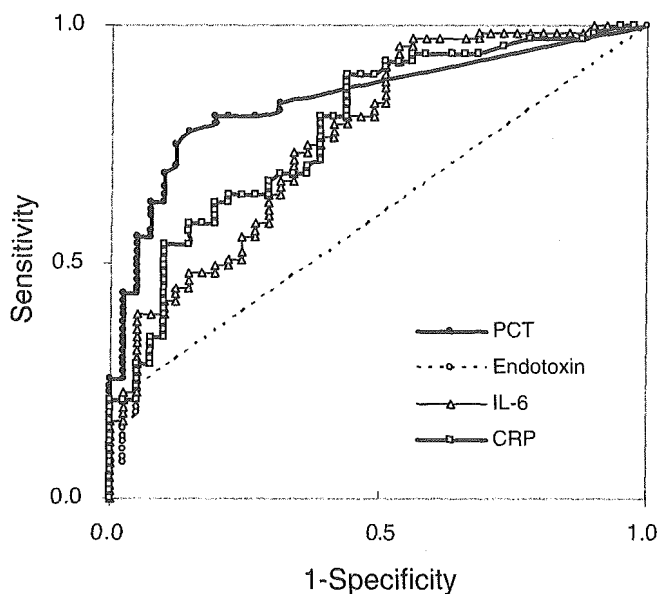


Table 6. Sensitivity of PCT, endotoxin, β -D-glucan, IL-6, and CRP with respect to the type of infection

Type of infection	PCT	Endotoxin	β -D-glucan	IL-6	CRP
	0.5 ng/ml	1.0 pg/ml	11 pg/ml	100 pg/ml	5 mg/dl
Gram-negative infection	65.2% (15/23)	21.7% (5/23)	17.4% (4/23)	58.8% (10/17)	87.0% (20/23)
Gram-positive infection	61.0% (25/41)	7.5% (3/40)	16.2% (6/37)	69.0% (20/29)	85.4% (35/41)
Mixed Gram-negative and -positive infection	64.3% (9/14)	21.4% (3/14)	16.7% (2/12)	72.7% (8/11)	71.4% (10/14)
Mixed bacterial and fungal infections	87.5% (7/8)	25.0% (2/8)	57.1% (4/7)	83.3% (5/6)	100.0% (8/8)
Fungal infection	0.0% (0/1)	0.0% (0/1)	100.0% (1/1)	0.0% (0/1)	100.0% (1/1)
Mycoplasmal infection	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	—	0.0% (0/1)
Viral infection	16.7% (4/24)	4.5% (1/22)	0.0% (0/19)	50.0% (1/2)	20.8% (5/24)
Malarial infection	100.0% (1/1)	100.0% (1/1)	0.0% (0/1)	100.0% (1/1)	100.0% (1/1)

**Fig. 3.** Receiver operating characteristic curves (ROCs) of serum parameters (PCT, endotoxin, IL-6, and CRP) in patients with bacterial infectious diseases and those with non-bacterial infectious diseases

role in inducing PCT release.²² Many studies have established that the determination of serum PCT concentrations can be used to differentiate bacterial from viral infections and to identify bacterial infections in patients admitted to intensive care units because of systemic inflammatory response syndrome (SIRS). Some studies have compared the diagnostic value of PCT with those of other parameters of inflammation, such as CRP and cytokine concentrations.^{23,24} Thus, we conducted a prospective, multicenter study in patients diagnosed with or suspected of having infections. We obtained a cutoff value of 0.5 ng/ml for the PCT concentration, with acceptable sensitivity and high specificity. When assessed in 90 patients diagnosed with localized bacterial infectious disease and 86 patients diagnosed with nonbacterial infectious disease, the sensitivity, specificity, positive predictive value, and negative predictive value of PCT were 64.4%, 86.0%, 82.9%, and 69.8%, respectively. Al-Nawas et al.²⁵ showed that PCT determination in adult patients with sepsis had a lower specificity

Table 7. Sensitivity of PCT and blood culture in patients with systemic bacterial infections and localized bacterial infections

	n	PCT	Blood culture
Systemic bacterial infections	20	11 (55.0%)	20 (100%)
Localized bacterial infections	70	47 (67.1%)	0 (0.0%)
Blood culture negative	27	22 (81.5%)	0 (0.0%)
Blood culture not performed	43	25 (58.1%)	No test

(79%) and higher negative predictive value (78%), but lower sensitivity (60%) and positive predictive value (61%) than in our study, as above. The study by Liaudat et al.²⁶ intended to evaluate PCT concentration as an early predictive marker of bacteremia. In their hospital, where the prevalence of bacteremia was 8%, they found that PCT evaluation had a negative predictive value of 96%. Gendrel et al.⁵ pointed out that low PCT serum concentrations in bacteremic patients may be due to previous administration of antibiotics. In the present study, 17 of 32 patients with bacterial infectious disease with a PCT concentration of less than 0.5 ng/ml had received antibiotics within 2 days of the testing. With the diagnostic criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference,²⁷ we classified 18 of these 32 patients as having non-SIRS ($n = 6$) or sepsis ($n = 12$), but none of them were classified as having severe sepsis. The AUC for PCT differed significantly from that for endotoxin, and tended to be higher than those for IL-6 and CRP. PCT is specific for bacterial infectious disease, but CRP and IL-6 may have elevated values in patients with SIRS.

The sensitivity of PCT was compared with respect to the classification of bacteria. No significant difference was observed for PCT serum concentrations between Gram-negative and Gram-positive bacterial infections, similar to already published data.²⁶

The study by Assicot et al.⁴ indicated that patients with viral infection had normal or only slightly increased concentrations of PCT. In the present study, 4 of 24 patients with viral infection had PCT concentrations higher than 0.5 ng/ml, and the mean PCT concentration in the viral infection group was 0.36 ± 0.76 ng/ml, while the highest concentration was 3.67 ng/ml.

PCT yielded negative results in one patient with fungal infection. The sensitivity of PCT for mixed bacterial and

fungal infection was 87.5% (7/8 cases). Endo et al.²⁸ have suggested that blood PCT does not increase in patients with deep-seated mycoses. Thus, although additional studies are necessary, PCT could be useful to distinguish bacterial from fungal infections.

In a patient with malaria, the PCT concentration was 8.72 ng/ml. Chiwakata et al.²⁹ showed that patients with severe and complicated *Plasmodium falciparum* malaria had significantly higher concentrations of serum PCT than those with uncomplicated malaria.

In conclusion, serum PCT concentration is specific for bacterial infection. The PCT concentration may contribute to a decision to withhold antibiotic treatment. Thus, it may be useful in detecting febrile patients suffering from severe focal infections or culture-negative sepsis who should be treated promptly with antibiotics, as well as patients suffering from benign occult bacteremia (who could avoid hospitalization), irrespective of the results of blood cultures.

References

- Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. *Clin Microbiol Rev* 1997;10:444–65.
- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303–10.
- Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotics use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004;363:600–7.
- Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993;341:515–8.
- Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guerin S, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differential of bacterial vs viral infections. *Pediatr Infect Dis* 1999;18:875–81.
- Delevaux I, Andre M, Colombier M, Albuissou E, Meylheuc F, Begue RJ, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? *Ann Rheum Dis* 2003;62:337–40.
- Gendrel D, Bohuon C. Procalcitonin in pediatrics for differentiation of bacterial and viral infections. *Intensive Care Med* 2000;26:S178–81.
- Ugarte H, Silva E, Mercan D, Mendonca AD, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med* 1999;27:498–504.
- Meisner M, Tschaikowsky K, Schmidt J, Schuttler J. Procalcitonin (PCT) – Indications for a new diagnostic parameter of severe bacterial infection and sepsis in transplantation, immunosuppression and cardiac assist devices. *Cardiovasc Eng* 1996;1:67–76.
- Nylen ES, Whang KT, Snider RH, Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med* 1998;26:1001–6.
- Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. *Intensive Care Med* 2000;26:1193–200.
- Kambayashi J, Yokota M, Sakon M, Shiba E, Kawasaki T, Mori T, et al. A novel endotoxin-specific assay by turbidimetry with *Limulus* amoebocyte lysate containing β -glucan. *J Biochem Biophys Methods* 1991;22:93–100.
- Mori T, Ikemoto H, Matsumura M, Yoshida M, Inada K, Endo S, et al. Evaluation of plasma (1-3)- β -D-glucan measurement by the kinetic turbidimetric *Limulus* test, for the clinical diagnosis of mycotic infections. *Eur J Clin Chem Clin Biochem* 1997;35:553–60.
- Mori T, Matsumura M. Clinical evaluation of diagnostic methods using plasma and/or serum for three mycoses: *Aspergillosis*, *Candidosis*, and *Pneumocystosis*. *Jpn J Med Mycol* 1999;40:223–30.
- Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W. Serum procalcitonin levels in bacterial and abacterial meningitis. *Crit Care Med* 2000;28:1828–32.
- Gendrel D, Raymond J, Assicot M, Moulin F, Iniguez JL, Lebon P, et al. Measurement of procalcitonin levels in children with bacterial or viral meningitis. *Clin Infect Dis* 1997;24:1240–2.
- Chiesa C, Panero A, Rossi N, Stegagno M, De Giusti D, Osborn JF, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. *Clin Infect Dis* 1998;26:664–72.
- Nylen ES, O'Neill W, Jordan MH, Snider RH, Moore CF, Lewis M, et al. Serum procalcitonin as an index of inhalation injury in burns. *Horm Metab Res* 1992;24:439–42.
- Russwurm S, Wiederhold M, Oberhoffer M, Stonans I, Zipfel PF, Reinhart K. Molecular aspects and natural source of procalcitonin. *Clin Chem Lab Med* 1999;37:789–97.
- Muller B, White JC, Nylen ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab* 2001;86:396–404.
- Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* 1994;79:1605–8.
- Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis related cytokines in vitro. *J Lab Clin* 1999;134:49–55.
- Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumor necrosis factor receptor II. *Br J Haematol* 2000;111:1093–102.
- Schroder J, Staubach KH, Zabel P, Stuber F, Kremer B. Procalcitonin as marker of severity in septic shock. *Langenbecks Arch Surg* 1999;384:33–8.
- Al-Nawas B, Krammer I, Shah PM. Procalcitonin in diagnosis of severe infections. *Eur J Med Res* 1995/96;1:331–3.
- Liaudat S, Dayer E, Praz G, Bille J, Troillet N. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. *Eur J Microbiol Infect Dis* 2001;20:524–7.
- American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864–74.
- Endo S, Inada K, Okamoto K, Kuboi M, Kasai T, Yamada Y, et al. Procalcitonin level was not elevated in patients with deep-seated mycosis (in Japanese). *Jpn Soc Surg Infect* 2000;12:141–5.
- Chiwakata CB, Manegold C, Bonicke L, Waase I, Julch C, Dietrich M. Procalcitonin as a parameter of disease severity and risk of mortality in patients with *Plasmodium falciparum* malaria. *J Infect Dis* 2001;183:1161–4.

