Received: 24 January 2024 | Accepted: 13 May 2024

DOI: 10.1002/ams2.970

ACUTE MEDICINE & SURGERY

WILEY

ORIGINAL ARTICLE

The timing of death in burn patients

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Abstract

Aim: When treating burn patients, some patients die in the chronic phase, even if they overcome the acute phase of the burn. To elucidate the timing of death and its underlying causes among burn patients.

Methods: Patients evaluated were admitted to our burn center between January 2015, and December 2019. Patient information, time, and cause of death were retrospectively collected from their medical records.

Results: Among 342 admitted patients, 49 died. The time of death was as follows: within 24 h ($n=9$), within 3 days ($n=7$), within 1 week ($n=5$), within 2 weeks ($n=4$), within 3 weeks ($n=3$), within 30 days ($n=6$), within 60 days ($n=5$), and after 60 days ($n=9$). The causes of death within 3 days were hypoxic encephalopathy, extensive burns (>80%), severe heat stroke, and acute coronary syndrome. The causes of death after 3 days were sepsis, pneumonia, intestinal ischemia, pancreatitis, and worsening of chronic diseases. The mortality rate was similar for patients ≥65 years of age and those with a burn area of ≥20%, with both groups showing a particularly poor prognosis.

Conclusions: The timing of death in hospitalized burn patients showed a bimodal distribution as approximately 40% of patients who survived the resuscitation period died after 30 days. Elderly patients were at particularly high risk for mortality. In burn care, treatment planning should consider not only the short-term but also the long-term prognosis.

KEYWORDS

burn, elderly, mortality, persistent inflammation immunosuppression and catabolism syndrome

BACKGROUND

As is known by burn physicians, patients with severe burns die because of burn shock, sepsis, acute kidney injury, acute respiratory distress syndrome, among others, during the acute phase of burn. In many intensive care studies, 28-day mortality is considered a meaningful outcome and is, of course, valid in the acute setting.[1–5] In fact, there were some studies that mention about the timing of death in acute phase of burn injuries. They noted that severe burned patients die within 3 days or after 7 days.[6,7] However, we sometimes experience cases in which patients die after surviving the acute phase of the burn injury. According to some research, patients with burns, regardless of their severity, have lower long-term mortality than the general population, but the timing and cause of death during each burn phase period have not been analyzed in detail.[8–11]

Furthermore, it is unknown why patients with severe burns die in the chronic phase of burns. We think that this phenomenon is due to burn-induced persistent inflammation immunosuppression and catabolism syndrome (PIICS). In 2012, Gentile et al. first proposed the concept of PIICS, which is defined by four factors: length of hospital stay, persistent inflammation, immunosuppressive status, and metabolic abnormalities (Data S1). Critically ill patients (e.g., those with sepsis or trauma, or those in the perioperative period) who develop PIICS cannot survive even if they overcome the acute phase.[12] This is similar to what occurs with burn patients. The concept of PIICS has become increasingly prevalent in the intensive care setting, particularly in infectious diseases and postoperative management, but not in the area of burns,[13–15] because prolonged inflammation and hypermetabolism occur in most patients with severe burns.[16] A better understanding of what is happening in the chronic phase of burn injuries would help to save more patients.

We hypothesized that PIICS would be found in burn patients. To prove this, it is crucial to establish the occurrence of patient deaths during the chronic phase, and explain the pathogenesis of burn patients in this phase. The primary goal of this study is to provide clarity on the initial section.

PATIENTS AND METHODS

This was a retrospective descriptive study. The criterion for admission of patients who are transported directly to our hospital is moderate to severe burn injury according to the Artz criteria. Transferred patients are admitted under the Burn Patient Referral Guidelines of the American Burn Association. All patients admitted to our burn center between January 1, 2015, and December 31, 2019, were eligible for inclusion. The following background data were collected from the patients' medical records: age, sex, % total body surface area (TBSA) burned, presence of inhalation injury, transfer from another hospital, and survival outcome at 6 months after injury. Missing data were collected in a phone interview.

To provide an overview of the deceased patients, the age and burn size of all patients were plotted as a scatter plot. To determine the timing of death in the elderly patients and patients with large burns, survival curves were drawn for two groups of patients, one divided by age (cutoff value: 65 years) and the other by burn size (cutoff value: 20% TBSA). For comparing death timing, we defined the period over 28 days as the chronic phase. The time of death was visualized by drawing a Pareto chart. The cause of death and time of death were tabulated for all deceased patients. Data in the tables are presented as the median (interquartile range) or number. R version 3.3.2 (www.rproject.org) was used to draw the Kaplan–Meier curves.

