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Complete List of Authors:	Toida, Chiaki; The University of Tokyo, Department of Disaster Medical Management; Yokohama City University Graduate School of Medicine, Department of Emergency Medicine Muguruma, Takashi; Yokohama City University Graduate School of Medicine, Department of Emergency Medicine Gakumazawa, Masayasu; Yokohama City University Graduate School of Medicine, Department of Emergency Medicine Shinohara, Mafumi; Yokohama City University Abe, Takeru; Yokohama City University Graduate School of Medicine, Department of Emergency Medicine Takeuchi, Ichiro; Yokohama City University

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Article

Evaluating the definition of Severely Injured Patients: A Japanese Nationwide 5-Year Retrospective Study

Chiaki Toida [1,2]*, Takashi Muguruma [2], Masayasu Gakumazawa [2], Mafumi Shinohara [2], Takeru Abe [2], and Ichiro Takeuchi [2]

1 Department of Disaster Medical Management, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; toida-ygc@umin.ac.jp

2 Department of Emergency Medicine, Yokohama City University Graduate School of Medicine, 4-57 Urafunecho, Minami-ku, Yokohama 232-0024, Japan; mgrmtks@gmail.com (T.M.); gakumazawa-tuk@umin.ac.jp (M.G.); s_mafumi@yokohama-cu.ac.jp (M.S.); abet@yokohama-cu.ac.jp (T.A.); takeqq@yokohama-cu.ac.jp (I.T.)

* Correspondence: toida-ygc@umin.ac.jp; Tel.+81-3-3815-5411

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Abstract:

Objectives: The definition of severely injured patients lacks universal consensus based on quantitative measures. The most widely used definition of severe injury is based on the Injury Severity Score (ISS), which is calculated using the Abbreviated Injury Scale (AIS) in Japan. This study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with ISS ≥16, ISS ≥18, and ISS ≥26 by age groups.

Design: Retrospective cohort study.

Setting: Japan Trauma Data Bank, which is a nationwide trauma registry with data from 280 hospitals.

Participants: We utilized data of 117,201 injured patients from a national database. We included injured patients who were transferred from the scene of injury by ambulance and/or physician.

Primary and secondary outcome measures: Prevalence, in-hospital mortality, and odds ratio (OR) for mortality with respect to age and injury level (ISS group).

Results: In all age categories, the in-hospital mortality of patient groups with an ISS≥16, ISS≥18, and ISS≥26 was 13.3%, 17.4%, and 23.5%, respectively. The in-hospital mortality for patients aged > 75 years was the highest (20% greater than that of the other age groups). Moreover, in-hospital mortality for age group 5–14 years was the lowest (4.0–10.9%). In all the age groups, the OR for mortality for patients with ISS≥16, ISS≥18, and ISS≥26 was 12.8, 11.0, and 8.4, respectively.

Conclusions: Our results revealed the lack of an acceptable definition, with a high in-hospital mortality and high OR for mortality for all age groups.

Keywords: severely injured patient; trauma scoring system; anatomical severity definition; mortality risk; Japan Trauma Data Bank

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Strengths and limitations of this study

- This study is the first nationwide study in Japan to evaluate in-hospital mortality and odds ratio for mortality in patients with severe injury according to age.
- We used a nationwide multi-institutional trauma database with a large sample size.
- The Japanese nationwide dataset with more missing data may have led to selection bias.
- The Japan Trauma Databank had used AIS 90 until 2018, which is not newest measure.

1. INTRODUCTION

The terminology used to quantify anatomical injury severity has been vaguely described for many decades using various phrases, such as severely injured and major trauma.[1–5] Although the most widely used definitions continue to rely on patients who have a high mortality and morbidity risk and require intense medical resources, such as massive resuscitation, multiple surgical operations, intensive care, and complex rehabilitation programs,[4,5] the definition lacks a universal consensus with quantitative measures.[2,3]

The most widely used definition of severely injured patients is the Injury Severity Score (ISS),[6] which is calculated using the Abbreviated Injury Scale (AIS).[7] Thirty years ago, an ISS cutoff value of ≥16 was defined as ‘severely injured’ because patients with an ISS ≥16 had an expected mortality rate of > 20%.[1] However, the mortality of patients with an ISS ≥16 and ISS ≥26 decreased from 12.4% to 9.3% and from 25.4% to 20.3%, respectively, during the 10-year study period, due to a reduction in mortality and/or morbidity associated with organized trauma systems.[8]

