 cases [1]. Nevertheless, burn mortality remains high, with over 180,000 deaths annually [2].

Burn mortality in the first 24–72 hours can be attributed to anoxic damage, hemodynamic instability, or carbon-monoxide (CO) poisoning. Following that time frame, infection is associated with approximately 75% of burn-caused mortality [3]. Some have noted the gender-specific nature of sepsis [4], race, age, and cause of injury [5] as possible identifiers for sepsis-prone patients. However, biomarkers have not yet been identified in Burn patients. The hypermetabolic state of the patient [6] makes sepsis diagnosis and initiation of treatment a challenge to physicians and the burn-treatment team.

In this study, we assessed the predictors of morbidity and mortality among severe burn patients.

PATIENTS AND METHODS

Rambam Health Care Campus is the burn care center for the north of Israel and the referral center for over 2.4 million people. Rambam has a modern intensive care unit (ICU) offering cutting-edge treatments for burn patients.

Burn patient records were collected from patients admitted to the hospital between 2016 and 2021. Inclusion criteria were patients with burns over 20% of total body surface area (TBSA) and recorded sepsis. The exclusion criteria were patients under 18 years of age. Sepsis was diagnosed based on the quick sequential organ failure assessment score (qSOFA)[3]2(9), combined with a suspected or documented infection.

Data recorded included demographic characteristics such as sex, age, prior medical history; burn features including TBSA, cause, areas; laboratory results; detection of bacteria or fungus; length of stay (LOS); time after injury; and discharge status.

A cohort of age- and sex-matched burn patients hospitalized during the same timeframe as the sepsis group but not presenting with sepsis was also reviewed. We extracted the same data on these patients to distinguish the sepsis-prone group from the non-sepsis group.

Statistical analyses were performed using R Statistical Software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Chi-square and Fisher's exact test were used for categorical variables. For continuous variables, Wilcox-Mann-Whitney test and Student's *t*-test were used. Last, for the correlation between variables, Pearson's test was used.

RESULTS

During the research timeframe, 30 patients were diagnosed with sepsis. The control cohort included 28 patients with burns and no diagnosis of sepsis. Patients in both groups were usually healthy, and most patients had no medical history. Table 1 shows the selected demographic and burn characteristics of both groups.

The average age of the patients was 48.89 ± 17.75 years. There was no difference in age or sex in the sepsis vs. non-sepsis groups.

Table 1. Demographics and injury characteristics

Characteristic	Overall	Non-sepsis	Sepsis	*P*-value*
Number	58	28	30	
Department				
ICU	13 (22%)	2 (7.1%)	11 (37%)	**0.007**
Plastic surgery	45 (78%)	26 (93%)	19 (63%)	
Sex: Female	10 (17%)	5 (18%)	5 (17%)	
TBSA				
10–19%	1 (1.8%)	0 (0%)	1 (3.4%)	
20–29%	16 (28%)	11 (39%)	5 (17%)	
30–39%	13 (23%)	10 (36%)	3 (10%)	
40–49%	13 (23%)	3 (11%)	10 (34%)	
50–59%	5 (8.8%)	2 (7.1%)	3 (10%)	
60–69%	5 (8.8%)	1 (3.6%)	4 (14%)	
70–79%	1 (1.8%)	0 (0%)	1 (3.4%)	
> 80%	3 (5.3%)	1 (3.6%)	2 (6.9%)	
Total over 40%	27	7	20	**0.004**
Average TBSA	42.1 ± 17.7%	36.6 ± 14.9%	47.4 ± 18.8%	**0.005**
Cause				
Fire	42 (72%)	18 (64%)	24 (80%)	0.072
Chemical burn	5 (9.3%)	3 (11%)	2 (7.4%)	0.18
Electrical	2 (3.7%)	1 (3.7%)	1 (3.7%)	0.9
Scald	5 (9.3%)	5 (19%)	0 (0%)	**0.019**

ICU = intensive care unit, TBSA = total body surface area

*Bold signifies statistical significance

SEPSIS VS. NON-SEPSIS GROUPS ANALYSIS

Sepsis patients were more often hospitalized in the ICU during parts of their hospitalization (11 vs. 2, $P = 0.007$). There was no difference in the body parts burned in the sepsis vs. non-sepsis groups. TBSA over 40% was associated with sepsis (21 vs. 9, $P = 0.004$). Fire was the most common cause of burns, listed as the cause in 13 patients in the sepsis group and 14 in the non-sepsis group. Scald was the cause in only five patients, all in the non-sepsis group ($P = 0.021$).

