Length of hospital stay and mortality associated with burns from assault: a retrospective study with inverse probability weighting analysis

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Abstract

Background: Burns resulting from assaults account for considerable morbidity and mortality among patients with burn injuries around the world. However, it is still unclear whether unfavorable clinical outcomes are associated primarily with the severity of the injuries. To elucidate the direct relationship between burns resulting from assaults and mortality and/or length of hospital stays, we performed this study with the hypothesis that burns from assault would be independently associated with fewer hospital-free days than would burns from other causes, regardless of the severity of burn injuries.

Methods: We conducted a retrospective cohort study, using a city-wide burn registry (1996–2017) accounting for 14 burn centers in Tokyo, Japan. Patients who arrived within 24 hours after injury were included, and those with self-inflicted burn injuries were excluded. Patients were divided into two groups according to mechanism of burns (assault vs. accident), and the number of hospital-free days until day 30 after injury (a composite of in-hospital death and hospital length of stay) was compared between the groups. To estimate the probability that an injury would be classified as an assault, we calculated propensity scores, using multivariate logistic regression analyses adjusted for known outcome predictors. We also performed an inverse probability weighting (IPW) analysis to compare adjusted numbers of hospital-free days.

Results: Of 7419 patients in the registry with burn injuries during the study period, 5119 patients were included in this study. Of these, 113 (2.2%) were injured as a result of assault; they had significantly fewer hospital-free days than did those with burns caused by accident (18 [27] vs. 24 [20] days; coefficient = −3.4 [−5.5 to −1.3] days; p = 0.001). IPW analyses similarly revealed the independent association between assault burn injury and fewer hospital-free days (adjusted coefficient = −0.6 [−1.0 to −0.1] days; p = 0.009).

Conclusions: Burn from assault was independently associated with fewer hospital-free days, regardless of the severity of burn injuries. The pathophysiological mechanism underlying the relationship should be further studied in a prospective observational study.

Key words: Assault, Burn, Mortality, Length of hospital stay, Inverse probability weighting
Background

Burns resulting from assaults, which are relatively uncommon injuries, account for considerable morbidity and mortality among patients with burn injuries around the world [1–4]. Particular types of assault-related burn injury, such as that resulting from child abuse, have been investigated as important social issues, and thoughtful treatment of victims is legally mandated [5,6]. While the prevalence of burns from assault and the motives involved could depend on a victim’s age, sex and socioeconomic circumstances [1–3,7–9], results of some studies have suggested that assault-related burn injuries are associated with higher rates of mortality and longer hospital stays [4,10,11].

Despite the significant clinical outcomes, the pathophysiological relationship between assault burn injuries and unfavorable outcomes has not been elucidated. Several studies have revealed that patients who suffered assault-related burns had larger partial- or full-thickness burns, a higher incidence of inhalation injury and escharotomies were more frequently required, in comparison with patients with accidental burns [4,12]. Nonetheless, it is still unclear whether the higher mortality or longer length of hospital stay is simply a result of the severity of assault burns. A more recent study also demonstrated that more than 50% of patients with assault-related burn injuries had psychiatric comorbidities, which might also affect clinical outcome of burns from assault [13].

Because additional care would be needed if assault is an independent predictor of unfavorable outcome of burn injuries, we sought to clarify the association between assault-related burn injuries and clinical consequences. Using analyses with propensity scores that could reduce the effects of confounding factors in a retrospective study, we examined hospital-free days, a composite of in-hospital death and hospital length of stay, among patients with such injuries in a city-wide database in Japan. We hypothesized that burns from assault would be independently associated with fewer hospital-free days, higher rates of in-hospital mortality and/or longer hospital stays than would accidental burns.

Methods

Study design and setting

We conducted a retrospective cohort study using a Japanese city-wide burn registry that was established in 1984. The registry has been maintained by the Tokyo Burn Unit Association (TBUA), which comprises 14 participating burn centers in Tokyo, Tokyo Fire department, and Tokyo Metropolitan Government. TBUA developed criteria for designation of burn centers and pre- and inter-hospital patient transportation, in which patients with moderate-to-severe burn injury or complicated injury, such as chemical injury, electrical injury or burn injury involving face or genitalia, have been transported directly from scene or transferred from non-burn centers. While 300–400 burn injuries occur among 9.5 million inhabitants in Tokyo, the TBUA covers more than 90% of severe burn patients [14]. Data of patients who needed admission or died before admission were collected prospectively and entered into the online data collection portal by treating physicians or volunteer registrars designated by each hospital.