Research based on the Japanese nationwide trauma registry has also shown that the in-hospital mortality trend has decreased in injured patients.[9–11] Moreover, there are more age-related differences in the mortality of severely injured patients in Japan than in the other developed countries because Japan has faced issues with the declining birth rate and aging population.[11,12] To date, no study has evaluated the validity of the definition of severe injury in a Japanese cohort using a detailed classification of the definition cutoff values and age groups. Therefore, this study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with ISS ≥16, ISS ≥18, and ISS ≥26 as the commonly used anatomical injury definitions by age group.[2]

2. MATERIALS AND METHODS

2.1. Study setting and population

This retrospective observational nationwide study was conducted based on data obtained from the Japan Trauma Data Bank (JTDB), which registers data of patients with an injury and/or burn, and records prehospitalization- and hospital-related information. The JTDB includes data on demographic characteristics, comorbidities, injury types, mechanism of injury, means of transportation, vital signs, AIS score, prehospital/in-hospital procedures, injury diagnosis as indicated by the AIS, and clinical outcomes. In most cases, physicians trained in AIS coding record the online registration of individual patient data. There were 280 participating hospitals in all 47 prefectures in Japan, including 92% of the Japanese government-approved tertiary emergency medical centers in March 2019. The Japan Association for the Surgery of Trauma permits open access and updating of existing medical information, and the Japan Correlation for Acute Medicine evaluates the submitted data.

In this study, we used the JTDB dataset that included information from January 1, 2014 to December 31, 2018, which initially yielded the data of 181,971 patients. The inclusion criterion for this study was injured patients who were transferred from the scene of injury by ambulance and/or physician. Patients with cardiac arrest on hospital arrival or with missing key data such as mechanism, age, ISS, and/or survival outcome were excluded from this study. Figure 1 presents a flow diagram of the patient selection process in this study.

2.2. Data collection

We collected information from the JTDB, including the following variables: demographic characteristics (age [years], sex, injury mechanism, transportation type, transfer process), and clinical parameters (AIS of the injured region, ISS). In the JTDB, a patient with an AIS of the injured region ≥3 was defined as a case of a severely injured region.

2.4. Ethics statement

This study was approved by the hospital ethics committee of Yokohama City University Medical Center (approval no. B170900003). The approval authority for data access was provided by the Japanese Association for the Surgery of Trauma (Trauma Registry Committee). The requirement for informed consent from the patients was waived owing to the observational nature of the study.

2.5. Statistical analysis

The outcomes were as follows: prevalence, in-hospital mortality, and OR for mortality with respect to age group (0−4, 5−14, 15−24, 25−34, 35−44, 45−54, 55−64, 65−74, ≥75 years) and injury severity (ISS ≥16, ISS ≥18, and ISS ≥26; the ISSs of these groups were used as the definitions of anatomical injury in a previous review article.[2]

Continuous variables are presented as medians with interquartile range (IQR, Q1–Q3), and categorical variables are presented as the number and percentage of patients. The Mann–Whitney U test and Wilcoxon's rank-sum test were used to analyze continuous variables, whereas the chi-square test was used to analyze categorical variables. OR (95% confidence intervals, CI) for mortality was calculated using a logistic regression model. All statistical analyses were performed using STATA/SE software (version 17.0; StataCorp; College Station, Texas, USA). Statistical significance was defined as a two-tailed P-value of <0.05.

2.6. Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. We will not directly disseminate our findings to involved participants but plan to disseminate them through publication of this study.

3. RESULTS

During the 5-year study period, we analyzed the data of 117,201 injured patients transferred from the scene of injury; 113,435 (97%) of them had blunt trauma (Figure 1) (Table 1). The median age and ISS score were 64 years (IQR, 41–78) and 10 (IQR, 9–19), respectively. The overall in-hospital mortality rate was 9.0%.

Table 1 shows the characteristics by age group and injury severity group during the 5-year study period. The number of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 48,028 (41% of all the patients), 32,225 (28%), and 15,343 (13%), respectively.