Prognostic implications of inhalation injury in burn patients in Tokyo

Masaru Suzuki^{a,*}, Naoki Aikawa^a, Kunio Kobayashi^b, Ryouhei Higuchi^b

^aDepartment of Emergency and Critical Care Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

^bThe Tokyo Burn Unit Association, Tokyo, Japan

Accepted 21 October 2004

Abstract

Inhalation injury has recently emerged as the major cause of mortality in burn patients. However, the prognostic value of inhalation injury has not been thoroughly assessed in Japanese burn facilities. The aim of the present study was to evaluate the impact of inhalation injury on burn patients' mortality in Tokyo. Of 6416 patients admitted to 13 burn facilities of the Tokyo Burn Unit Association between 1984 and 2002; the 5560 eligible patients were included in this study (mean age, 40 ± 20 years; male, 61.6%; mean partial- and full-thickness burn size, $10.7 \pm 13.0\%$ and $9.6 \pm 20.5\%$). Of the 5560 patients, 1690 patients (30.4%) had experienced inhalation injury. The overall in-hospital mortality rate of the patients with inhalation injury was higher than that of those without inhalation injury (33.6% versus 8.1%, odds ratio, 5.72 [95% CI, 4.91–6.67]). The results of the multivariate analysis indicated that inhalation injury; full- and partial-thickness burn size, and age were independent predictors of outcome (relative risk, 2.58 [2.03–3.29], 1.10 [1.09–1.11], 1.06 [1.06–1.07], 1.05 [1.05–1.06], respectively). In conclusion, inhalation injury was the most important predictor of overall mortality among burned patients in Tokyo.

© 2004 Elsevier Ltd and ISBI. All rights reserved.

Keywords: Burns; Inhalation; Burn size; Prognosis; Mortality; Multicenter study

1. Introduction

Until recently burn size and age of the patient had been accepted as the predictors of death following burn injury [1,2]. Over the last several decades advances in burn care that have contributed to a decrease in burn mortality have included new fluid resuscitation formulas, nutritional support regimens, the use of antimicrobials, and early surgical excision of eschar to reduce the occurrence of sepsis [3,4]. Despite advances in the respiratory management of burn patients, inhalation injury has emerged as their leading cause of death [1,2,5–8]. The incidence of inhalation injury in burn patients who require hospitalization ranges from 20% to 30% [1,2,9], and at least 30% of patients with inhalation injury die [1,6,7,10].

Each year approximately 1500 burn patients in Japan die of burn-related complications [11], but the mortality of burn patients who require hospitalization has not been thoroughly investigated in Japan. A recent study in Tokyo has linked the

mortality of burn patients with inhalation injury [12], but the effect of inhalation injury on burn mortality has never been assessed in burn units operating within the Japanese health care system. The aim of the present study was to elucidate prognostic implications of inhalation injury among burn patients in 13 burn centers in Tokyo.

2. Methods

This multi-center retrospective observational study was conducted to analyze the relationships between age, sex, burn size, presence of inhalation injury, and risk of death in burn patients. Between 1984 and 2002, 6416 patients admitted to 13 burn facilities of the Tokyo Burn Unit Association were enrolled in the prospectively maintained burn registry. Data recorded in the registry included age, sex, partial- and full-thickness burn size, presence or absence of inhalation injury, length of stay on the unit, and outcome. The presence or absence of inhalation injury was based on documentation in the registry data. The diagnosis of inhalation injury was made clinically in patients who had smoke-inhalation or

* Corresponding author. Tel.: +81 3 3225 1323; fax: +81 3 3353 2232.
E-mail address: suzuki@sc.itc.keio.ac.jp (M. Suzuki).

Table 1
Eligible patients with cutaneous thermal burn injury

Total patients, number (%)	5560 (100)
Males, number (%)	3427 (100)
Age, mean (S.D.), years	40.1 (26.2)
% Burn size, mean (S.D.)	
Partial-thickness	10.7 (13.0) %BSA
Full-thickness	9.6 (20.5) %BSA
Total	20.3 (23.0) %BSA
Patients with inhalation injury, number (%)	1690 (30.4)
Length of stay on the unit, mean (S.D.), days	16.5 (20.9)
Deaths, number (%)	881 (15.8)

flame-inhalation and one or more of the following signs and/or symptoms: sore throat, bronchial irritation, cough, productive sputum containing soot, hypoxemia, and bronchoscopic findings of respiratory tract injury. The diagnosis of cutaneous and respiratory tract injuries was verified retrospectively by a quarterly reviewing meeting attended by delegates from all burn units of the association. The cause of death and comorbid conditions were not recorded in the registry. Survival was defined as discharge from the burn unit, either to home or to another facility. Permission for registry review was obtained from the subcommittee for Clinical Studies of the Tokyo Burn Unit Association. Of the 6416 records reviewed, the 756 records of the 52 patients who developed out-of-hospital cardiac arrest and the 704 patients with inhalation injury but no cutaneous thermal injury were excluded. The records of the remaining 5560 were included in this study as data from eligible patients (Table 1).

To identify changes in mortality trends over time, patients were divided into two groups according to year of admission, 1984–1993 and 1994–2002.

To identify multivariate predictors of mortality, age, sex, partial- and full-thickness burn size (% of body surface area), and presence of inhalation injury were entered in logistic regression model and the analysis was performed by the backward elimination method. Univariate analyses of variables were performed by using the χ^2 -test for categorical data and ANOVA for continuous data. Values are reported as mean \pm S.D. The statistical analyses, including calculations of means, standard deviations, and 95% confidence intervals, were performed with SPSS™ 12.0 J software (SPSS Japan Inc., Tokyo, Japan).

3. Results

The mean size of the partial- and full-thickness burns as a proportion of body-surface area was $10.7 \pm 13.0\%$ and $9.6 \pm 20.5\%$, respectively, and 1690 patients (30.4%) had inhalation injury (Table 1).

As shown in Fig. 1, the distribution of patients according to age and presence or absence of inhalation injury shows the largest number of patients but lowest incidence of inhalation injury in the group under 10 years old. The largest group of patients with inhalation injury was between the 50 and 59 years old (18.7%). The distribution of patients by burn size in Fig. 2 shows that the largest number of patients (42.2%) had a total burn size of less than 10%.

There were 881 deaths, and overall mortality was 15.8% (Table 1). The mortality rate significantly decreased from 18.0% in 1984–1993 to 13.7% in 1994–2002 (Table 2).

Of the 1690 patients with inhalation injury, 567 (33.6%) died on the units. The mortality rate of the patients with inhalation injury was significantly higher than that of the

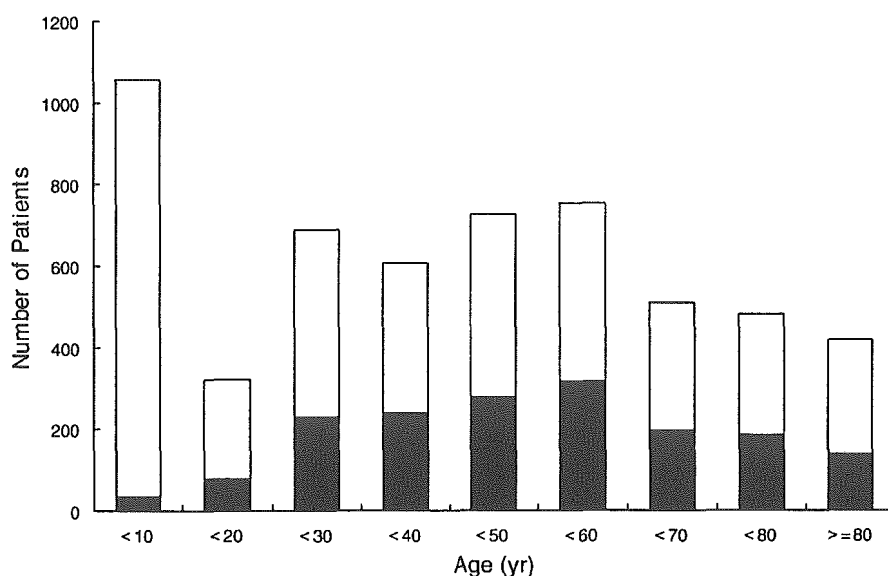


Fig. 1. Age distribution of patients with and without inhalation injury. Closed bars represent the number of patients with inhalation injury, and the open bars represent the number of patients without inhalation injury. The distribution of patients according to age shows that the largest group was under 10 years old (19.0%). The largest group of the patients with inhalation injury was between 50 and 59 years old (18.7%).

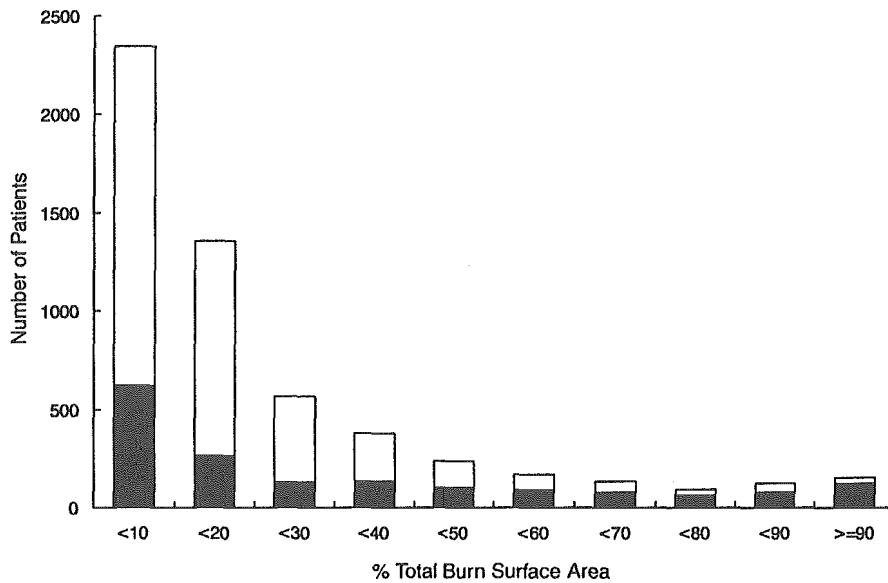


Fig. 2. Distribution according to burn size (%TBSA) of patients with and without inhalation injury. Closed bars show the distribution of patients with inhalation injury according to burn size, and open bars show their distribution without inhalation injury. The distribution of patients by burn size shows that the largest group of patients (42.2%) had a total burn surface area of less than 10%.

patients without inhalation injury (Table 3). The relationships among mortality, total burn size, age, and presence or absence of inhalation injury are summarized in Figs. 3 and 4. The analyses according to both age and burn size showed more deaths among the patients with inhalation injury.

Multivariate logistic regression analysis indicated that inhalation injury, full- and partial-thickness burn size, and age were independent predictors of the mortality of burn patients (Table 4).

4. Discussion

The overall mortality rate in this study was 15.8%. The mortality rate has decreased significantly during the last decade, and it was significantly higher in the patients with inhalation injury than in those without inhalation injury. The

multivariate analysis revealed inhalation injury to be the most important predictor of death.