This study was approved by the Institutional Review Board of the Keio University School of Medicine. The requirement for informed consent was waived because of the anonymous nature of the data being used.

Study population

We retrospectively screened cases in the TBUA registry and identified patients who presented with burn injury at all participating centers from 1996 to 2017. According to the registry, burns were classified by an attending physician as caused by assault on the basis of a history of intentional injury by others, whereas burns were classified as caused by accidents when patients were non-intentionally injured. We included: (1) patients who arrived within 24 hours after injury because delayed burn care would significantly affect outcomes of burn injuries; and (2) those who arrived with a pulse. We excluded patients with self-inflicted burn injuries and those in whom the mechanism of injury was unknown. Patients whose ages were unknown were also excluded.

Data collection and definition

Available patient data included age; gender; medical history; mechanism of burn injury; time of injury; time of hospital arrival; loss of consciousness (LOC) upon arrival; total cutaneous burn area, including full- and partial-thickness total body surface area (TBSA); length of hospital stay; and survival status. Delayed arrival was defined as when a patient presented later than 6 hours after the injury at a collaborating center. Assessment and diagnosis of burn injury, including determination of size and depth of cutaneous burns and recognition of inhalation injury, were made by an attending physician on hospital arrival and confirmed by a board-certified burn surgeon.

Outcome measures

The primary outcome was the number of hospital-free days (defined as the number of days alive and out of the hospital) until day 30 after injury, a composite of in-hospital death and hospital length of stay. Patients who died during the index hospitalization and those who were hospitalized for more than 30 days were classified as having 0 hospital-free days. In patients who were discharged alive before day 30, hospital-free days were calculated as 30 minus number of days of hospital stay [15]. This composite outcome was selected to clarify the effects of assault burn injuries, inasmuch as the mortality rate was expected to be low among these patients; in addition, length of the index hospitalization was another vital clinical outcome. It should also be noted that hospital-free days (mostly up to 28–30 days) have been considered as a metric to quantify the normalcy of life and examined as
primary outcome in several studies of other illnesses, in particular diseases with low in-hospital mortality rates [15,16]. The secondary outcomes included the survival to discharge, recorded in the database as discharge to the patient’s home or to other healthcare facilities, and length of hospital stay.

Statistical analysis

Patients were classified as victims of assault or as victims of accidents, depending on mechanism of injury. We compared the primary and secondary outcomes in these two groups using a generalized linear model as unadjusted analyses.

Because several confounding factors can affect both survival after injury and length of hospital stay, we performed inverse probability weighting (IPW) analyses with propensity scores to compare the primary outcomes of both groups and to assess secondary outcomes [17]. A multivariate logistic regression was used to find propensity scores to predict the probability of being classified as a victim of assault. Relevant covariates were carefully selected from known or potential variables that could predict favorable clinical outcomes of burn injury—such as TBSA, depth of burn injury, comorbidities and delayed hospital arrival—and entered into the propensity model to ensure high-fidelity propensity scores [18–23]. Although age might have affected clinical outcomes, it was not entered into the model because the influence of age would be different between pediatric and adult patients and would therefore have to have been adjusted separately from other covariates. Patients with missing covariates were excluded from the propensity score calculation. The precision of discrimination and calibration of propensity score were analyzed with the c-statistic and the Hosmer–Lemeshow goodness-of-fit test [24].

The IPW analyses were performed as adjusted analyses, in which primary and secondary outcomes were compared in a generalized linear model adjusted for age. Then we used Bayesian analysis for the primary outcome to perform sensitivity analyses to validate the primary results, in which an assumption of no effect from assault burn injuries was used as the prior probability [25].

Several subgroup analyses were also performed to evaluate the heterogeneity of patients with burns from assault. Because the effect of age might have been different between pediatric and adult patients, one of the selected subgroups included pediatric patients (aged ≤11 years; younger than adolescence based on the Age Stages Definition of the National Institute of Child Health and Human Development in the US [26]), and another subgroup consisted of elderly patients (aged ≥65 years). Primary outcomes of the assault and accident groups were compared for the selected patients in unadjusted and IPW analyses.