Table 2 shows in-hospital mortality and OR for mortality with respect to age group and injury severity. In all age categories, the in-hospital mortality of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 13.3%, 17.4%, and 23.5%, respectively. In each age category, the in-hospital mortality for patients aged > 55 years was higher than that for younger age groups, and that of patients aged > 75 years was higher (by more than 20%) than that of all patient groups for each level of injury severity. In-hospital mortality for the 5–14 years age group was 4.0–10.9% and lower than that for the other age groups.

In all age categories, the OR for mortality by patient group was 12.8 (11.9–13.8), 11.0 (10.4–11.6), and 8.4 (8.0–8.8), respectively, for the three levels of injury severity, and the OR in patients with ISS ≥16 or ISS ≥18 was higher than that in patients group ISS ≥26.

144 **Table 1. Characteristics by the nine age groups and three levels of injury severity groups.**

Variables	Overall n = 117,199	Age 0–4 n = 1095	Age 5–14 n = 4079	Age 15–24 n = 10,743	Age 25–34 n = 7919	Age 35–44 n = 9952	Age 45–54 n = 12,188	Age 55–64 n = 13,931	Age 65–74 n = 20,044	Age ≥ 75 n = 36,705
Age, years	64 (41–78)	2 (1–3)	10 (7–12)	20 (17–22)	29 (27–32)	40 (38–42)	49 (4[illegible]–52)	60 (57–62)	69 (67–72)	83 (79–87)
Male	16,317 (44)	675 (62)	2985 (73)	8095 (75)	6008 (75)	7710 (77)	[illegible] (76)	10017 (72)	12662 (63)	16317 (44)
Mechanism of injury										
Blunt	113,435 (97)	1073 (98)	4020 (99)	10,477 (98)	7508 (95)	9361 (94)	11,47[illegible] (94)	13,383 (96)	19,433 (97)	36,705 (99)
Injury region										
Head injury with AIS ≥ 3	36,244 (31)	439 (40)	1213 (30)	2798 (26)	1933 (24)	2527 (25)	3363 (28)	4451 (32)	7384 (37)	12,136 (33)
Facial injury with AIS ≥ 3	940 (0.8)	4 (0.4)	33 (0.8)	150 (1.4)	109 (1.4)	128 (1.3)	124 (1.0)	123 (0.9)	133 (0.7)	136 (0.4)
Neck injury with AIS ≥ 3	478 (0.4)	6 (0.6)	2 (0.1)	27 (0.3)	39 (0.5)	55 (0.6)	70 (0.6)	77 (0.6)	110 (0.6)	92 (0.3)
Chest injury with AIS ≥ 3	256,723 (22)	148 (14)	622 (15)	2831 (26)	2110 (27)	2759 (28)	3485 (29)	3726 (27)	4594 (23)	5448 (15)
Abdominal and pelvic injury with AIS ≥ 3	5407 (5)	27 (2)	185 (5)	805 (7)	591 (7)	682 (7)	709 (6)	684 (5)	831 (4)	893 (2)
Spinal injury with AIS ≥ 3	13,146 (10)	12 (1)	128 (3)	861 (8)	788 (10)	1120 (11)	1530 (13)	2106 (15)	3053 (15)	3548 (10)
Upper extremity injury with AIS ≥ 3	6562 (6)	57 (5)	590 (14)	581 (5)	522 (7)	711 (7)	849 (7)	798 (6)	1026 (5)	1428 (4)
Lower extremity injury with AIS ≥ 3	31,526 (27)	124 (11)	634 (16)	2143 (20)	1660 (21)	2055 (21)	2404 (20)	2691 (19)	4358 (22)	15,457 (42)
Injury Severity Score	10 (9–19)	9 (4–16)	9 (5–16)	10 (5–19)	10 (6–20)	13 (9–20)	13 (9–21)	14 (9–21)	14 (9–21)	9 (9–17)
Actual in-hospital mortality	3361 (9.0)	23 (2.1)	48 (1.2)	354 (3.3)	310 (3.9)	372 (3.7)	[illegible]33 (7.4)	762 (5.5)	1438 (7.2)	3361 (9.0)
Injury Severity Score ≥ 16	48,028 (41)	376 (34)	1166 (29)	3878 (36)	3043 (38)	4076 (41)	5297 (43)	6541 (47)	9711 (48)	13,940 (37)
Injury Severity Score ≥ 18	32,225 (28)	187 (17)	747 (18)	2954 (28)	2305 (29)	2985 (30)	3793 (31)	4372 (31)	6256 (31)	8626 (23)
Injury Severity Score ≥ 26	15,343 (13)	62 (6)	367 (9)	1595 (15)	1129 (14)	1481 (15)	1823 (15)	2038 (15)	2910 (15)	3938 (11)