The incidence of inhalation injury and mortality due to inhalation injury in the present study were consistent with the data in previous reports. Its incidence was 30% in this study, while previous studies have reported incidences of 20% to 30% [1,2,9]. The mortality rate of the patients with inhalation injury was 33.6% in this study, while other studies have reported that around 30% of patients with inhalation injury die (Table 5), which shows that the results of this study are comparable to those in other recently published case series [1,6,7,10].

Presence of inhalation injury, burn size, and age were significant determinants of death following burn injury in this study, and inhalation injury was the most significant predictor of mortality. Those findings confirmed previously reported findings [1,2,5–8].

Table 2
Burn mortality rates 1984–2002

	Admission year		P-values
	1984–1993 (no. of patients, %)	1994–2002 (no. of patients, %)	
Patients	2765 (100)	2795 (100)	
Death	498 (18.0)	383 ^a (13.7)	<0.001
Inhalation injury	811 (29.3)	879 (31.4)	0.09
Male	1711 (61.9)	1716 (61.4)	0.72
Age, years	38.3 (25.3)	41.8 (26.9)	<0.001
Partial-thickness burn size, mean (S.D.) (%)	12.0 (14.0)	9.5 (11.9)	<0.001
Full-thickness burn size, mean (S.D.) (%)	10.1 (21.3)	9.1 (19.7)	0.06

^a Odds ratio = 0.72 (95% confidence interval, 0.63–0.84).

Table 3
Patients with inhalation injury

	Inhalation injury		P-values
	(+) n = 1690	(-) n = 3870	
Age, mean (S.D.) years	49.0 (20.5)	36.2 (27.4)	<0.001
Males, number (%)	1126 (66.6)	2301 (59.5)	<0.001
Flame burns, number (%)	1445 (85.5)	1382 (35.7)	<0.001
Burn surface area, mean (S.D.) (%)			
Partial-thickness	9.5 (12.5)	11.3 (13.2)	<0.001
Full-thickness	20.4 (29.1)	4.9 (12.7)	<0.001
Total	29.9 (30.3)	16.1 (17.3)	<0.001
Length of stay on the unit, mean (S.D.) days	21.8 (29.8)	17.7 (23.0)	<0.001
Deaths, number (%)	567 ^a (33.6)	314 (8.1)	<0.001

^a Odds ratio = 5.72 (95% confidence interval, 4.91–6.67).

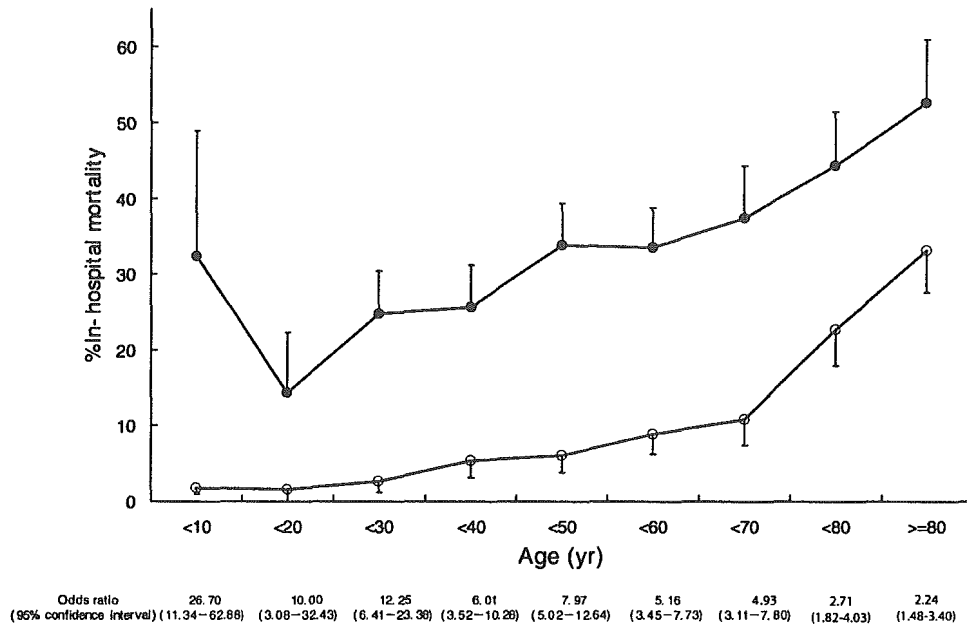


Fig. 3. Relationship between mortality and age of patients with and without inhalation injury. In every age groups the mortality rate of patients with inhalation injury (closed circles) was significantly higher than the mortality of those without inhalation injury (open circles).

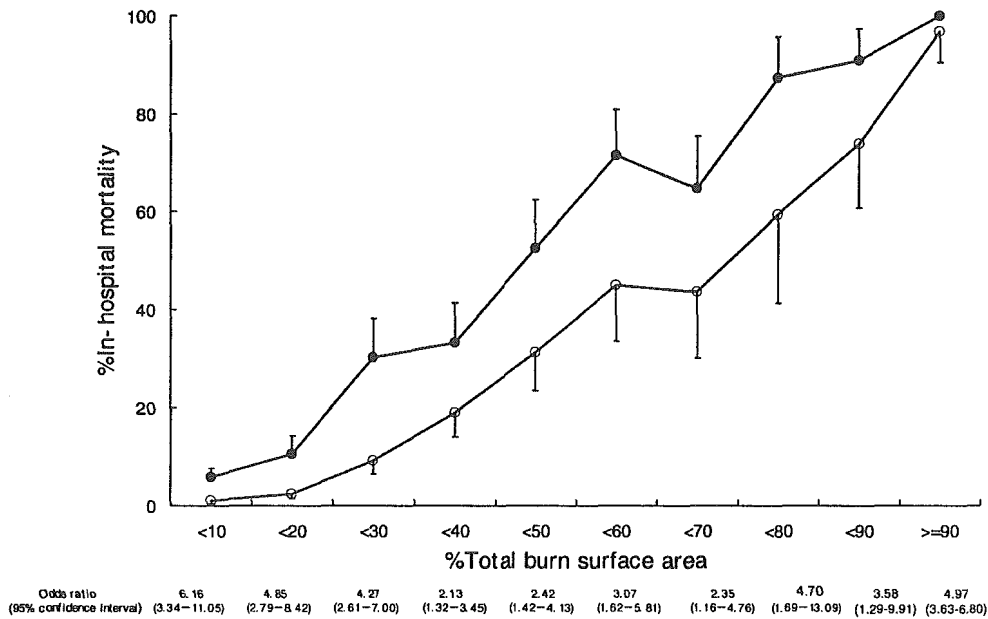


Fig. 4. Relationship between mortality and burn size of patients with and without inhalation injury. In every burn size groups the mortality rate of patients with inhalation injury (closed circles) was significantly higher than that of patients without inhalation injury (open circles).

Although the reason inhalation injury remained the most important cause of mortality has not been well elucidated, possible mechanisms have been discussed in previous studies. Inhaled products of combustion and respiratory tract thermal injury are known to activate oxygen radicals and cytokines, which further contribute to the pathophysiology of inhalation injury [13,14], and inhalation injury increases the risk of pneumonia by 42% per day, as compared with 1%

Table 4
Independent predictors of mortality in the multivariate analysis

	Odds ratio (95% confidence interval)
Inhalation injury	2.58 (2.03–3.29)
Full-thickness burn size	1.10 (1.09–1.11)
Partial-thickness burn size	1.06 (1.06–1.07)
Age	1.05 (1.05–1.06)

Table 5
Comparison of descriptive statistics from previous studies

Studies, [Reference]	Country	Number	Mortality (%)	Mean age (years)	Mean TBSA(%)	Inhalation injury mortality (%)
Suzuki et al., Present study	Japan	5560	15.8	40	20	33.6
Tredget et al. [7]	Canada	1705	4.1	26	15	34.7
Smith et al. [1]	USA	1447	9.5	30	18	31.0
Saffle et al. [6]	USA	6417	5.1	N/A	14	29.4
Ryan et al. [10]	USA	1665	4.0	21	14	24.2

per day in other ICU patients [15]. This may reflect the susceptibility of the injured airway and lung to bacterial invasion.

The mortality rate in this study was higher than in previous reports (Table 5). The patients in this study were older and had larger burns, and thus comparing overall mortality may have limitations. Further, it is difficult to compare the results with those in different countries, because the epidemiological circumstances, patient referral patterns, and standards of burn care are different.

During the past 19 years steady improvements in survival from burn injury have been documented in burn centers in Tokyo. Improvements in resuscitation, nutrition therapy, and wound management, and the introduction of early surgical excision have led to marked increase survival from burn injury during the last decade [1,2,5–8]. Although a longitudinal view of burn survival may be suitable for demonstrating advances in burn care, the same improvements should be expressed regarding data on other outcome variables.

There were some potential limitations in this study. First, there were no data to determine the severity of the condition of the registered patients, including comorbid conditions, cause of death, or presence or absence of a no-CPR order, and they may be important clinical variables in terms of outcome. Further, no information regarding treatment regimens was recorded in the registry, and the patient group in the present study may have been heterogeneous. The multi-center study design may have overcome these selection biases, since this study was conducted in 13 major burn units [12]. Second, no diagnostic criteria for inhalation injury were established in the present study, and there were no data to quantify the severity of the inhalation injury. Although the diagnosis of inhalation injury was clinically made, the diagnosis was verified retrospectively by a quarterly reviewing meeting attended by delegates from all burn units of the association. Further, the incidence of inhalation injury in this study was comparable to other previous studies. Finally, outcome should not be viewed solely in terms of death or survival, with no consideration for the patients' quality of life, and it was not measured in this study.

In conclusion, burn patients with inhalation injury had higher mortality than burn patients without inhalation injury, and inhalation injury was the most important predictor of overall mortality among burn patients in Tokyo.

Acknowledgements

The following member institutions of the Tokyo Burn Unit Association [12] participated in this study: Koto Hospital, Kyorin University Hospital, National Hospital Organization Disaster Medical Center, Nippon Medical School Hospital, Nippon Medical School Tama-Nagayama Hospital, Teikyo University Hospital, Tokyo Medical University Hospital, Tokyo Metropolitan Bokutoh Hospital, Tokyo Metropolitan Hiroo Hospital, Tokyo Metropolitan Fuchu Hospital, Tokyo Women's Medical University Hospital, The University of Tokyo Hospital, and Keio University Hospital. We thank all of those hospitals for their excellent assistance with data collection.

Conflict of interest statements: All authors did not have any financial and personal relations with other people or organizations, and this study did not receive any outside funding or support.