RESULTS

A total of 342 patients were admitted to our burn center during the study period. The background characteristics of the patients are shown in Table 1. More than half of the patients were transferred from other hospitals. A total of 49 patients died within 6 months. Figure 1 shows the relationships between the patient's age and the size of the burn. Older patients and patients with larger burns were more likely to die. We divided the patients into two groups according to age using a cutoff value of 65 years and plotted their survival curves (Figure 2), which showed that the older the patient, the worse was their prognosis. We also divided the patients into large and nonlarge burn area groups according to the size of the burn relative to the TBSA using a cutoff value of 20% (Figure 3). This analysis showed that the larger the burn area, the worse was the prognosis. Finally, we analyzed survival according to the combination of age and burn size. As shown in Figure 4, there were no deaths among nonelderly patients with small burns. The survival curves for nonelderly patients with large burns, and elderly patients with nonlarge burns looked almost the same. The mortality rate was overwhelmingly higher among elderly patients with large burns.

Patient age, burn size, prognostic burn index (PBI), and number of inhalation injuries according to the time of death of the 49 patients are shown in Table 2. Some relatively young patients died more than 1 month after sustaining their injuries. Figure 5 shows the number of patients who died at each time point. The timing of death has a bimodal distribution, with an acute phase occurring within 1 week and a chronic phase beginning after 1 month. The causes of death for all deceased patients are noted in Table 3. In the acute phase, the causes were carbon monoxide poisoning and burn shock. After 1 week,

TABLE 1 Patient background.

	$n = 342$
Age	49 [23, 76]
Sex (M/F)	236/106
Burn size	21 [8, 28]
Burn index	14 [4, 16]
Prognostic burn index	64 [34, 90]
Inhalation injury	107 (31%)
Referred patients	185 (54%)
Death	49 (14%)

Note: Data are shown as the median [IQR] or number (%).
Burn index is determined as: 1/2 second-degree burn +third-degree burn.
Prognostic burn index is determined as: burn index + age.

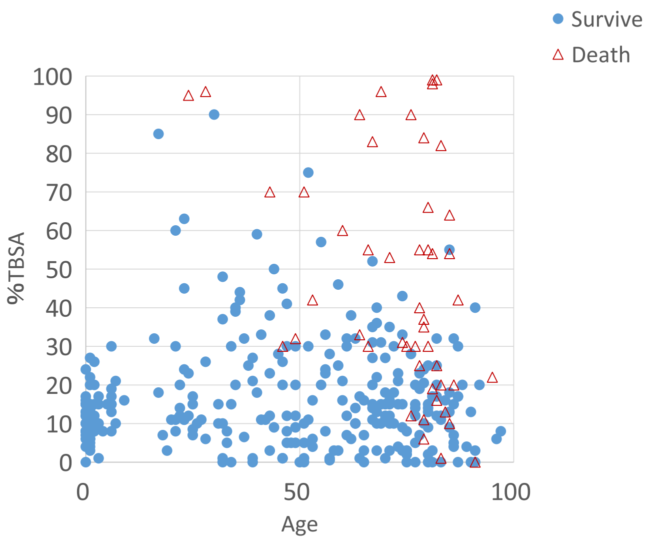

FIGURE 1 Scatter plot of patient age and burn size. The scatter plot of patient age and burn size is stratified into survivors and nonsurvivors. Older patients and patients with larger burns were more likely to die.