145 Data are presented as number (percentage) or median (interquartile range Q1–Q3); AIS, Abbreviated Injury Scale

146 **Table 2. In-hospital mortality and odds ratio for mortality of patient groups with ISS ≥ 16, ISS ≥ 18, and ISS ≥ 26.**

	Overall n = 117,199			Age 0–4 n = 1095			Age 5–14 n = 4079			Age 15–24 n = 10,743			Age 25–34 n = 7919		
	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)
ISS ≥ 16	48,028	13.3	12.8 (11.9–13.8)	376	5.9	44.6 (6.0–332.4)	1166	4.0	59.8 (14.5–246.7)	3878	8.6	34.1 (21.4–54.2)	3043	9.8	48.2 (26.4–88.1)
ISS ≥ 18	32,225	17.4	11.0 (10.4–11.6)	187	11.2	57.3 (13.3–246.7)	747	5.8	40.6 (16.0–103.0)	2954	11.0	33.1 (22.6–48.5)	2305	12.2	25.7 (17.6–37.6)
ISS ≥ 26	15,343	23.5	8.4 (8.0–8.8)	62	17.7	18.4 (7.7–43.6)	367	10.9	56.6 (26.3–122.0)	1595	16.1	17.9 (14.1–22.8)	1129	19.9	19.6 (15.2–25.4)

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Age 35–44 n = 9952			Age 45–54 n = 12,188			Age 55–64 n = 13,931			Age 65–74 n = 20,044			Age ≥ 75 n = 36,705		
No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)	No. of patients	Mortality, %	OR (95%CI)
4076	8.7	29.2 (18.4–46.5)	5297	9.3	17.1 (12.4–23.6)	6541	10.8	16.2 (12.3–21.3)	9711	13.6	13.2 (11.0–16.0)	13940	20.2	10.5 (9.5–11.5)
2985	11.2	23.7 (16.8–33.4)	3793	11.7	12.0 (9.6–15.1)	4372	14.4	11.9 (9.8–14.4)	6256	18.6	11.2 (9.8–12.9)	8626	27.4	10.5 (9.7–11.3)
1481	18.2	18.3 (14.5–23.2)	1823	17.7	10.3 (8.6–12.4)	2038	20.9	9.1 (7.8–10.6)	2910	24.6	7.4 (6.6–8.3)	3938	34.0	8.0 (7.3–8.6)

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158 ISS, Injury Severity Score; OR, odds ratio; CI, confidence interval.

4. DISCUSSION

To the best of our knowledge, this is the first nationwide study in Japan to evaluate in-hospital mortality and OR for mortality in patients with severe injury according to age. Our study showed that in all three groups with ISS ≥16, ISS ≥18, and ISS ≥26, which are the commonly used anatomical injury definitions, in-hospital mortality for patients aged < 55 years was between 4.0% and 17.7% for each level of injury severity. Moreover, after evaluating the validity of the definition for severely injured patients in a Japanese cohort via the detailed classification of the definition cutoff values and age groups, there was no acceptable definition, with not only a high in-mortality but also a high OR for mortality for all age groups.

Previous studies demonstrated that in 1990 when severe injury was defined as an ISS cutoff of ≥16 points, the mortality of patients with an ISS ≥16 was more than 20%; however, the mortality of these patients decreased; therefore, an ISS cutoff of ≥18 or 26 might be suitable for defining severely injured patients with a high mortality rate.[1–3,8] This study also showed that patients with ISS ≥26 had the highest in-hospital mortality in all age categories. However, the OR for mortality in patients with ISS ≥26 was lower than that in patients with ISS ≥16 and ISS ≥18. There are possible explanations for the lack of an accepted definition with a high in-hospital mortality and high OR for mortality in a Japanese cohort.