References

- [1] Smith DL, Cairns BA, Ramadan F, et al. Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients. *J Trauma* 1994;37:655–9.
- [2] Anous MM, Heimbach DM. Causes of death and predictors in burned patients more than 60 years of age. *J Trauma* 1986;26:135–9.
- [3] Aikawa N, Aoki K, Yamazaki M. Recent advances in the management of severely burned patients. *Nippon Geka Gakkai Zasshi* 1999;100:424–9.
- [4] Monafó WW. Initial management of burns. *N Engl J Med* 1996;335:1581–6.
- [5] Muller MJ, Pegg SP, Rule MR. Determinants of death following burn injury. *Br J Surg* 2001;88:583–7.
- [6] Saffle JR, Davis B, Williams P. Recent outcomes in the treatment of burn injury in the United States: a report from the American Burn Association Patient Registry. *J Burn Care Rehabil* 1995;16:219–32. discussion 288–219.
- [7] Tredget EE, Shankowsky HA, Taerum TV, et al. The role of inhalation injury in burn trauma. A Canadian experience. *Ann Surg* 1990;212:720–7.
- [8] Barrow RE, Spies M, Barrow LN, et al. Influence of demographics and inhalation injury on burn mortality in children. *Burns* 2004;30:72–7.
- [9] Shirani KZ, Pruitt Jr BA, Mason Jr AD. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg* 1987;205:82–7.
- [10] Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med* 1998;338:362–6.
- [11] Minister's Secretariat, Ministry of Health, Labour and Welfare. Vital statistics of Japan 2002. Tokyo: Health and Welfare Statistics Association; 2004.

- [12] Kobayashi K, Ikeda H, Higuchi R, et al. Epidemiological and outcome characteristics of major burns in Tokyo. *Burns* 2005; 31(1S):S3–S11.
- [13] Nguyen TT, Cox Jr CS, Herndon DN, et al. Effects of manganese superoxide dismutase on lung fluid balance after smoke inhalation. *J Appl Physiol* 1995;78:2161–8.
- [14] Aikawa N. Cytokine storm in the pathogenesis of multiple organ dysfunction syndrome associated with surgical insults. *Nippon Geka Gakkai Zasshi* 1996;97:771–7.
- [15] Darling GE, Keresteci MA, Ibanez D, et al. Pulmonary complications in inhalation injuries with associated cutaneous burn. *J Trauma* 1996;40:83–9.



International Emergency Medicine

EMERGENCY MEDICAL SERVICES IN JAPAN: AN OPPORTUNITY FOR THE RATIONAL DEVELOPMENT OF PRE-HOSPITAL CARE AND RESEARCH

Matthew R. Lewin, MD, PhD,* Shingo Hori, MD, PhD,† and Naoki Aikawa, MD, PhD†

*Division of Emergency Medicine, University of California, San Francisco (Fresno), California and †Department of Emergency Medicine and Acute Care, Keio University Hospital, Tokyo, Japan

Reprint Address: Matthew R. Lewin, MD, PhD, Division of Emergency Medicine, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143-0208

□ **Abstract**—Japan is at a crossroads in the development of its Emergency Medical Services (EMS). At present, Japan has an essentially pure scoop-and-run, defibrillation system. However, there is a strong movement toward expanding the scope of paramedic practice to include more complex, Advanced Life Support (ALS) and trauma protocols to its nationally standardized pre-hospital protocols. The implications of introducing complex pre-hospital protocols guided by the use of existing scientific evidence to support such action is discussed in the context of Japan's unique opportunity to test many fundamental questions in pre-hospital medical care and the public's understanding and acceptance of these practices. Japan, a technologically advanced country that is not encumbered by entrenched "standards of care," has the opportunity to develop an efficient and rational EMS system. © 2005 Elsevier Inc.

□ **Keywords**—EMS; pre-hospital; Japan; paramedic

INTRODUCTION

Japan, a technologically advanced country of 130 million citizens, has a national Emergency Medical Services (EMS) system comprised of highly trained Emergency Life Support Technicians (ELST) whose complete protocols appear on six faces of a small, folded card containing the essence of their scoop-and-run-defibrillate pre-hospital philosophy. ELSTs in Hokkaido, Kyushu, or giant Tokyo—regions and cities differing in geography,

transport distance, and epidemiology—are bound by the same protocols. A Japanese ELST can defibrillate ventricular tachycardia, perform CPR, and insert an oral-esophageal airway in a patient with no detectable vital signs. An ELST does not administer any drug, except for oxygen. On more than several occasions, we have heard and read that Japanese ELSTs and the Japanese public feel the pre-hospital scope of practice is severely limited compared with their counterparts in North America and other countries in the western hemisphere (1).

This is not altogether surprising. By contrast to the Japanese ELST, a comparably certified paramedic in New York City, population 8 million, has at least 58 separate protocols (2). Fresno County, California, which has a mixed rural, suburban and urban environment, has a population of just 750,000 people. Paramedics serving this diverse area have over 36 protocols, which run the gamut of advanced cardiac life support to the treatment of burns, snakebite, and seizures (3). Paramedics in Fresno, New York City, San Francisco or Houston, Texas can administer any one of 30 or more medications (from aspirin, adenosine, amiodarone and morphine all the way to terbutaline and verapamil) based on protocols developed and elaborated by EMS programs starting in the late 1960s and early 1970s. A paramedic in Maine or Sacramento, California can perform naso-tracheal intubation, a cricothyrotomy or decompress a tension pneumothorax using a thoracostomy needle. All U.S. para-

medics can instill intravenous fluids in the setting of hypotension and trauma, yet, the evidence for the benefits of pre-hospital management of trauma using intravenous fluids remains controversial (4). Similarly, no clinical trial has yet proven that epinephrine or amiodarone improves survival to discharge from the hospital and the most rigorous clinical trials to date only suggest that endotracheal intubation might have a beneficial effect on overall survival in the setting of cardiac arrest, despite well-known and common complications associated with the procedure (5,6). In some regions of the United States, many pre-hospital practices are being scrutinized, with some being withdrawn or curtailed as data on the inefficacy or danger of certain pre-hospital practices have emerged (7–10).

In this article, comparisons of health care economics, health care culture, epidemiology, and topics such as continuous quality improvement (CQI) are generally avoided, though useful tools for comparison do exist (11). Although our focus is the scientific basis for developing EMS in Japan, it is important to recognize that politics, the emotional and economic cost to society, corporate financial profits, and decisions about what pre-hospital system is right for Japan all enter the equation. We emphasize that in Japan, EMS is an entirely publicly funded service and patients do not individually pay the expense of their ambulance ride to the hospital. Thus, the economic significance of expanded practice, training costs, and utilization are not small.

The development of EMS in Japan has some temporal and philosophical parallels to that in North America. The Meiji Empress founded the Japanese Red Cross during the Reformation and Japanese physicians developed field treatments for the sick and wounded during their wars and natural disasters of the 19th and 20th centuries (12). The first ambulance services were started in pre-World War II days by the Tokyo Police Department and were intended for trauma, rather than medically ill victims. In 1935, there were six ambulances in the old Tokyo City. In 1961, the first designated hospitals providing 24-h emergency services were assigned (13,14). The impetus for increased emergency services was twofold. First, an increase in the economic power of Japan was represented by an increase in car ownership—and in fatal car accidents, as well as a successful bid to host the 1964 Olympics. Thus, the first great expansion of ambulance services and designated emergency facilities was organized with the 1964 Tokyo Olympics in sight (15). Through the 1960s and into the early 1970s, emergency medical care in Japan was dominated by surgeons (14). It was not until 1973 that the Japan Association of Acute Medicine (JAAM) was founded, largely by surgeons, ironically with little collaborative effort between surgeons, intensivists, internists and members of other specialties wishing to provide comprehensive

emergency services in dedicated emergency departments (EDs). In 1991, members of JAAM, other dedicated physicians, citizens and politicians collaborated to implement the Emergency Life Saving Technicians (ELST) Act (13). That same year saw the introduction of the privately and publicly funded Foundation for Ambulance Development. Japanese EMS, in contrast to the U.S. EMS system, is a government-sponsored service managed through the auspices of the Fire Department. In 2001, there were approximately 5517 ambulances (16). In contrast to U.S. EMS systems, even those run by fire departments, patients calling 119, the national equivalent to the U.S. 911, are not charged for the service of transportation to the ED.

In 2002, approximately 207 ambulance units of the Tokyo Fire Department, alone, made 629,883 runs in response to “119” calls. Of these, more than 50% were made for patients over the age of 50 years (17). Thus, as the Japanese population ages, the nation faces an important issue: What is the agenda for the future of EMS in Japan?

Two recent events have pushed the EMS development agenda to the forefront of the Japanese public’s consciousness. The first event was in Akita City, where the practice of endotracheal intubation was being performed illegally by pre-hospital ELST units for several years. When this was revealed, and the paramedics indicted, the citizens of Akita City regarded the paramedics as heroes, stirring debate about their professional fates and the “backwardness” of Japanese EMS. A second occurrence, in November 2002, was the tragic, sudden cardiac death of Prince Takamadonomiya at the Canadian embassy in Tokyo. As a result, there has been public outcry to expand the scope of practice in Japanese EMS from its basic life-support-based system.

In response to these events, and recent research in Osaka Prefecture and Tokyo, the Ministry of Public Management and Home Affairs, along with Japan Medical Association and JAAM, formed three committees to address fundamental issues of EMS practice in Japan (18,19). The three committees are for: 1) defibrillation by paramedics, 2) endotracheal intubation, and 3) the use of drugs. Each committee is composed of 9 to 10 individuals representing different specialties and sectors of society. For example, the defibrillation committee was composed of two physicians from Emergency Medicine, one pediatrician and one from the Japanese Medical Society. In addition, there was one legal advisor, two members from the fire department and two from related bureaucracies.

COMMENTARY

Until the death of the beloved cousin of the Emperor, ELSTs could not defibrillate without consent of a base

hospital physician. This event, and the abundant data supporting the use of rapid defibrillation to save lives in the setting of cardiac arrest, accelerated the policy of defibrillation without calling into the base hospital (20–22). Since April of 2003, Japanese ELSTs have been interpreting, with the aid of interpretive computers, cardiac monitor rhythm strips in the setting of pulseless ventricular tachycardias and fibrillation. However, Japanese paramedics are still highly restricted in their scope of practice. They are trained in the basics of advanced life support (ALS) and basic trauma life support (BTLS). Thus, they may maintain and protect the airway using the bag-valve-mask (BVM), laryngeal mask airway (LMA), or esophageal obturator airway (EOA, similar to combitube), but only in the setting of cardiac arrest. Because they are now permitted to defibrillate without consulting a base-hospital physician, ELSTs may avoid life-threatening delays in the use of semi-automatic defibrillators. Consistent with other interventions in the Japanese EMS system, ELSTs may only start intravenous lines and administer lactated Ringer's solution in the setting of cardiopulmonary arrest. These restrictions in practice are in sharp contrast to the wide variety of interventions used in North America.

Our observation is that in Japan, there is building popular and political pressure to rapidly expand the scope of practice of ELSTs to be more comparable to that of North American paramedics and other western EMS systems. Although appealing, this is bound to be an expensive and controversial undertaking. By expensive, it is meant threefold: in economic, social and professional terms. By controversial, we mean that many of the general practices of pre-hospital ACLS and BTLS, although appealing and empirically useful, have not necessarily been proven effective by prospective studies and, at this time, the most rigorous data are lacking (5,6,23–31). Thus, in the United States and in North America in general, there are 30 to 50 protocols for any paramedic to choose from in any given situation—many of which probably do not require attention in the span of an ambulance's arrival and delivery of the patient to an ED, especially in an urban setting with short transport times. The most fundamental questions in pre-hospital care seem to have the same foci: how much to do at the scene of an accident, a cardiac arrest, an acute exacerbation of a chronic illness? For most prehospital interventions, there is little evidence of a positive effect on outcome (23,31). However, shorter prehospital time—inherent in scoop-and-run systems such as that in Japan, has been shown to be a critical factor for patients with cardiac arrest and trauma activation of prehospital systems (32,33).