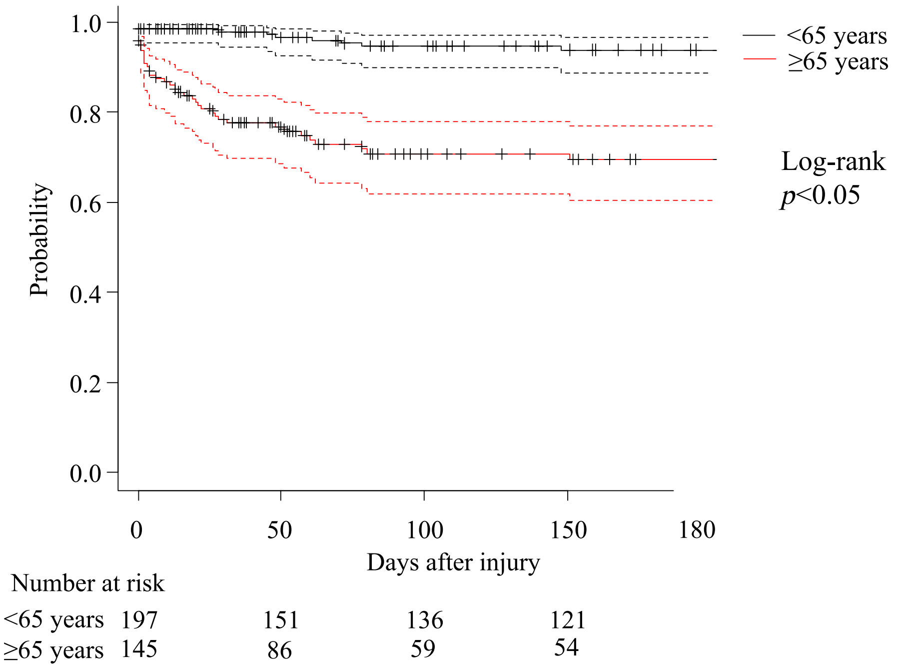

FIGURE 2 Survival curves for elderly and nonelderly burn patients. Survival curves for elderly and nonelderly burn patients are divided using a cutoff value of 65 years. The older the patient, the worse was the prognosis.

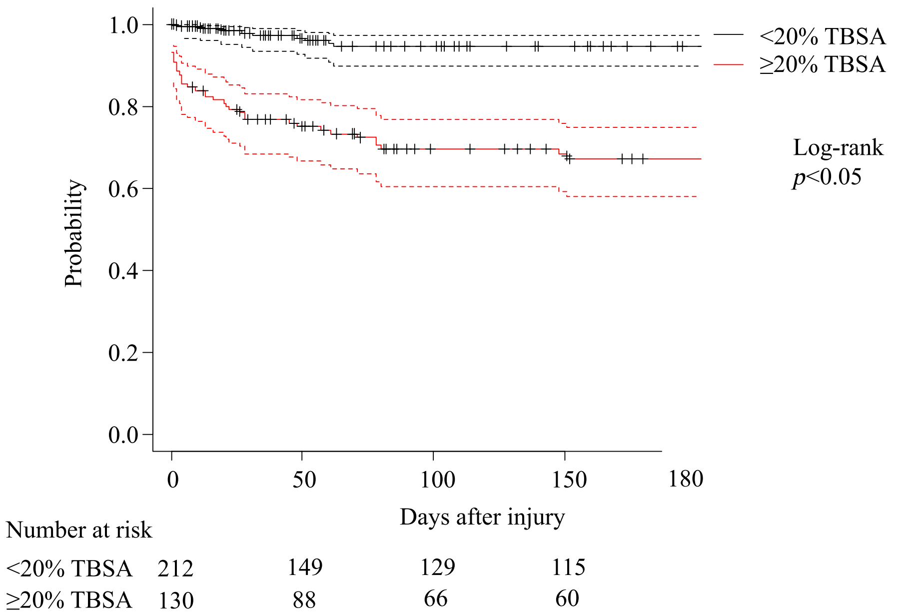

FIGURE 3 Survival curves for patients with large and nonlarge burns. Survival curves for large and nonlarge burns are divided according to the size of the burn relative to the TBSA using a cutoff value of 20%. The larger the burn area, the worse was the prognosis.

the incidence of infectious complications increased, and after 60 days, death occurred due to complications such as pancreatitis and nonocclusive mesenteric ischemia.

DISCUSSION

As we reported, burn injury is one of the major causes of traumatic death.[6] It is still estimated that 6000 fires occur annually in Japan, killing around 1500 people, although the mortality of thermal injury is improving compared to the past.[17,18] The proportion of burn injuries received by the elderly is on the increase, which is due in no small part to the fact that Japan has become a hyper-aged society.[19] It is known that burn area and age are closely related to mortality, as evidenced by the PBI and Baux score.[11,20–22] As described in Advanced Burn Life Support, 20% TBSA is considered the cutoff value for major burns, and initial infusion resuscitation and monitoring are considered necessary. We set the cutoff value of 20%TBSA for large burns. To investigate whether