First, there are differences in the study era and/or cohorts at the time of development.[1] A previous 10-year nationwide study using the JTDB dataset from 2004 to 2013 demonstrated that the in-hospital mortality of patients with ISS ≥16 decreased from 28.5% to 15.7% due to improvements in trauma care and medical ambulance services.[9] Moreover, in the Japanese cohort, unlike the aging population in the rest of the world, the characteristics and survival outcome of severely injured patients varied widely according to age, and the mortality risk of elderly patients with severe injury was higher than that of the other age groups.[12] A previous Japanese nationwide study showed that the incidence rate of severe traumatic brain injury among severely injured patients aged > 65 years was high (40.7%).[13] Moreover, the in-hospital mortality of these patients was higher than that of the other age-groups.[13] These results suggest that the elderly patient groups had a higher mortality because of the high proportion and mortality of severe traumatic head injury. This study also showed that the prevalence and in-hospital mortality of severely injured patients aged 55–64, 65–75, and ≥75 years increased stepwise. However, in pediatric patients, a previous study suggested that the ISS cutoff of ≥16 in adult patients was equivalent to that of ≥26 in pediatric patients.[14] A Japanese nationwide study using the JTDB dataset also showed that the in-hospital mortality of pediatric patients with ISS ≥16 was 8.9% in 2018. However, this study showed that the in-hospital mortality even for pediatric patients aged 5–14 years with ISS ≥26 was low (10.9%). Therefore, it is important to develop an acceptable definition of severe injury by considering the age-related characteristics and mortality risks in a Japanese cohort.

Second, there was a limitation in evaluating only anatomical severity as a definition of severe injury. A more recent approach suggests that the addition of other physiological variables to the anatomical severity score has the advantage of identifying severely injured patients with a high mortality risk.[2,15,16]. Although the mortality of patients with ISS ≥16 was 18.7%, that of patients with ISS ≥16 in addition to one other physiological parameter increased from 35% to 38%.[2] Moreover, patients with an increasing number of the physiological variable, such as the Glasgow coma scale, hypotension, and laboratory values (e.g., acidosis and/or coagulopathy), may have an increased risk of mortality.[15–17] However, we could not evaluate the variables according to physiological parameters and findings of blood tests. Therefore, it seems important to evaluate these parameters together with the anatomical severity used in this study to develop a well-validated definition of severely injured patients.

Our study had some limitations. First, there was selection bias because not all Japanese hospitals that treat severely injured patients were registered in the JTDB. Moreover, the JTDB dataset has missing data, especially for pediatric patients.[18] A high-quality Japanese nationwide dataset with less missing data should be constructed to improve the accuracy of predicting the survival of injured patients. Second, because the number of patients aged 0−4 and 5−14 years was small (0.9% and 3.5% of all the patients, respectively), it is possible that the ORs of these patient groups with small sample sizes were overestimated. In addition, the number of participating hospitals differed across the study period. Furthermore, the JTDB used AIS 90 until 2018 and is now using the AIS 2005 updated 2008 coding scale. Similar studies need to be conducted using the newest measure to verify our results.

5. CONCLUSIONS

This is the first nationwide study in Japan to evaluate the prevalence, in-hospital mortality, and OR for mortality in patients with severe injury according to age categories. In all the three levels of anatomical injury, the in-hospital mortality for patients aged < 55 years was low. Evaluating the validity of the definition for severely injured patients in a Japanese cohort based on the detailed classification of the definition cutoff values and age categories revealed the lack of an acceptable definition, with not only a high in-hospital mortality, but also a high OR for mortality in all age categories.

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Informed Consent Statement: The requirement for informed consent from the patients was waived due to the observational nature of the study design.

Data Availability Statement: The approving authority for data access was the Japanese Association for the Surgery of Trauma (Trauma Registry Committee).

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Conflicts of Interest: The authors declare no conflict of interest.