Descriptive statistics were calculated as medians (interquartile range [IQR]) or numbers (and percentages). Results were compared using unpaired \( t \) tests, the Mann–Whitney \( U \) test, chi-square tests or Fisher’s exact test, as appropriate. To test all hypotheses, a two-sided \( \alpha \) threshold of 0.05 was considered statistically significant. All statistical analyses were conducted with SPSS Statistics, version 25.0 (IBM, Armonk, NY, US), and with Microsoft Excel (Microsoft, Redmond, WA, US).

Results

After the screening process, 7419 patients with burn injuries who presented to collaborating hospitals during the study period were identified. Of these patients, 6205 arrived within 24 hours after injury (1110 arrived more than 24 hours after injury), but 287 arrived in cardiac arrest. Although the remaining 5918 patients satisfied all the inclusion criteria, 476 were excluded from the study because their burn injuries were self-inflicted, and another 322 were excluded because the mechanism of injury was unknown. The patient flow diagram is depicted in Fig. 1.

In total, 5119 patients were eligible for inclusion in this study; 113 (2.2%) of them had been injured through assault and 5006 (97.8%) were injured accidentally. The patient characteristics are summarized in Table 1. Injuries in assault victims were more severe than those in accident victims: for percentage of TBSA burned, the median values were 10% (IQR, 26) versus 6% (IQR, 13), respectively; for partial-thickness burn areas, the median values were 7% (IQR, 14) versus 4% (IQR, 10), respectively; and for full-thickness burn areas, the median values were 0% (IQR, 9) versus 0% (IQR, 1), respectively. The percentage of assault victims who presented with chemical burns was higher than that of accident victims (14 [12.4%] versus 98 [2.0%], respectively), and a higher percentage of assault victims had delayed hospital arrivals (12 [10.6%] versus 284 [10.1%], respectively). A lower percentage of assault victims than of accident victims suffered from inhalation injury (8 [7.1%] versus 845 [16.9%], respectively). Age, comorbidities and other mechanisms of burn injuries were statistically comparable between the two groups.

Because the distributions of the known confounding variables that predict clinical outcomes of patients with burn injuries were biased, we performed IPW analyses with propensity scores. The final propensity model that could predict which patients would be classified as assault victims included covariates such as sex, comorbidities, mechanism of burn injuries (scalding, flame, explosion or inhalation), LOC on arrival, partial- and full-thickness burn areas and the time between injury and hospital arrival. In the final model, sufficient discrimination and calibration were validated for the propensity scores (c-statistic = 0.667; and Hosmer–Lemeshow goodness-of-fit \( p = 0.811 \)). Eighteen assault victims and 706 patients in the accident group were excluded from IPW analyses because of missing covariates for the calculation of propensity scores, and so IPW analyses were performed for 4395 patients. The characteristics of the patients are summarized with standardized differences in covariates before and after IPW in Table 1.
There were significantly fewer hospital-free days until day 30 after injury for patients with burns from assault than for those with burns from accidents in unadjusted analyses (medians of 18 days [IQR, 27] versus 24 days [IQR, 20], respectively; coefficient = −3.4 days; 95% confidence interval [CI], −5.5 to −1.3 days; \( p = 0.001 \); Table 2), and the IPW analyses similarly revealed the independent association between assault burn injuries and decrease in hospital-free days (medians of 21 days [IQR, 17] versus 24 days [IQR, 20], respectively; coefficient = −0.6 days; 95% CI, −1.0 to −0.1 days; \( p = 0.009 \); Table 2).

Bayesian analysis for the primary outcome was performed as a sensitivity analysis with an assumption that assault burn injuries had no effect on hospital-free days. The posterior distribution demonstrated that burns from assault were independently associated with fewer hospital-free days until day 30 after injury, with significant high probability (95% credible interval, −1.0 to −0.1 days; Supplemental Figure S1).

Secondary outcomes, including survival to discharge and length of hospital stay, did not differ between the assault and accident groups in unadjusted analyses (100 [88.5%] versus 4326 [92.6%]; \( p = 0.104 \), and 10 days [IQR, 21] versus 5 days [IQR, 15]; \( p = 0.057 \), respectively). In the IPW analyses, the rate of survival to discharge was higher among assault victims than among accident victims, whereas lengths of hospital stay were similar for both groups (Table 2).