Japanese ELSTs, as well as many medical doctors, are professionals who truly believe that expanding their

scope of practice will result in lives saved. All medical professionals, doctors and emergency life-saving technicians alike, are sincerely dedicated to the proposition that our first duty is not to harm the patient. Many members of the medical profession in Japan have met proposed expansions of EMS services with skepticism and resistance. Because policies are set at a national level, all cities and prefectures are subject to the policies set by the Ministry of Health. Many involved in pre-hospital medical services in Japan may harbor resentment toward the medical profession, which can be perceived as holding back EMS development for reasons not entirely related to patient care. It is our opinion that in the long run, the best chance to help patients and not harm them is to test each proposed intervention in a randomized (and when possible, blinded), controlled trial (RCT). This type of testing is the gold standard of clinical inquiry and minimizes bias. For conditions such as cardiac arrest, meaningful endpoints such as "survival to discharge" would be used, rather than the dubious "return of spontaneous circulation (ROSC)" or "survival to admission" (5,23,24).

We know from Japan's centralized, Utstein-based EMS databases that 5517 ambulance units made 4,399,195 runs in response to "119" calls in 2001. The mean response time from call to arrival on scene for 4,399,195 ambulance runs was 6.2 min (35). In the year there were 88,058 out-of-hospital cardiac arrests (16). Japan's EMS databases and hospital record keeping, and essentially pure scoop-and-run/defibrillate system make it well situated to perform first-rate pre-hospital science.

Thus, Japan has an opportunity to test many fundamental hypotheses important to the practice of pre-hospital patient care. Though there are legal barriers (e.g., nationally uniform pre-hospital practice laws that prevent local and regional clinical trials), and perhaps cultural ones as well, there is no standard of care to interfere with the ethical performance of randomized controlled clinical trials of interventions such as endotracheal intubation vs. "simple" hyperventilation by BVM, LMA or combitube. Similarly, there is no technical barrier to a trial of epinephrine vs. placebo. Even landmark studies such as the OPALS series from Canada have had to use retrospective controls (whose results are subject to the Hawthorne Effect type biases) (6,21,22,32). In Japan, methodological shortcuts can and should be assiduously avoided when possible and validated tools, such as the Utstein template and true randomization, should be standard and, fortunately, are already the basis for record keeping by Japanese ESLTs and their base hospitals (36).

The public, anywhere in the world, expects and deserves the protection that effective government oversight provides. Many arguments have been put forth suggesting that endotracheal intubation, vasopressors and anti-dysrhythmics, applied in certain pre-hospital settings,

may save lives (36,37). These interventions deserve the most rigorous scrutiny and testing (25).

Other interventions, such as pre-hospital administration of anti-seizure medications, oral dextrose for hypoglycemia, and morphine for the pain of a fractured long-bone indeed may be convenient and warrant less scrutiny, while broadening the repertoire of Japanese ELSTs in the field. The tenets of evidence-based medicine suggest that evidence from research is only one component to be considered in clinical decision-making, with individual clinical circumstances, patient and citizenry preferences, and clinician's expertise determining therapeutic action or restraint. When rigorous scientific evidence is lacking, yet years of clinical experience and acumen suggest an intervention is effective and safe, it is reasonable to try that intervention until there are data to suggest otherwise.

In the broader picture, basic questions are: whose judgment and under whose control will protocols be driven, based on what quality of evidence? How much money will be dedicated to research and how much time is needed for that research? Who will be accountable when patients come to harm through ELST error and how will policy disagreements be handled at a national level? (10,38) New interventions such as endotracheal intubation and the administration of potentially dangerous medications increase the complexity of the ELST's or paramedic's curricula and will likely add significant expense to the publicly funded pre-hospital system. In the United States (even with rapid sequence intubation), misplaced endotracheal tubes and multiple intubation attempts in the field are a common and dangerous occurrence (39-42). The limited *clinical* experience of technicians, lack of evidence for positive effects on outcome, and the prolongation of scene times the more interventions are introduced should be primary considerations before the scope of EMS practice is broadened. Furthermore, skills requiring the most technical knowledge—and judgment—deteriorate fastest, thus increasing danger to patients before they have ever arrived in the hospital where larger teams can work together with the ELSTs to clarify the patients' needs (43). Everyone needs to consider, also, the cost of expanded protocols in terms of drugs, equipment acquisition and maintenance, as well as extra training and re-certification costs. In Japan, if ESLTs are to start giving medications, their legal status as healthcare providers certified to do so will need to be revisited.

The "Chain of Survival" concept that is generally embraced should be based on rigorous evidence that the chain, in fact, improves survival and minimizes harm (44). In North America, we have a system that is based at least as much on tradition as on evidence. Invasive field procedures and risky medications may be overused

due to the so-called "technical imperative." The technical imperative has been expressed as, "if a procedure can be taught, it will be used with a frequency greater than its indication" (45). Any system introducing new practices should consider this pitfall with the greatest of attention not only to the risks and benefits of such practices but to the adversarial relationship that may be created among physicians, nurses and paramedics (45).

Fortunately, there has been a recent surge in high quality pre-hospital research that might clarify longstanding controversies in EMS practice (7,21,22,32,44). Some research, which has been performed with rigor, could still introduce new practices prematurely due to overenthusiastic endorsement or over-interpretation about its applicability (46-48). Thus, individual studies showing promise for a particular therapy should be repeated before being put into general practice and sub-group analyses showing significant effects should be viewed with caution, though the finding may be excellent for hypothesis generation (48).

Opportunities for international collaboration to further the development of EMS in Japan, for its benefit and that of the rest of the world, abound. The results of systematic and rigorous scientific inquiry will surely benefit all Japanese citizens and help enlighten the practice of EMS worldwide. With good public education and a rational approach to EMS development, there is good reason for optimism that victims of cardiac arrest and other critically ill patients can be given optimal treatment or therapeutic restraint to optimize survival in the out-of-hospital setting (6,8,49). However, before the people of Japan commit vast amounts of time, money and emotion to an expanded EMS system, we urge caution and scientific rigor.

Acknowledgments—We thank staff members of the Tokyo Fire Department, Drs. Peter Rosen, Marc Shalit and Louise Crowley for their perspective and comments.

REFERENCES

1. Yamamoto Y. The birth of the emergency life support technician (in Japanese). *Emerg Nurs* 1992;5:34-6.
2. Regional Emergency Medical Advisory Committee of New York City. Prehospital paramedic advanced life support protocols. New York: The Regional Emergency Medical Services Council of New York City, Inc.; 1996:1-57.
3. Fresno Kings Madera Emergency Medical Services. Paramedic Treatment Protocols. 2002.1-61, including, but not limited to protocols 530-11, 530-12, 530-19, 530-24, 530-26.
4. Bickell W, Wall MJ, Pepe P, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331:1105-9.
5. Stiell I, Wells G, Spaite D, et al. OPALS study phase III: what is the impact of Advanced Life Support on out of hospital cardiac arrest? *Acad Emerg Med Abstr* 2003;10:423.

6. Stiell I, Wells GA, Field B, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. *N Engl J Med* 2004;351:647-56.
7. Dunford J, Davis D, Ochs M, Doney M, Hoyt D. Incidence of transient hypoxia and pulse rate reactivity during paramedic rapid sequence intubation. *Ann Emerg Med* 2003;42:721-8.
8. Spaite D, Criss E. Out-of-hospital rapid sequence intubation: are we helping or hurting our patients? *Ann Emerg Med* 2003;42:729-30.
9. Perron A, Sing R, Branas C, Huynh T. Predicting survival in pediatric trauma patients receiving cardiopulmonary resuscitation in the prehospital setting. *Prehosp Emerg Care* 2001;5:6-9.
10. Krentz M, Wainscott M. Medical accountability. *Emerg Med Clin North Am* 1990;8:17-32.
11. VanRooyen M. Development of prehospital emergency medical services: strategies for system assessment and management. *Pac Health Dialog* 2002;9:86-92.
12. Olive C. Humanitarianism and the Emperor's Japan. London: Campbell Thompson & McLaughlin Ltd; 1994.
13. Hirokazu M. Advancement of postwar system of emergency medical services in Japan (in Japanese). *J Jpn Assoc Acute Med* 2000;11:311-22.
14. Gando S. The past and future prospects of acute medicine. *Hokkaido Igaku Zasshi (Japanese)* 2002;77:9-12.
15. O'Malley RN, O'Malley GF, Ochi G. Emergency medicine in Japan. *Ann Emerg Med* 2001;38:441-6.
16. Tokyo Fire and Disaster Management Agency. Current status of emergency and rescue services (in Japanese). Tokyo, 2002.
17. Committee E. Current status in EMS: 2002. Tokyo: Tokyo Fire Department; 2002.
18. Hayashi Y, Hiraide A, Morita H, et al. An analysis of time factors in out-of-hospital cardiac arrest in Osaka Prefecture. *Resuscitation* 2002;53:121-5.
19. Nagao K, Kikuti S, Hayashi N, Kanmatsuse K. The issues of emergency medical system in patients with prehospital cardiac arrest complicating acute coronary syndrome in Japan. *Nippon Rinsho (Japanese)* 1998;56:2666-74.
20. Stiell I, Wells G, Field B, et al. Improved out-of-hospital cardiac arrest survival through an inexpensive optimization of an existing defibrillation program: OPALS study phase II. *JAMA* 1999;281:1175-81.
21. Stiell I, Wells G, De Maio V, et al. Modifiable factors associated with improved cardiac arrest survival in a multicenter BLS-D system: OPALS study phase I results. *Ann Emerg Med* 1999;33:44-50.
22. Callahan ML, Madsen C. Relationship of timeliness of paramedic advanced life support interventions to outcome in out-of-hospital cardiac arrest treated by first responders with defibrillators. *Ann Emerg Med* 1998;27:638-48.
23. Callahan ML. Quantifying the scanty science of prehospital emergency care. *Ann Emerg Med* 1997;30:785-90.
24. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002;346:884-90.
25. Wayne M, Racht E, Aghababian R, Kudenchuk P, Ornato J, Slovis C. Prehospital management of cardiac arrest: how useful are vasopressor and antiarrhythmic drugs? *Prehosp Emerg Care* 2002;6:72-80.
26. Xavier L, Kern K. Cardiopulmonary resuscitation Guidelines 2000 update: what's happened since? *Curr Opin Crit Care* 2003;9:218-21.
27. Pepe P, Copass M, Joyce T. Prehospital endotracheal intubation: rationale for training emergency medical personnel. *Ann Emerg Med* 1985;14:1085-92.
28. Copass M, Oreskovich M, Bladergroen M, Carrico C. Prehospital cardiopulmonary resuscitation of the critically injured patient. *Am J Surg* 1984;148:20-6.
29. Smith J, Bodai B. The urban paramedic's scope of practice. *JAMA* 1985;253:544-8.
30. Winchell R, Hoyt D. Endotracheal intubation in the field improves survival in patients with severe head injury. *Arch Surg* 1997;132:592-7.
31. Callahan ML. Managed care and pre-hospital EMS: wake-up call or Taps? *Emerg Med News* 2003;25:40.
32. Feero S, Hedges J, Simmons E, Irwin L. Does out-of-hospital time affect trauma survival? *Am J Emerg Med* 1995;13:133-5.
33. Stiell I, Wells G, Spaite D, et al. The Ontario Prehospital Advanced Life Support (OPALS) Study part II: rationale and methodology for trauma and respiratory distress patients. *Ann Emerg Med* 1999;34:256-62.
34. Kudenchuk P, Cobb L, Copass M, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341:871-8.
35. Statistics Bureau Management and Coordination Agency. Japan statistical yearbook 1999. Tokyo, Japan: Government of Japan; 1999:224.
36. Mashiko K, Otsuka T, Shimazaki S, et al. An outcome study of out-of-hospital cardiac arrest using the Utstein template—a Japanese experience. *Resuscitation* 2002;55:241-6.
37. Stiell I, Nesbitt L, Wells G, et al. Multicenter controlled clinical trial to evaluate the impact of Advanced Life Support on out of hospital chest pain patients. *Acad Emerg Med Abstr* 2003;10:501-2.
38. Roush W. Medical accountability. In: Roush W, ed. *Principles of EMS systems*, 2nd edn. Dallas, TX: American College of Emergency Physicians; 1994:227-43.
39. Sayer M, Sackles J, Mistler A, Evans J, Kramer A, Pancioli A. Field trial of endotracheal intubation by basic EMTs. *Ann Emerg Med* 1998;31:128-33.
40. Jemmett M, Kendal K, Foure M, Burton J. Unrecognized misplacement of endotracheal tubes in a mixed urban to rural emergency medical services setting. *Acad Emerg Med* 2003;10:961-5.
41. Katz S, Falk J. Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. *Ann Emerg Med* 2001;32:32-7.
42. Ochs M, Davis D, Hoyt D, Bailey D, Marshall L, Rosen P. Paramedic-performed rapid sequence intubation of patients with severe head injuries. *Ann Emerg Med* 2002;40:159-67.
43. Skelton M, McSwain N. A study of cognitive and technical skill deterioration among trained paramedics. *JACEP* 1977;6:436-8.
44. Cummins R, Ornato J, Thies W, et al. Improving survival from sudden cardiac arrest the "chain of survival" concept. *Circulation* 1991;83:1832-47.
45. Rosen P, Dinerman N, Pons P, Marlin R, Hansen H, Kanowitz A. The technical imperative: its definition and an application to pre-hospital care. *Top Emerg Med* 1981;2:79-86.
46. Wenzel V, Kisser A, Arntz H, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105-13.
47. McIntyre K. Vasopressin in asystolic cardiac arrest. *N Engl J Med* 2004;350:179-81.
48. Solomon R. Vasopressin for asystole? Available at: <http://www.acep.org/1,33308,0.html>. Accessed July 27, 2004.
49. Stiell I, Nichol G, Wells G, et al. Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation* 2003;108:1939-44.