References

1 Champion HR, Copes WS, Sacco WJ et al. The major trauma outcome study: Establishing national norms for trauma care. *J Trauma* **1990**;30:1356–65. DOI:10.1097/00005373-199011000-00008.

2 Butcher N, Balogh ZJ. The definition of polytrauma: The need for international consensus. *Injury* **2009**;40;Supplement 4:S12–22. DOI:10.1016/j.injury.2009.10.032.

3 Butcher N, Balogh ZJ. AIS > 2 in at least two body regions: A potential new anatomical definition of polytrauma. *Injury* **2012**;43:196–9. DOI:10.1016/j.injury.2011.06.029.

4 Rosoff L, Berne CJ. Management of acute hemodynamic and respiratory disturbances in the severely injured patient. *Surg Clin North Am* **1968**;48:1187–96. DOI:10.1016/s0039-6109(16)38679-0.

5 Mahoney JW. Evaluation and diagnosis in the multiply injured patient. *Clin Orthop Relat Res* **1968**;60:227–30. DOI:10.1097/00003086-196809000-00029.

6 Baker SP, O'Neill B, Haddon W Jr. et al. The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* **1974**;14:187–96. DOI:10.1097/00005373-197403000-00001.

7 Association for the Advancement of Automotive Medicine. The abbreviated injury scale. *Revision updated 1998*. https://www.tarn.ac.uk/content/downloads/72/coding.pdf 1990.

8 Wong TH, Lumsdaine W, Hardy BM et al. The impact of specialist Trauma Service on Major Trauma Mortality. *J Trauma Acute Care Surg* **2013**;74:780–4. DOI:10.1097/TA.0b013e3182826d5f.

9 Nagata I, Abe T, Uchida M et al. Ten-year inhospital Mortality trends for patients with trauma in Japan: A multicentre observational study. *BMJ Open* **2018**;8:e018635. DOI:10.1136/bmjopen-2017-018635.

10 Hondo K, Shiraishi A, Fujie S et al. In-hospital trauma mortality has decreased in Japan possibly due to trauma education. *J Am Coll Surg* **2013**;217:850–7.e1. DOI:10.1016/j.jamcollsurg.2013.05.026.

11 Toida C, Muguruma T, Gakumazawa M et al. Ten-year in-hospital mortality trends among paediatric injured patients in Japan: A nationwide observational study. *J Clin Med* **2020**;9:3273. DOI:10.3390/jcm9103273.

12 Kojima M, Endo A, Shiraishi A et al. Age-related characteristics and outcomes for patients with severe trauma: Analysis of Japan's nationwide trauma registry. *Ann Emerg Med* **2019**;73:281–90. DOI:10.1016/j.annemergmed.2018.09.034.

13 Toida C, Muguruma T, Gakumazawa M et al. Age- and Severity-Related In-Hospital Mortality Trends and Risks of Severe Traumatic Brain Injury in Japan: A Nationwide 10-Year Retrospective Study. *J Clin Med* **2021**;10:1072. DOI:10.3390/jcm10051072.

14 Keskey EC, Hampton DA, Bierman H et al. *Novel trauma composite score in a more reliable predicator of mortality than injury severity score in pediatric trauma*.

15 Pape HC, Lefering R, Butcher N; et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg* **2014**;77:780–6. DOI:10.1097/TA.0000000000000453.

16 Driessen MLS, Sturms LM, van Zwet EW; et al. Evaluation of the Berlin polytrauma definition: A Dutch nationwide observational study. *J Trauma Acute Care Surg* **2021**;90:694–9. DOI:10.1097/TA.0000000000003071.

17 Brockamp T, Maegele M, Gaarder C; et al. Comparison of the predictive performance of the BIG, TRISS, and PS09 score in an adult trauma population derived from multiple international trauma registries. *Crit Care* **2013**;17:R134. DOI:10.1186/cc12813.

18 Toida C, Muguruma T, Gakumazawa M et al. Validation of age-specific survival prediction in pediatric patients with blunt trauma using trauma and injury severity score methodology: A ten-year nationwide observational study. *BMC Emerg Med* **2020**;20:91. DOI:10.1186/s12873-020-00385-0.

Figure Legend

Figure 1. Flow diagram of the patient selection process.

JTDB, Japanese Trauma Data Bank.