Subgroup analyses were performed to evaluate the heterogeneity of patients with burn injuries. Among the pediatric patients (aged \( \leq 11 \) years), unadjusted and IPW analyses showed that the assault victims had fewer hospital-free days than did the accident victims (unadjusted coefficient = −7.4 days; 95% CI, −13.4 to −1.5 days; \( p = 0.014 \), and adjusted coefficient = −1.8 days; 95% CI, −3.2 to −0.3 days; \( p = 0.016 \); Table 3). The rate of survival to discharge was also lower among the assault victims than among the accident victims (5 [71.4%] versus 808 [99.0%], respectively; odds ratio = 0.03; 95% CI, 0.004 to 0.15; \( p = 0.003 \); Table 3).
### Table 1. Characteristics of patients with burn injury

| Characteristic                        | Before IPW | After IPW<sup>a</sup> | Standardized difference | P   | Standardized difference |
|---------------------------------------|------------|-------------------------|--------------------------|-----|-------------------------|
| Cases, n                              | 113        | 5006                    |                          |     |                         |
| Age: median (IQR), years              | 47 (27)    | 47 (43)                 | 3.2%                     | 0.457 |                          |
| Sex: male, n (%)                      | 70 (61.9%) | 3153 (63.0%)            | 2.2%                     | 0.815 |                          |
| Mechanism of burn injury, n (%)       |            |                         |                          |     |                         |
| Scalding or contact                   | 32 (28.3%) | 1654 (33.0%)            | 10.3%                    | 0.291 |                          |
| Flame                                 | 59 (52.2%) | 2163 (43.2%)            | 18.1%                    | 0.056 |                          |
| Electrical                            | 0 (0.0%)   | 158 (3.2%)              | 25.5%                    | 0.051 |                          |
| Chemical                              | 14 (12.4%) | 98 (2.0%)               | 41.3%                    | <0.001 |                          |
| Inhalation                            | 8 (7.1%)   | 845 (16.9%)             | 30.5%                    | 0.006 |                          |
| Others                                | 0 (0.0%)   | 88 (1.8%)               |                          |     |                         |
| Comorbidities, n (%)                  | 9 (8.0%)   | 683 (13.6%)             | 18.4%                    | 0.081 |                          |
| Psychiatric disease                   | 5 (4.4%)   | 183 (3.7%)              |                          |     |                         |
| Neurological disease                  | 1 (0.9%)   | 123 (2.5%)              |                          |     |                         |
| Disability                            | 0 (0.0%)   | 53 (1.1%)               |                          |     |                         |
| Significant past medical history<sup>b</sup> | 3 (2.7%)   | 374 (7.5%)              |                          |     |                         |
| LOC on arrival, n (%)                 | 10 (8.8%)  | 400 (8.0%)              | 3.1%                     | 0.734 |                          |
| Missing data                          | 4 (3.5%)   | 167 (3.3%)              |                          |     |                         |
| Total burn area: % TBSA, median (IQR) | 10 (26)    | 6 (13)                  | 45.6%                    | <0.001 |                          |
| Partial-thickness burn area: % TBSA, median (IQR) | 7 (14) | 4 (10) | 24.7% | 0.001 | 5 (10) | 4 (10) | 5.7% |
| Missing data                          | 0 (0.0%)   | 5 (0.1%)                |                          |     |                         |
| Full-thickness burn area: % TBSA, median (IQR) | 0 (9) | 0 (1) | 37.4% | 0.001 | 0 (1) | 0 (1) | 1.8% |
| Missing data                          | 1 (0.9%)   | 57 (1.1%)               |                          |     |                         |
| Time from injury to arrival: hours, median (IQR) | 1.0 (2.0) | 1.0 (1.3) | 16.3% | 0.947 | 1.0 (1.3) | 1.0 (1.3) | 1.9% |
| Missing data                          | 20 (14.8%) | 914 (14.6%)             |                          |     |                         |
| Delayed arrival at hospital<sup>c</sup>, n (%) | 12 (10.6%) | 284 (5.7%) | 18.2% | 0.020 | 342 (7.9%) | 278 (6.3%) | 6.0% |
| Missing data                          | 14 (12.4%) | 506 (10.1%)             |                          |     |                         |

<sup>a</sup>IPW inverse probability weighting, IQR interquartile range, LOC loss of consciousness, TBSA total body surface area

<sup>b</sup>The ns in these columns indicate estimated numbers of patients, adjusted by weighting with propensity scores.