Epidemiological and outcome characteristics of major burns in Tokyo

K. Kobayashi*, H. Ikeda, R. Higuchi, M. Nozaki, Y. Yamamoto, M. Urabe,
S. Shimazaki, A. Sugamata, N. Aikawa, N. Ninomiya, H. Sakurai,
Y. Hamabe, N. Yahagi, H. Nakazawa

*The Tokyo Burn Unit Association, Department of Trauma and Critical Care Center,
Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8606, Japan*

Abstract

The Tokyo Burn Unit Association (TBUA) was established in 1983 funded by the Tokyo Metropolitan Government, and is organized by 13 burn units in Tokyo. TBUA covers more than 90% of severe burn patients occurring in Tokyo, and all of the cases are registered according to the burn injury registration format. The purpose of this study is to analyze the registered data and to elucidate epidemiological and outcome characteristics of major burn injuries in Tokyo.

The total of 6988 hospitalized patients had data for epidemiological analysis, and 6401 patients had complete data for outcome analysis as well, and were included in this study. The characteristic profiles for the analysis included age, sex, cause of burns, inhalation injury, %BSA, burn index (BI), length of burn unit stay, and outcome, and were analyzed by age groups.

The mean age of the patients was 40.4 years, and 63% of them were male. It was noteworthy that 25% of the total patients were elderly patients over 60 years of age. Flame was the most common cause making up 45.6% followed by scalding (32.0%). The overall mortality rate was 15.4%. Inhalation injury was accompanied in 27.3% of burn patients. The mortality rate was 34.6% with inhalation injury, and 8.2% without inhalation injury. Causes of death showed that multiple organ failure made up 36.9% of total mortality, followed by sepsis 25.2 and shock 19.0%. The burn size (%BSA and BI) and inhalation injury were the factors for high mortality rate in all age groups whereas age was a predictor for high mortality in the patients older than 16 years of age. Gender was not a factor for high mortality in any age group. The mortality rate showed mildly decreasing tendency since 1995 for which implementation of skin bank was thought to be responsible.

© 2004 Published by Elsevier Ltd and ISBI.

Keywords: Burn; Thermal injury; Epidemiology; Elderly; Survival; Skin bank

1. Introduction

Burn is a unique injury which is not only devastating for the patients but also puts a great burden to society by consuming enormous health care resources. As there is no registration system for burn injuries in Japan, little is known on epidemiology and outcome characteristics of burns although a few institution-based analyses with small number of patients have been reported. The Tokyo Burn Unit Association (TBUA) was established in 1983 funded by the Tokyo Metropolitan Government, and the fundamental epidemiological data have been collected for the past 20 years.

The purpose of this study is to elucidate epidemiological and outcome characteristics of major burn injuries in Tokyo.

2. Materials and methods

2.1. Tokyo Burn Unit Association (TBUA)

Two horrible fire accidents triggered to establish TBUA. In 1980, a man set fire with gasoline at a bus in busy Shinjuku area causing 6 dead and 14 severely injured. In 1982, the Hotel New Japan in downtown Tokyo got a big fire resulting in 33 people dead and 29 severely injured. These two events made a sensational press campaign for implementing more capable burn care system in Tokyo. Thus, in 1983, the Tokyo Burn Unit Association was

* Corresponding author. Tel.: +81 3 3964 2898; fax: +81 3 5375 3120.
E-mail address: k-kunio@med.teikyo-u.ac.jp (K. Kobayashi).

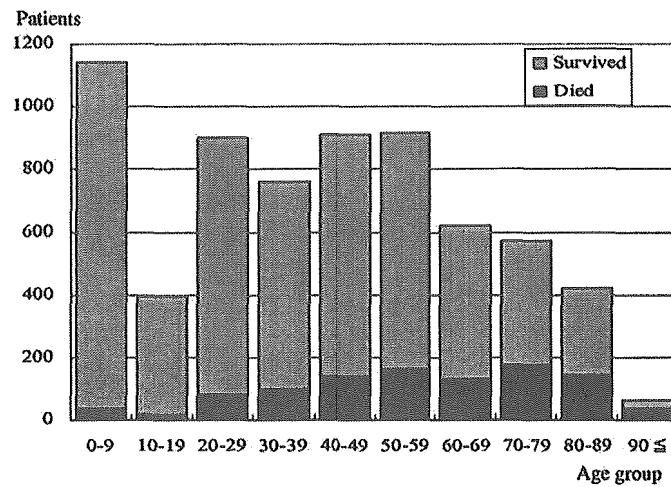


Fig. 1. Age histogram for total admission of TBUA burn patients: elderly patients over 60 years of age were 25% of the total patients.

established funded by the Metropolitan Tokyo Government with a help of the Tokyo Medical Association, which is organized by 13 burn units. A burn unit is required to be prepared for accepting at least one severe burn patient any time, and to have a team with burn care specialists. Although each burn unit qualifies required conditions for a burn unit, treatment for burns, such as resuscitation fluids, a timing of burn surgery or use of antibiotics, may be different from one unit to another. However, the quality of burn care is considered not much different among the 13 burn units as TBUA holds business as well as scientific review meetings four times annually.

The Emergency Medical Service System is well organized in Tokyo, and the Tokyo Fire Department covers the whole area of Metropolitan Tokyo for ambulance services. The total ambulance runs reached as many as 629,883 in the year of 2002 among which 2488 were for burn patients. Only the severely burned patients were transported to the burn units, and 346 burn patients were admitted to the TBUA burn units in the same year. Selection of patients to the burn units is made by ambulance personnel under the medical control system of Tokyo. Although some of the major burn patients may be admitted to nearby tertiary emergency hospitals, it may be said that TBUA covers more than 90% of major burn patients in Tokyo.

2.2. TBUA data base

A total of 6988 hospitalized patients with major burns and/or inhalation injuries treated in 13 burn units were registered in TBUA data file between April 1983 and March 2003. All cases had fundamental epidemiological data, and were included in the epidemiological analysis. As some of the data were lacking from 587 patients in early years, 6401 cases had complete data for outcome analysis, and were included in the outcome study. The characteristic profiles for analysis included age, sex, cause of burn, presence or

absence of inhalation injury, %BSA, burn index (BI = 1/2%BSA of second-degree burns plus %BSA of third-degree burns), length of burn unit stay, hospital outcome, and cause of death. Data were collected using a uniformed format, and the registered data in the file were kept confidential.

2.3. Statistical analysis

For multivariate analysis, multiple logistic regression analysis was used to assess the relative predictive power of age, gender, %BSA, BI, presence of inhalation injury, length of burn unit stay as predictors of mortality. Data management and analysis were proceeded with SPSS 11.0 for windows.

3. Results

Of the 6988 patients there were 4373 male patients and 2615 female patients with male to female ratio of 1.7:1. Average age was 40.4 years ranging from 2 months to 96 years. Age distribution showed that there were 1674 elderly patients over 60 years of age which was 25% of the total (Fig. 1). Average %BSA was 18.8%, and the mortality rate for the 6711 patients was 15.4% excluding 277 patients whose outcome was unknown (Table 1).

Table 1
Characteristics of burn patients admitted to TBUA between April 1983 and March 2003

Total patients	6988
Age (mean \pm S.D.)	40 \pm 25.1
%BSA (mean \pm S.D.)	18.8 \pm 22.9
Burn index (BI) (mean \pm S.D.)	13.9 \pm 20.5
Mean stay in burn unit (days) (mean \pm S.D.)	17.8 \pm 24.7
Mortality rate	15.4% ^a

^a Data of 6711 patients excluding those outcome unknown.