Bacteria were isolated in the sepsis and non-sepsis groups, usually from a wound swab. There was no notable difference in the sepsis vs. non-sepsis patients, with gram-positive bacteria isolated in 20 patients (11 vs. 9, sepsis vs. non-sepsis, respectively) and gram-negative bacteria isolated in 36 patients (19 vs. 19). Thirteen patients in the sepsis group died due to sepsis. Two patients in the non-sepsis group died from reasons other than sepsis.

There was no notable difference in the bloodwork results in the sepsis vs. non-sepsis groups, with both groups presenting with leucocythemia, elevated C-reactive protein (CRP), and procalcitonin.

SEPSIS SURVIVAL VS. SEPSIS MORTALITY ANALYSIS

The sepsis survivors were younger than the sepsis mortality group (40 ± 16.3 years vs. 55 ± 16.9 years, $P = 0.014$). In addition, two of the patients surviving sepsis were females, vs. three who died of sepsis. There was no notable difference between the groups in TBSA, organs involved, or cause of burns.

Bloodwork at admission revealed that patients who later died had higher platelets count (326 vs. 183, $P = 0.025$), lower alanine transferase (ALT) (18 vs. 31, $P = 0.044$), and more significant leucocythemia (18,000 vs. 12,000, $P = 0.028$). When examining values of laboratory tests taken immediately after a diagnosis of sepsis, mortality group patients showed higher values of direct bilirubin (0.66 vs. 0.2, $P < 0.001$) and total bilirubin (1.63 vs. 0.54, $P = 0.002$). Furthermore, mortality group patients had a high alkaline phosphatase (ALP) at diagnosis of sepsis (166 vs. 60, $P = 0.041$). This difference was not noted at admission.

Mortality group patients had no previous medical history, which could have caused fragility in the patient. Only a single patient in the mortality group had kidney failure before hospitalization. In contrast, survivors included two active smokers at the time of diagnosis, a patient with asthma, and a patient after a cerebrovascular accident).

There was no difference in the cause of the infection, with 53% of survivors and 69% of the mortality group having a gram-positive bacterial infection. Methicillin-resistant *Staphylococcus aureus* was isolated in one patient who survived sepsis and none in the mortality group. Three patients in each group had a fungal infection.

The relevant characteristics of the groups are in Table 2.

DISCUSSION

SEPSIS VS. NON-SEPSIS GROUPS

Higher TBSA was found to be the primary predictor of sepsis. That finding is unsurprising, as higher TBSA is a factor in higher mortality [7]. Furthermore, most septic patients were hospitalized in the ICU. Nevertheless, ICU admission might have been a factor in sepsis. Most patients in the ICU are intubated, increasing the probability of developing ventilation-associated pneumonia. Sepsis in a burn patient is often caused by pneumonia [8]. Fire and flame burns were not associated with a higher percentage of mortality in our cohort, in contrast to other studies [9]. Our results could be due to our case-match design, which matched a cause or TBSA in each group. Scald, however, was not observed in the sepsis group, which may be due to the limited TBSA in our scald patients, thus mitigating the risk of bacteria penetrating the bloodstream.

We found no correlation between body parts burned and the development of sepsis. This result shows the im-