<sup>c</sup>Significant medical history includes diabetes mellitus, chronic kidney disease, chronic liver disease, cerebrovascular accident, chronic obstructive pulmonary disease, congestive heart failure and malignant neoplasm.

<sup>d</sup>Delayed arrival at hospital is defined as hospital arrival 6 hours or more after injury

### Table 2. Effect of assault injury on number of hospital-free days and secondary outcomes

|                           | Assault | Accident | Coefficient/odds ratio | 95% CI | P       |
|---------------------------|---------|----------|------------------------|--------|---------|
| Hospital-free days before day 30, median (IQR) | 18 (27) | 24 (20) | -3.4                   | -5.5 to -1.3 | 0.001   |
| Survival to discharge, n (%) | 100 (88.5%) | 4326 (92.6%) | 0.61                  | 0.34 to 1.11 | 0.104   |
| Length of hospital stay, days: median (IQR)    | 10 (21) | 5 (15)  | -0.9                   | -1.8 to 0.03 | 0.057   |

<sup>a</sup>Unadjusted analyses

<sup>a</sup>IPW analyses<sup>a</sup>

<sup>a</sup>CI confidence interval, IPW inverse probability weighting, IQR interquartile range

<sup>a</sup>In the IPW analyses, assault burn injury was examined in generalized linear model adjusted for age
Table 3. Effect of assault injury in subgroup analyses

|                      | Assault | Accident | Coefficient/odds ratio | 95% CI | P      |
|----------------------|---------|----------|------------------------|--------|--------|
| Pediatric patients (age ≤11 years) |          |          |                        |        |        |
| Hospital-free days before day 30, median (IQR) | 19 (29) | 26 (9)   | −7.4                   | −13.4 to −1.5 | 0.014 |
| Survival to discharge, n (%) | 5 (71.4%) | 808 (99.0%) | 0.03          | 0.004 to 0.15 | 0.003 |
| Adjusted hospital-free days before day 30, median (IQR) | 29 (10) | 25 (9) | −1.8                   | −3.2 to −0.3  | 0.016 |

Elderly patients (age ≥65 years)

| Hospital-free days before day 30, median (IQR) | 2 (22) | 17 (27) | −5.2                   | −12.2 to 1.9  | 0.150 |
| Survival to discharge, n (%) | 401 (92.2%) | 1009 (82.9%) | 2.43          | 1.66 to 3.56  | <0.001 |
| Adjusted hospital-free days before day 30, median (IQR) | 23 (14) | 18 (27) | 4.1                   | 2.8 to 5.3   | <0.001 |

CI confidence interval, IPW inverse probability weighting, IQR interquartile range
*IPW analyses were performed as adjusted analyses, in which assault burn injury was examined in generalized linear model further adjusted for age

Subgroup IPW analyses of elderly patients (aged ≥65 years) showed that assault victims had more hospital-free days than did accident victims (coefficient = 4.1 days; 95% CI, 2.8 to 5.3 days; p < 0.001; Table 3).

Discussion

In this study, we demonstrated that assault burn injury was independently associated with fewer hospital-free days. The relationship was consistent according to a sensitivity analysis, which indicates that the results were not dependent on the method of IPW, propensity scores or statistical approach.

Directness behind the relationship between assault burn injuries and unfavorable outcomes remains unclear. Several studies have shown that burn from assault was related to higher rates of mortality and longer length of hospital stay [10–12,27]; however, it was not clear whether the worse outcome of assault burn injury was associated primarily with the severity of burn, such as higher TBSA injured or higher incidence of inhalation injury, or with the fact that it resulted from assault. O’Halloran et al. [4] retrospectively analyzed 25 adult patients with assault-related burn injury and found that a higher percentage of TBSA was injured, the incidence of concomitant fracture was higher and the rate of admission to an intensive care unit was higher than for patients with unintentional burns; these events might have increased mortality and lengthened hospital stay. However, Hodgman et al. [28], who performed another retrospective study at a pediatric burn center in the US, found that abuse-related burn was a significant predictor of mortality after adjustments for age, mechanism of burn injury and TBSA injured; this finding was similar to our results. Because the effects of assault-related burn injury on clinical outcomes were more severe among pediatric patients than elderly patients in the subgroup analyses of our study, the independent association between burns from assault and unfavorable outcome are robust, at least among younger patients.