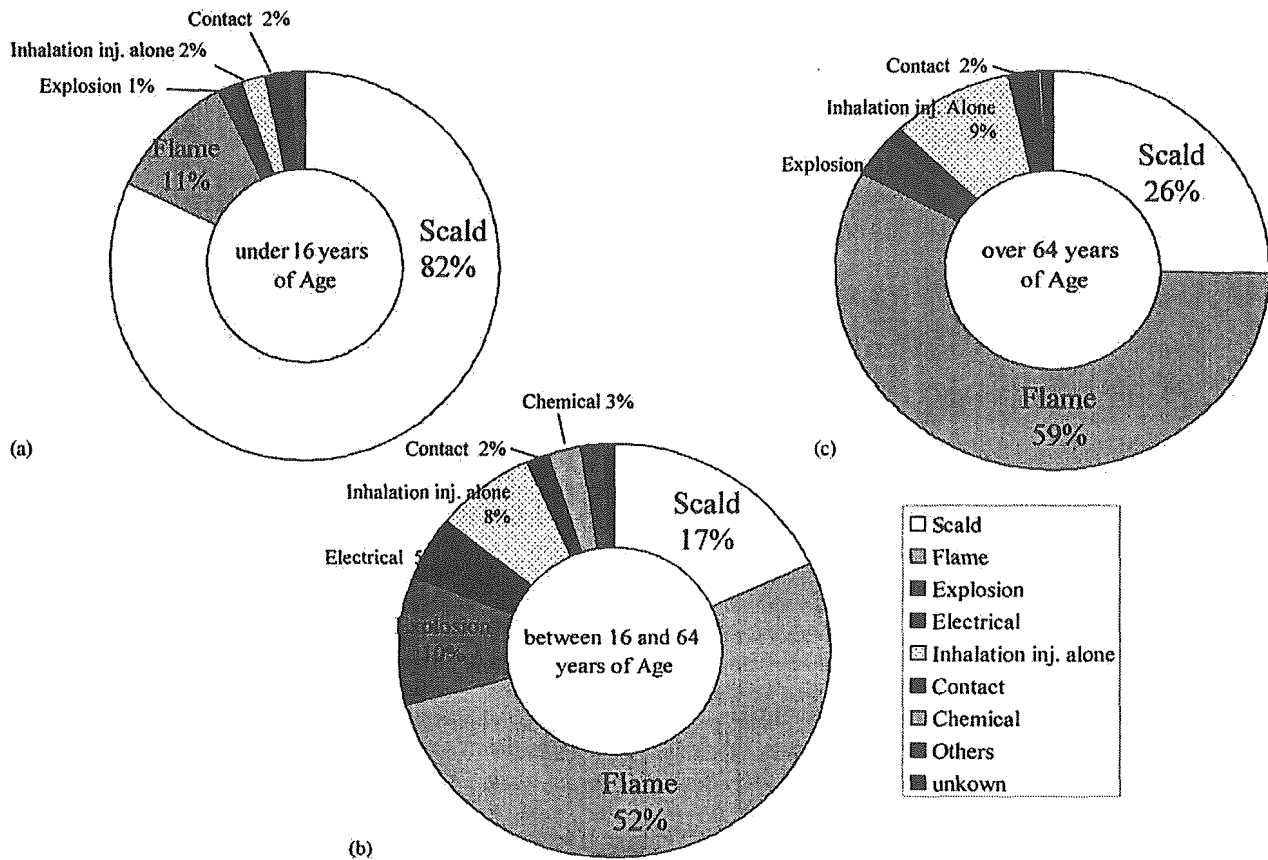


Fig. 2. Causes of burn by age groups: (a) under 16 years of age; (b) between 16 and 64 years of age; (c) over 64 years of Age.

Of the causes of burns flame burns were the most common (46%) followed by scald burns (32%) and burns caused by explosions (7%). When they were stratified by age, causes of burns were very different by the age groups. In the patients under 16 years of age, 82% of the patients had scald burns whereas only 11% had flame burns. In the elderly patient group over 65 years of age, flame was the cause in 59% of burn patients, and scald in 26% of the patients (Fig. 2).

There are many different ways when flame and scalding caused burns. Data were available on 952 patients for flame burns from 1997 to 2002, and on 2064 patients for scald burns from 1984 to 2002. The leading cause of flame burns was a house/building fire with 34%, while those inflicted with daily indoor activities were 21%, and with suicide attempt 19%. The flame burns with a household Buddhist altar caused 4% of the total which may be a unique type of flame burn in Japan. Burn injuries from a hot bath was one of the main causes among various scald burns, accounting for 30.2% of the scald burns. Young children and elderly people were more likely to be injured by a hot bath. Burns sustained in a hot bath are extensive and severe, mostly resulting in high mortality. The mortality rate of scald burn with hot bath was 19.7%, and that of other causes was 1.2%.

Data were available in 6401 patients to estimate association of age, gender, %BSA, BI, flame burns, inhalation injuries, and length of burn unit stay as independent variables with mortality. When independent variables similar to each other were used for logistic regression analysis, the analysis may become incorrect. Thus, each of %BSA (model 1) and BI (model 2) was analyzed as an independent model. It was demonstrated that inhalation injury, %BSA, and BI were factors associated with mortality in all age groups. Although age, flame burns, and length of burn unit stay were significantly related to mortality of the total patients, they were not significant in the younger age group under 16 years of age. Gender was not a factor related to mortality in any age groups (Table 2). The accuracy to predict mortality was 65.5% in model 1 and 66.9% in model 2, indicating that BI was a stronger indicator than %BSA to predict mortality in burn patients.

It is well known that the presence of inhalation injury makes mortality of burn patients significantly higher. Inhalation injuries were seen in 27.3% of the patients included in this study. The mortality rate of the patients with inhalation injury was 34.6%, while in those without inhalation injury the mortality rate was 8.2%. However, it may be speculated that a patient with very severe cutaneous

Table 2
Factors affecting mortality of severe burns by age groups

	A coefficient	Standard error	p-Value	Odds ratio
Model 1: Logistic regression analysis using %BSA as an independent variable				
Whole age, 6401 Cases				
Gender	0.081	0.112	0.469	1.084
Age	0.050	0.003	<0.01	1.051
Inhalation injury	0.927	0.114	<0.01	2.526
Flame burns	0.574	0.120	<0.01	1.776
Burn unit stay	-0.034	0.003	<0.01	0.967
%BSA	0.092	0.003	<0.01	1.096
A constant term	-6.693	0.225	<0.01	0.001
<16 years of age, 1234 Cases				
Gender	0.455	0.483	0.347	1.576
Age	-0.039	0.053	0.463	0.962
Inhalation injury	2.656	0.771	<0.01	14.239
Flame burns	-0.537	0.783	0.492	1.711
Burn unit stay	-0.014	0.008	0.085	0.986
%BSA	0.092	0.011	<0.01	1.096
A constant term	-6.862	0.682	<0.01	0.001
16–64 years of age, 3858 Cases				
Gender	-0.059	0.155	0.704	0.943
Age	0.044	0.006	<0.01	1.045
Inhalation injury	1.118	0.155	<0.01	3.060
Flame burns	0.683	0.167	<0.01	1.980
Burn unit stay	-0.039	0.004	<0.01	0.962
%BSA	0.087	0.004	<0.01	1.090
A constant term	-6.356	0.346	<0.01	0.002
≥65 years of age, 1309 Cases				
Gender	0.250	0.179	0.163	1.284
Age	0.072	0.012	<0.01	1.075
Inhalation injury	0.853	0.193	<0.01	2.348
Flame burns	0.059	0.194	0.760	1.061
Burn unit stay	-0.032	0.004	<0.01	0.969
%BSA	0.114	0.007	<0.01	1.121
A constant term	-8.788	1.015	<0.01	0.000
Model 2: Logistic regression analysis using burn index as an independent variable				
Whole age, 6401 Cases				
Gender	0.120	0.116	0.299	1.128
Age	0.048	0.003	<0.01	1.049
Inhalation injury	0.762	0.116	<0.01	2.143
Flame burns	0.200	0.121	0.098	1.221
Burn unit stay	-0.041	0.003	<0.01	0.960
Burn index	0.123	0.004	<0.01	1.131
A constant term	-6.115	0.220	<0.01	0.002
<16 years of age, 1234 Cases				
Gender	0.466	0.525	0.374	1.594
Age	-0.042	0.058	0.466	0.959
Inhalation injury	2.388	0.809	<0.01	10.891
Flame burns	-0.383	0.860	0.656	0.682
Burn unit stay	-0.021	0.010	0.035	0.980
Burn index	0.148	0.018	<0.01	1.159
A constant term	-6.414	0.655	<0.01	0.002
16–64 years of age, 3858 Cases				
Gender	0.013	0.164	0.937	1.013
Age	0.045	0.006	<0.01	1.046
Inhalation injury	0.971	0.159	<0.01	2.640
Flame burns	0.369	0.168	0.029	1.446
Burn unit stay	-0.047	0.004	<0.01	0.954
Burn index	0.116	0.006	<0.01	1.123
A constant term	-5.990	0.354	<0.01	0.003

Table 2 (Continued)

	A coefficient	Standard error	p-Value	Odds ratio
≥65 years of age, 1309 Cases				
Gender	0.269	0.181	0.137	1.309
Age	0.069	0.012	<0.01	1.071
Inhalation injury	0.787	0.195	<0.01	2.198
Flame burns	0.059	0.194	0.760	1.061
Burn unit stay	-0.037	0.005	<0.01	0.964
Burn index	0.152	0.010	<0.01	1.164
A constant term	-8.105	1.013	<0.01	0.000

burns may die regardless of inhalation injuries. In fact, the mortality rate was significantly higher in the patients with inhalation injury whose %BSA was less than 60%, while those with 60–100%BSA burns showed no difference in mortality with or without inhalation injury. (Fig. 3).

It is interesting to note that mortality rate was markedly increased with inhalation injury in the younger patients under 16 years of age with the odds ratio of 10.89 (Table 2).

The BI resulting in 50% mortality was significantly higher in the non-inhalation injury group than that in the

inhalation injury group (Fig. 4). In both groups of patients BI resulting in 50% mortality showed a tendency to increase after 1995. As there were no revolutionary changes in treatment modalities during these years except implementation of skin bank system in 1994, it was assumed that skin bank had a role in this change. Data on 2559 patients between 1995 and 2002 were analyzed to estimate the association of skin bank implementation with mortality. The implementation of skin bank significantly decreased the risk of mortality with the odds ratio of 0.444 (Table 3).

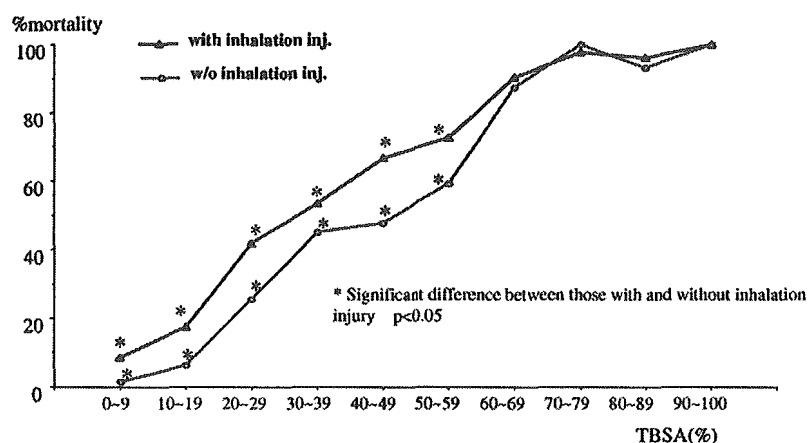


Fig. 3. Mortality of flame burns with or without inhalation injury by TBSA.