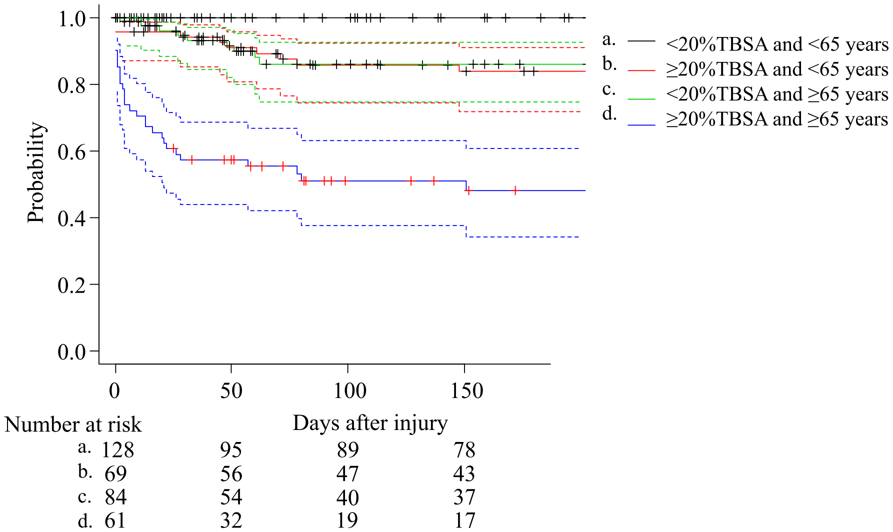

FIGURE 4 Survival curves for age and burn size. Survival curves according to age and burn size. All nonelderly patients with small area burns survived (black line). The survival curves of nonelderly patients with extensive burns (red line) and elderly patients with nonextensive burns (green line) look almost the same. The mortality rate was overwhelmingly higher in elderly patients with large burns.

TABLE 2 Patient characteristics of nonsurvivors.

Days after injury	Number of deaths	Age	%TBSA	PBI	Inhalation injury
≤1	9	75 [64, 82]	90 [60, 98]	165 [120, 179]	9 (100%)
≤3	7	82 [73, 83]	30 [23, 83]	103 [98, 137]	3 (43%)
≤7	5	80 [79, 81]	55 [54, 55]	118 [110, 128]	3 (60%)
≤14	4	81 [79, 84]	32.5 [23, 40]	100 [93, 106]	2 (50%)
≤21	3	82 [78, 85]	31 [24, 37]	103 [97, 113]	0 (0%)
≤30	6	80 [78, 85]	26 [21, 38]	110 [88, 116]	3 (50%)
≤60	6	80 [60, 83]	22 [12, 39]	91 [90, 94]	2 (40%)
>60	9	66 [49, 76]	53 [25, 70]	98 [87, 116]	3 (33%)
Total	49	79 [67, 82]	40 [25, 70]	106 [91, 123]	25 (52%)

Note: Data are shown as the median [IQR] or number (%).
TBSA total body surface area, *PBI* prognostic burn index.

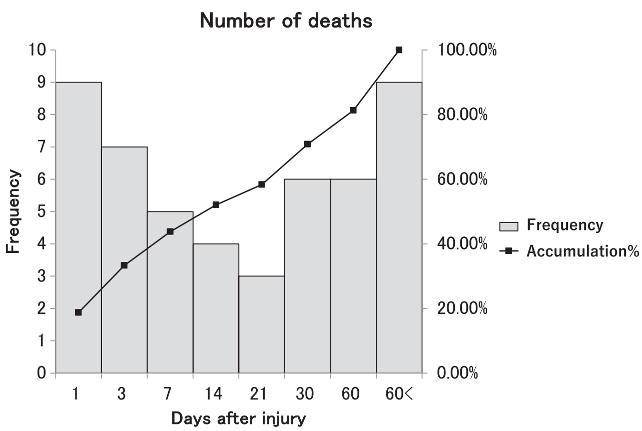

FIGURE 5 Timing and number of patients who died. The timing of death showed a bimodal distribution.

burn area or age has a stronger influence on mortality, we drew survival curves for each factor (Figure 4). For the most part, both curves overlapped, and there was no significant difference in the timing of death. These results suggest that both burn area and age contribute to death to a similar extent. In addition, more deaths occurred among patients with both older age and extensive burns. This result is similar to that of previous studies and supports the utility of the PBI and Baux score as prognostic indicators.[8–10]

Our primary outcome is shown in Figure 5. In our study, 9 of the 49 patients (18.4%) died at >60 days. The timing of death showed a bimodal distribution, with 21 of the 49 patients (42.9%) dying after 1 month. Most studies to date have assessed 28-day mortality, with most deaths occurring within 48 hours in the case of very extensive burns. However, few paper focused on the chronic death, if any, the cause of death is not analyzed in detail.[8,9,11,12,22,23] These studies focused primarily on post-discharge evaluation, not examine the time during hospitalization when so-called PIICS may begin to occur. We analyzed the period around 6 months, when the systemic immune response is likely to be out of balance, and the result proves our hypothesis that there are many deaths even in the chronic phase of burns.