Several pathophysiological reasons should be considered for the relationship between assault burn injuries and the lower number of hospital-free days observed in this study. A prospective observational study on 311 intentional burns identified psychological disturbances in all victims [13], and another retrospective study on 43 patients with assault-related burn injuries demonstrated that 19% of the patients had incomplete burn care because they left the healthcare center prematurely [29]. Furthermore, a considerable number of patients with burns who suffered from assaults reportedly lacked knowledge about first aid requirements for their injuries, failing to seek immediate medical assistance or sufficient acute care [30,31]. Other possible factors, such as psychosocial consequences of assault burn victims, might be reasons for unfavorable outcomes in patients with assault-related burn injury. Previous studies reported that individuals who suffered from assault burn injuries showed high levels of psychological distress, including social anxiety and avoidance, depression and uncooperative behavior [32,33].

We conducted this study to elucidate the independent association between assault burn injuries and unfavorable clinical outcomes by adjusting for known or potential confounding factors—including age and percentage of TBSA injured, as well as depth of burn injury, comorbidities and delayed hospital arrival—that had not been adjusted for in previous studies. We believe that burn from assault was validated as an independent predictor of fewer hospital-free days, one of the significant clinical outcomes.

The results in this study must be interpreted within the context of the study design. We examined composite outcome as the primary outcome, not mortality or length of hospital stay, which might have led to overestimates of the effect of assault-related burn injury on clinical consequences. However, survival is not necessarily a favorable outcome in patients who sustain disability or lose independence in the performance of daily activities; moreover, prolonged hospitalization of up to 30 days after injury might be considered an unfavorable outcome. Therefore, fewer hospital-free days would reflect another undesired outcome of assault-related burn injuries.

Another limitation of this study is the fact that the independent relationship between burns from assault and fewer hospital-free days might not be applicable in all age groups. Subgroup analyses for elderly patients (aged ≥65 years) with burn injuries revealed that they had more hospital-free days,
which was contrary to findings in the other age groups; thus, our results might not be pertinent among elderly patients.

Furthermore, this study included only 113 assault burn injuries in Tokyo, where we believe infrastructure and health systems are well organized with minimal variations of sociodemographic condition across regions, which may limit the generalizability of our findings. As patients in an underdeveloped social environment, those living with suboptimal access to healthcare facilities or those who experienced delayed arrival to hospitals more than 24 hours after injury were not examined in this study, our results might be adopted only in patients across regions with similar socioeconomic circumstances.

Finally, because this was a retrospective study, residual confounding and unmeasured outcome predictors would exist. It should be emphasized that several important covariates, such as fluid resuscitation, timing and type of surgery, and respiratory management, were not available in the database, which might be impediments to confirming the independent association between assault-related burn injury and fewer hospital-free days. Additional clinical investigations, including a prospective observational study, must be conducted to validate our results.

**Conclusions**

Assault-related burn injuries were independently associated with fewer hospital-free days. Management of patients with such injuries should be undertaken with extra caution, regardless of the severity of burn injury, because of the unfavorable consequences and the potential need for additional care because of uncooperative behavioral or psychiatric symptoms.

**Abbreviations**

IPW: inverse probability weighting; LOC: loss of consciousness; TBSA: total body surface area; TBUA: Tokyo Burn Unit Association

**Supplementary data**

Supplementary data is available at *Burns & Trauma Journal* online.

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**Availability of data and materials**

The data related to this study were used under license from the Tokyo Burn Unit Association, and restrictions apply to the public availability of these data. Data are, however, available from the authors upon reasonable request and with permission of the Tokyo Burn Unit Association.

**Authors’ contributions**

RY and JS conceived and designed the study. RY and MT acquired and managed the data. RY contributed to analysis and interpretation of the data and drafted the manuscript. RY, MT, and TK contributed substantially to critical revision of the manuscript for important intellectual content. JS contributed to statistical expertise and study supervision.

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of the Keio University School of Medicine. Requirement for informed consent was waived because of the anonymous nature of the data being used.

**Consent for publication**

Not applicable.

**Conflicts of interest**

The authors declare that they have no competing interests.

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