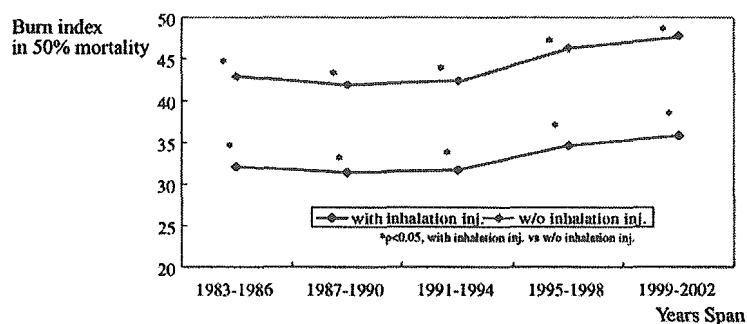


Fig. 4. Changes of burn index (BI) resulting in 50% mortality in 4 years span with and without inhalation injury. BI resulting in 50% mortality was significantly higher in the non-inhalation injury group ($p < 0.05$). BI resulting in 50% mortality showed a tendency to increase in both groups of patients after the year of 1995.

Table 3
Logistic regression analysis estimating mortality with skin bank use 2559 cases from 1995 to 2002

	A coefficient	Standard error	p-Value	odds ratio
Gender	0.337	0.172	0.050	1.401
Age	0.046	0.004	<0.01	1.047
Inhalation injury	1.065	0.177	<0.01	2.900
Flame burns	-0.078	0.187	0.675	0.925
Skin bank use	-0.813	0.300	<0.01	0.444 ^a
Burn index	0.088	0.005	<0.01	1.093
A constant term	-6.667	0.373	<0.01	0.001

^a The use of skin bank allograft significantly decreased the risk of mortality with the odds ratio of 0.444.

With a steady increase of elderly populations, management of elderly burn patients remains a big issue in burn care. It is obvious that the number of elderly burn patients over 65 years of age has increased since 1996, which consists of more than 25% of the total patients in recent years. Fortunately, the mortality rate of these elderly patients shows a tendency of gradual decrease (Fig. 5).

When the causes of death of burn patients were analyzed, they were obviously very different in those who died within 30 days and in those who died after 30 days of burn unit admission. Those who died within 30 days died of shock and inhalation injuries in nearly 40% of the cases. More than 60% of patients who died after 30 days of admission died of multiple organ failure with or without septic complications, followed by sepsis of 28% (Fig. 6).

4. Discussion

The available data are very limited for burn injuries in Japan, and the precise number of burn patients which occur in Tokyo is unknown. The only data available come from Tokyo Fire Department which covers whole area of Tokyo for ambulance services. The annual ambulance runs for burn patients are around 200 per million population, which are somewhat less than the burn patients admitted in a hospital in the US which are reported to be 270–300 per year per million population [1].

Since TBUA was established in 1983, the fundamental epidemiological data have been accumulated for the past 20 years. As TBUA is considered to cover more than 90% of major burn patients in Tokyo, this study represents epidemiological and outcome characteristics of major burns in Tokyo.

The incidence of major burns in Tokyo is 25–30 per year per million population. This is a bit larger than that of 18.37 in urban France [2], and somewhat smaller than that of 42 in USA although major burn is not clearly defined [1].

It is interesting to note that the causes of major burns are quite different by age groups. The patients under 16 years of age sustained scald burns in 82% of cases and flame burns in 11%, whereas in adults more than half of the cases had flame burns. These results were compatible with the reports from the US [3,4]. One-third of scald burns are by hot bath, which may be unique in Japan. A plastic cover board of hot bath softens with hot steam, and a young child

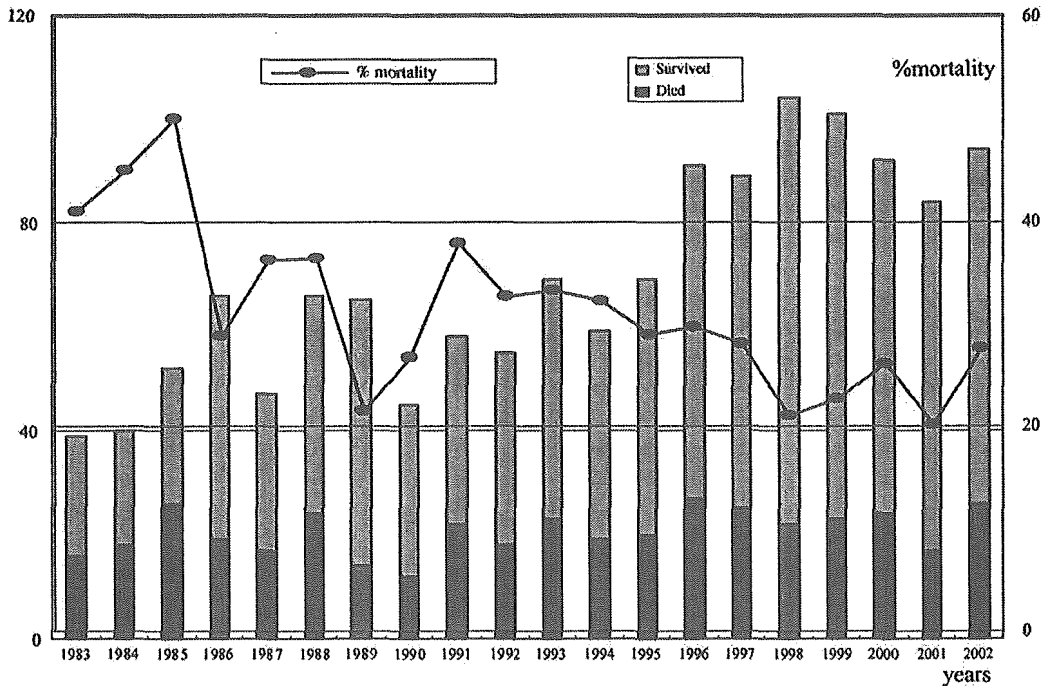


Fig. 5. Annual admission of elderly patients over 65 years of age and changes of mortality.

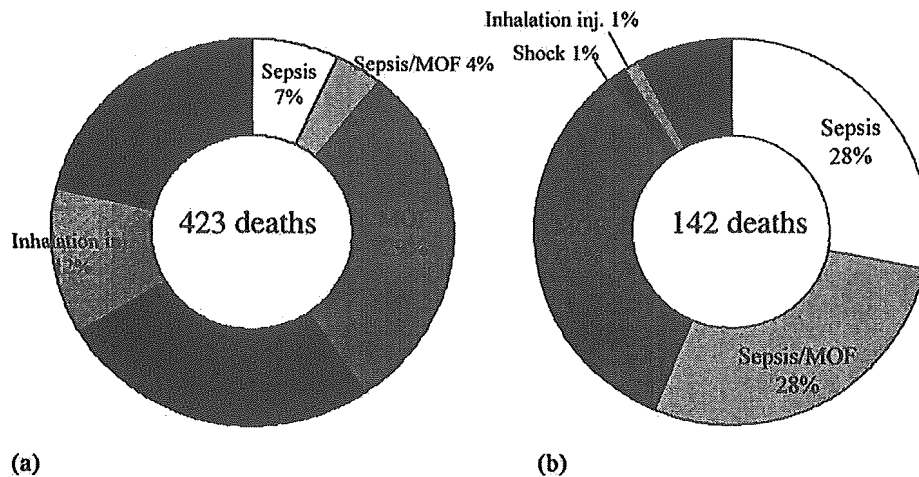


Fig. 6. Causes of death: (a) within 30 days in the burn units; (b) over 30 days in the burn units.

playing on the board may drop into the hot bath. The best management for burn injury is prevention, and the epidemiological study should be utilized for this purpose. The TBUA made a campaign 10 years ago to the manufacturing industry to improve the cover board against heat steam with remarkable decrease of this type of accidents. Among the flame burns fire is the leading cause as in many other countries in the world. Self-inflicted or homicide burn was seen in 19% of cases, which is much more common than that in USA which is reported as 2.5% [1]. Many of the self-inflicted burn patients have psychiatric problems in the background, and set fire after pouring gasoline resulting in very extensive and deep burns. The flame burns with a household Buddhist altar were seen in 4% of flame burn cases, which may be a unique type of burn in Japan. As the candle sits in the front of an altar, elderly people may catch fire with the clothes from a candle when they offer flowers or cakes over a candle, and get deep burn injury mainly in the upper extremity and the chest wall on one side.

Some of the features of 6988 patients included in this study are different from those data of 28 burn centers in USA [3]. Mean burn size was 18.8% in our study versus 14.1%, and the mortality rate was 15.4% versus 5.1%. Among the causes of burn flame burn was seen in 46% of patients in our study versus 50.3% in the US study. The mortality rate among patients with inhalation injury was 34.6% in our study versus 29.4% in the US study. It seems as if care of major burns in Tokyo may not be as efficient as it is in active burn centers in the US. However, age distribution is very different as 25% of patients are elderly patients over 60 years of age in our study while it is 10% in the US study. A report from China documents that high survival rate of major burn is related primarily to the low percentage of elderly patients [5]. The mortality rate of our elderly patients over 65 years of age fluctuates around 30% (Fig. 5), and this is compatible with 30.2% mortality of elderly patients over 60 years of age reported by Wibbenmeyer et al. [4].

According to the logistic regression analysis of our patients with age, gender, inhalation injury, flame burns, %BSA, BI, and length of burn unit stay as independent variables, %BSA, BI, and inhalation injury were the factors affecting mortality of severe burns of all age groups. Age, flame burns, and length of burn unit stay did not affect the mortality of those patients under 16 years of age, and gender was not a factor in all age groups. It has been reported that %BSA, age, and presence of inhalation injury are the major determinants of mortality in major burns [1,3,6–8]. These facts are also confirmed in our study.

There have been controversial reports on gender as a risk factor of septic mortality [9,10]. Recent reports demonstrated increased risk of female sex for high mortality in burn injury [6,11,12]. Our data demonstrated female sex is not a risk factor for burn mortality. Takuma et al using the same data base of TBUA reported that female sex only in the reproductive age group from 16 to 45 years of age was an independent predictor of late mortality after 15 days of admission [13]. These two conflicting results from the same data base suggest that female sex in reproductive age group may have some effect to increase the risk of mortality of major burns, but the effect of gender is only a minor one.

Although it is well known that presence of inhalation injury raises mortality of burn patients, the mortality rate is the same with or without inhalation injury in those patients with %BSA of 60% or more. Barrow et al. reported that those with 81–100% TBSA burns showed no significant difference between burn only and burn plus inhalation injury in children [8]. When survival of extensive burn in adults is improved in future, survival of patients with extensive burn will become significantly different with and without inhalation injury. It is also noteworthy that mortality rate was extremely high when accompanied by inhalation injury in those patients under 16 years of age with odds ratio exceeding 10. The reason for this high risk is unknown. However, flame burn was only 11% of the total in this age group, and the mean %BSA of 43 children with inhalation