Table 2. Selected laboratory results at admission and following sepsis diagnosis

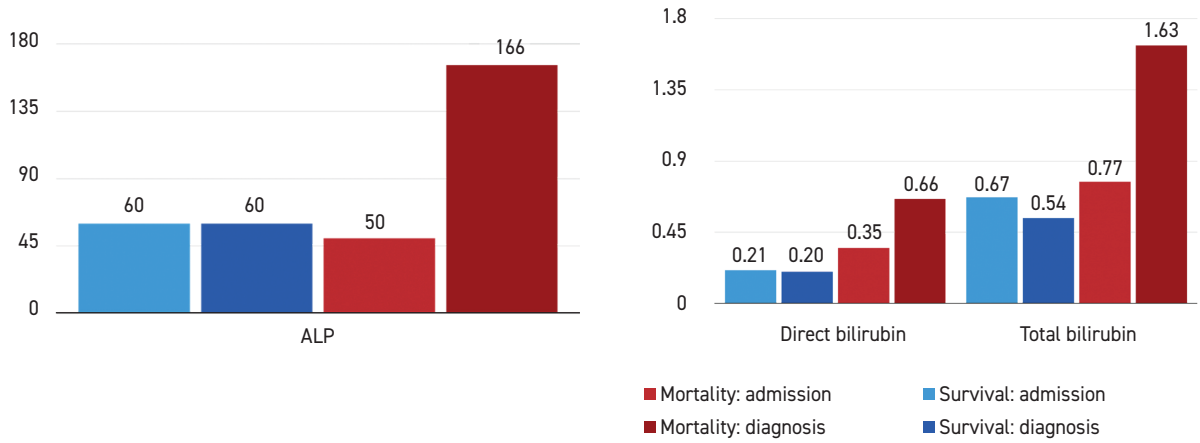
Characteristic	Died, N (IQR)	Survived sepsis, N (IQR)	*P*-value*
Number	13	17	
At admission			
Total bilirubin	0.77 (0.67–1.40)	0.67 (0.42–1.01)	0.2
Direct bilirubin	0.35 (0.20–0.64)	0.21 (0.14–0.30)	0.079
WBC	18 (14–28)	12 (10–18)	**0.028**
ALT	18 (9–29)	32 (29–38)	**0.044**
Platelet	326 (238–359)	183 (151–251)	**0.025**
Creatinine	1.09 (0.75–1.43)	0.85 (0.70–0.97)	0.1
CRP	26 (13–31)	7 (7–81)	> 0.9
ALP	50 (40–73)	60 (50–85)	0.3
pH	7.31 (7.19–7.34)	7.33 (7.23–7.38)	0.3
Albumin	3.45 (3.00–3.62)	3.10 (2.55–3.53)	0.3
At diagnosis			
Total bilirubin	1.63 (1.06–2.49)	0.54 (0.27–0.84)	**0.002**
Direct bilirubin	0.66 (0.50–1.47)	0.20 (0.14–0.30)	**< 0.001**
WBC	9.7 (5.0–16.1)	6.9 (4.4–10.9)	0.2
ALT	34 (18–68)	31 (24–44)	> 0.9
Platelet	92 (85–108)	101 (80–132)	0.6
Creatinine	1.08 (0.66–1.90)	0.67 (0.51–0.82)	0.065
CRP	164 (156–173)	23 (16–27)	0.2
ALP	166 (70–230)	60 (48–93)	**0.041**
pH	7.34 (7.28–7.41)	7.38 (7.31–7.42)	0.4
Albumin	2.50 (2.10–3.10)	2.60 (1.58–3.12)	0.7
Days until sepsis	5 (3–15)	3 (2–5)	0.11

ALP = alkaline phosphate, ALT = alenine transferase, CRP = C-reactive protein, IQR = interquartile range, M = median, pH = potential of hydrogen, WBC = white blood cell

*Bold signifies statistical significance

Figure 1. Bilirubin and ALP in burn patients at admission and following sepsis diagnosis

ALP = alkaline phosphate



portance of TBSA as one of the predominant factors in developing sepsis [7].

SURVIVING SEPSIS VS. SEPSIS MORTALITY ANALYSIS

Sepsis survivors had several distinguishing factors compared to the sepsis mortality group. At admission, survivors were younger. This phenomenon is observed in other studies examining trauma patients and survival [10]. Higher platelet values and higher leukocyte counts may suggest an underlying illness or a cause of infection. However, these blood count variables are not surprising. Thrombocytes are known to be an acute phase reactant, which rises sharply after an injury [11].

The thrombocyte count in both groups was in the normal range, which limits the ability to induce practical implications based on this test. Leukocytosis can be due to acute injury or can be the beginning of an infection cascade. The values of leukocytes in both groups were not in the normal range. Thus, we cannot suggest it as a prognostic factor. Lower ALT levels might imply initial damage to hepatocytes. However, higher ALT levels have been associated with higher mortality in trauma settings [12]. This initial damage to the liver can implicate a more severe injury in ways a clinical assessment cannot.

Following the diagnosis of sepsis, the two groups had more distinct laboratory values. In addition to lower ALT values at admission, mortality group patients had a higher bilirubin count, both conjugated and total, and higher ALP values. Figure 1 shows bilirubin and ALP at admission and immediately following diagnosis of sepsis.