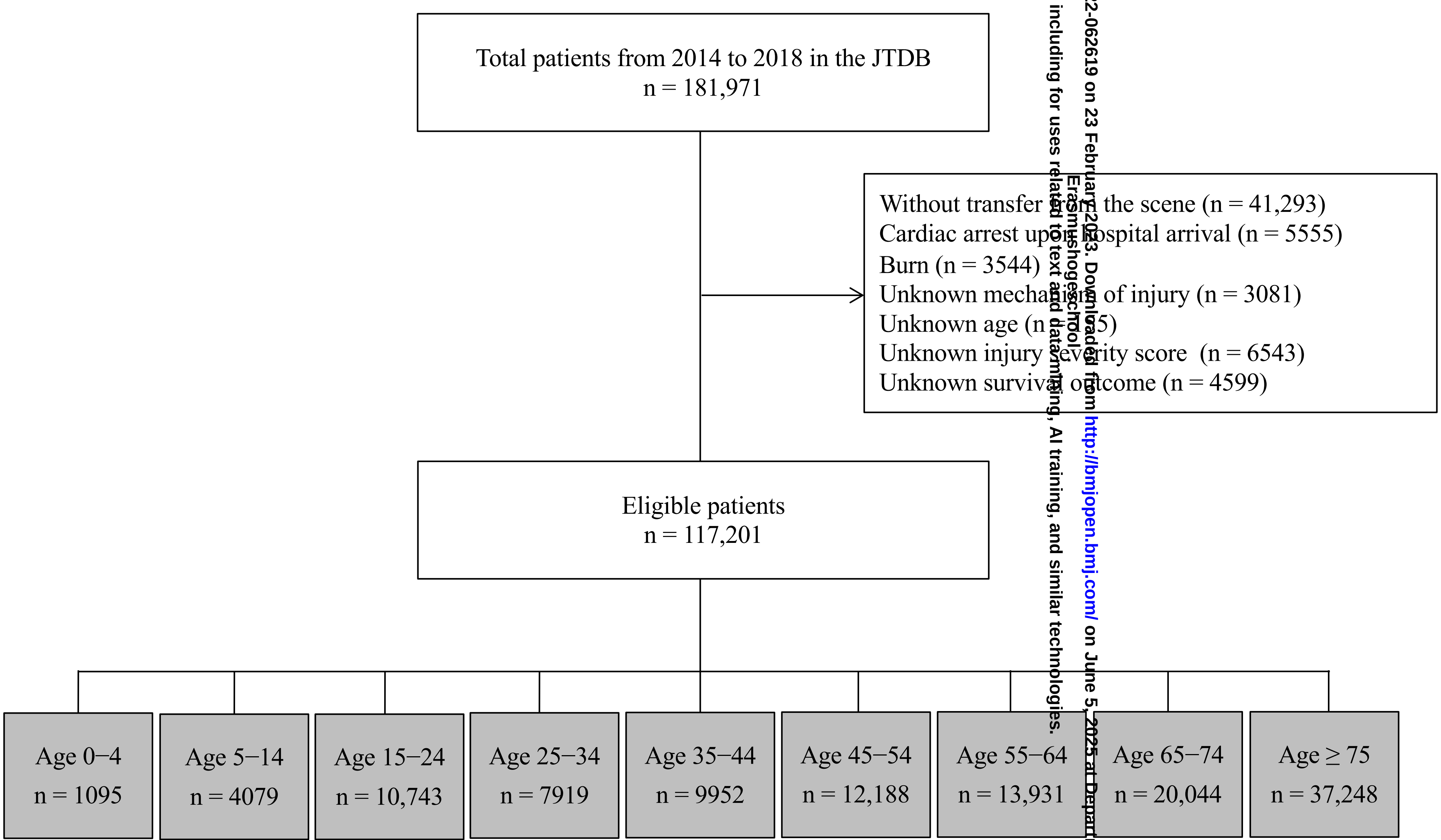

Figure 1. Flow diagram of the patient selection process.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	2,3
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3,4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	4,5
		(*c*) Explain how missing data were addressed	3,4
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3,4,5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3,4,5
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) Summarise follow-up time (eg, average and total amount)	3
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Article