TABLE 3 Causes of death.

	Cause of death									
Days after injury	**CO poisoning**	**Total (>90%)**	**Subtotal (>80%)**	**Extensive (>60%)**	**Heat-stroke**	**Sepsis**	**Pneumonia**	**NOMI**	**Pancreatitis**	**Chronic illness**
≤1	4 (CPA)	5								
≤3	1		3		2					1
≤7				1		4				
≤14						2	1			1
≤21						1	1			1
≤30						1	3			2
≤60						3	3			
>60						4	1	3	1	
Total	5	5	3	1	2	15	8	3	1	5

Note: *CPA* cardiopulmonary arrest, *NOMI* nonocclusive mesenteric ischemia.
Total TBSA>90%, *Subtotal* TBSA>80%, *Extensive* TBSA>60%.

Dvorak et al. reported that the incidence of sepsis in patients with burns to ≥20% of the TBSA ranged from 3 to 30%, making sepsis the most common cause of death among burn patients, with pneumonia the most common cause of sepsis.[24] Pham et al. reported that 8.6% of patients hospitalized for burns had pneumonia, with the risk increasing with advanced age.[25] Furthermore, we experienced the case of a patient with severe burns who developed acute pancreatitis on the 28th day after injury and also reported that subsequent intestinal damage is a problem in patients with extensive burn injuries.[26] All of these reports suggest that many systemic complications, not just wound infection, might occur in the chronic phase of burn injuries.

Previous studies have shown that invasion of the body by sepsis or trauma triggers a danger signal called alarmin, which simultaneously triggers inflammation and anti-inflammatory responses in the body. Systemic inflammatory response syndrome and comparative anti-inflammatory response syndrome refer to a state in which inflammation is out of control and a state of excessive anti-inflammatory activity, respectively. Normally, the balance between inflammation and anti-inflammation is achieved within approximately 2 weeks, and the patient becomes well. However, control of this balance is lost some severely ill patients, and they develop a chronic condition called PIICS.[27,28] As shown in Table 3, the causes of death differed between patients who died in the acute phase and those who died after 1 month. Sepsis, pneumonia, and intra-abdominal complications, which are common in so-called frail patients, were more common in the late phase. The presence of PIICS and other serious diseases in burn patients may result in patients becoming frail, leading to increased mortality in the chronic phase.

Though PIICS existence in burn patients is uncertain, it is necessary to clarify what is occurring in the body of burn patients. Thus, further accumulation of data on the chronic phase of burns is needed to elucidate the pathogenesis of PIICS, and it will be important to seek diagnostic criteria and treatment methods for burn PIICS based on these collected data.

LIMITATIONS

Limitations of the study included a single-center design and a Japanese patient population. However, our Burn Center is one of the largest in Japan and may therefore reflect the current situation in high-income countries.

CONCLUSIONS

To the best of our knowledge, this is the first study to show that burn mortality is bimodal in the acute and chronic phases. The timing of death in hospitalized burn patients showed a bimodal distribution as approximately 40% of patients who survived the resuscitation period died after 30 days. The age ≥ 65 years and burns to >20% TBSA had a strong impact on the prognosis of the burn patients.

CONFLICT OF INTEREST STATEMENT

Dr. Jun Oda is the Editor-in-Chief of the *AMS Journal* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. Peer-review was handled independently by *AMS Journal* editorial office and Dr. Kuwagata as the Editor to minimize bias.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: The Institutional Ethics Committee of JCHO Chukyo Hospital approved the research protocol of this retrospective cohort study.
Informed Consent: The board waived the requirement for informed consent due to the retrospective nature of the study, according to Japanese guidelines.[29]

Registry and the Registration no. of the Study/trial: 2018046. Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yoneda K, Osuka A, Ohnishi S, Matsuura H, Oda J. The timing of death in burn patients. Acute Med Surg. 2024;11:e970. https://doi.org/10.1002/ams2.970