Bilirubin has been suggested as a prognostic factor in cardiovascular mortality [13]. Adding conjugated bilirubin has improved the accuracy of predicting scales published as the quick sequential organ failure score [14].

The combination of these values suggests a liver failure in those patients. The liver produces acute phase reactants, which are essential in the immune reaction. Furthermore, the liver affects metabolism, immune response, and immunosuppression. Thus, liver failure in sepsis or septic shock is a prognostic factor indicating a severe situation for the patient [15]. Elevated bilirubin, even as a single marker for liver failure, increases the hazard ratio to 1.43 [16].

Procalcitonin levels following diagnosis of sepsis were also a distinguishing factor between the groups. In addition to CRP, procalcitonin is a marker for bacterial and viral infections, with wide usage and moderate-to-high specificity in diagnosing sepsis [17]. The rise in procalcitonin levels can be as early as 3 to 4 hours after the onset of sepsis. Unlike CRP, it is usually not secreted in non-infectious settings [18]. Our findings further emphasize the role of procalcitonin as an early sepsis marker.

Some variables did not reach statistical significance but are worth mentioning. At the time of sepsis diagnosis, mortality group patients had slightly higher levels of creatinine, 1.08 vs. 0.67 ($P = 0.065$). Although both values are in the normal range, the more elevated creatinine can imply the onset of renal failure. In addition, mortality group patients were diagnosed with sepsis on their fifth day of hospitalization, vs. the third day of hospitalization in sepsis survivors ($P = 0.11$). That result might suggest that mortality group patients had an infection with a more resistant nosocomial bacteria, while survivors had a community-acquired infection, which can result from a more assertive treatment.

PRACTICAL IMPLICATIONS

The use of prophylactic antibiotics in a burn patient is controversial. Some studies have found no benefit in implementing prophylaxis in the immediate post-burn settings. However, those trials had lower TBSA (7–10% on average), and the study population was entirely pediatric [19]. A meta-analysis found that a prophylactic regime can be applied in a ventilated burn patient setting, even in the immediate post-burn timeframe, and in severely burned patients [20]. Nevertheless, no trial demonstrated a decline in mortality due to prophylaxis but rather a decrease in the septic events and overall length of stay. The current protocol implemented at Rambam declines regular prophylactic antibiotics and preserves the use of antibiotics either preoperatively or for patients with suspected sepsis.

Our findings contribute to our understanding of potentially life-threatening sepsis. Specifically, the results show the effectiveness and dangers of specific treatments for sepsis (e.g., endotracheal intubation and ventilation), which could ultimately improve patient outcomes and save lives.

STUDY LIMITATIONS

This study has a few limitations. First, bloodwork protocols in the ICU and plastic and reconstructive departments differed, resulting in an inconsistent database. Second, this single-center study was susceptible to local germ flora and its biases. Third, a relatively low number of patients meant good infection control. Nevertheless, the results in a low number of variables, thus limiting the study's statistical power.

CONCLUSIONS

Sepsis in a burn patient is a life-threatening condition. It requires immediate treatment and a multidisciplinary team. Our research highlights several key points. First is the importance of standard blood test protocol, including liver enzymes and bilirubin, since it seems to be the most sensitive single factor for liver failure and severe prognosis.

Second, a high level of suspicion is needed in a severely burned patient. The hypermetabolic state makes diagnosis difficult. At the first sign of suspected sepsis, treatment should begin, including an empiric antibiotic regime and debridement of burned tissue.

Many patients may have presented initially pneumonia, which later developed into life-threatening sepsis. Therefore, physicians should be cautious about initiating and using endotracheal ventilation, as it may be a main point of entry for bacteria.

Prophylactic antibiotics should be considered in very selected cases. In ventilated patients, patients with over 40% TBSA, and patients with very high platelet counts and extreme leukocytosis.

Correspondence

Dr. Y.Y. Pikkel
Dept. of Plastic and Reconstructive Surgery, Rambam Health Care Campus, Haifa 3109601, Israel
Phone: (972-4) 777-2671
Email: y_pikkel@rambam.health.gov.il

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The rightness of a thing isn't determined by the amount of courage it takes.
Mary Renault (1905–1983), British writer best known for her historical novels set in ancient Greece

To want to meet an author because you like his books
is as ridiculous as wanting to meet the goose because you like pate de foie gras.
Arthur Koestler (1905–1983), Austro-Hungarian-born author and journalist