Evaluating the definition of Severely Injured Patients: A Japanese Nationwide 5-Year Retrospective Study

Chiaki Toida [1,2]*, Takashi Muguruma [2], Masayasu Gakumazawa [2], Mafumi Shinohara [2], Takeru Abe [2], and Ichiro Takeuchi [2]

1 Department of Emergency Medicine, Teikyo University School of Medicine Graduate School of Medicine, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8606, Japan; toida-ygc@umin.ac.jp

2 Department of Emergency Medicine, Yokohama City University Graduate School of Medicine, 4-57 Urafunecho, Minami-ku, Yokohama 232-0024, Japan; mgrmtks@gmail.com (T.M.); gakumazawa-tuk@umin.ac.jp (M.G.); s_mafumi@yokohama-cu.ac.jp (M.S.); abet@yokohama-cu.ac.jp (T.A.); takeqq@yokohama-cu.ac.jp (I.T.)

* Correspondence: toida-ygc@umin.ac.jp; Tel.+81-3-3815-5411

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Abstract:

Objectives: The definition of severely injured patients lacks universal consensus based on quantitative measures. The most widely used definition of severe injury is based on the Injury Severity Score (ISS), which is calculated using the Abbreviated Injury Scale (AIS) in Japan. This study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with ISS ≥16, ISS ≥18, and ISS ≥26 by age groups.

Design: Retrospective cohort study.

Setting: Japan Trauma Data Bank, which is a nationwide trauma registry with data from 280 hospitals.

Participants: We utilized data of 117,199 injured patients from a national database. We included injured patients who were transferred from the scene of injury by ambulance and/or physician.

Primary and secondary outcome measures: Prevalence, in-hospital mortality, and odds ratio (OR) for mortality with respect to age and injury level (ISS group).

Results: In all age categories, the in-hospital mortality of patient groups with an ISS≥16, ISS≥18, and ISS≥26 was 13.3%, 17.4%, and 23.5%, respectively. The in-hospital mortality for patients aged > 75 years was the highest (20% greater than that of the other age groups). Moreover, in-hospital mortality for age group 5–14 years was the lowest (4.0–10.9%). In all the age groups, the OR for mortality for patients with ISS≥16, ISS≥18, and ISS≥26 was 12.8, 11.0, and 8.4, respectively.

Conclusions: Our results revealed the lack of an acceptable definition, with a high in-hospital mortality and high OR for mortality for all age groups.

Keywords: severely injured patient; trauma scoring system; anatomical severity definition; mortality risk; Japan Trauma Data Bank

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Strengths and limitations of this study

- This study is the first nationwide study in Japan to evaluate in-hospital mortality and odds ratio for mortality in patients with severe injury according to age.
- We used a nationwide multi-institutional trauma database with a large sample size.
- The Japanese nationwide dataset with more missing data may have led to selection bias.
- The Japan Trauma Databank had used AIS 90 until 2018, which is not newest measure.

1. INTRODUCTION

The terminology used to quantify anatomical injury severity has been vaguely described for many decades using various phrases, such as severely injured and major trauma.[1–5] Although the most widely used definitions continue to rely on patients who have a high mortality and morbidity risk and require intense medical resources, such as massive resuscitation, multiple surgical operations, intensive care, and complex rehabilitation programs,[4,5] the definition lacks a universal consensus with quantitative measures.[2,3]

The most widely used definition of severely injured patients is the Injury Severity Score (ISS),[6] which is calculated using the Abbreviated Injury Scale (AIS).[7] Thirty years ago, an ISS cutoff value of ≥16 was defined as ‘severely injured’ because patients with an ISS ≥16 had an expected mortality rate of > 20%.[1] However, the mortality of patients with an ISS ≥16 and ISS ≥26 decreased from 12.4% to 9.3% and from 25.4% to 20.3%, respectively, during the 10-year study period, due to a reduction in mortality and/or morbidity associated with organized trauma systems.[8]

Research based on the Japanese nationwide trauma registry has also shown that the in-hospital mortality trend has decreased in injured patients.[9–11] Moreover, there are more age-related differences in the mortality of severely injured patients in Japan than in the other developed countries because Japan has faced issues with the declining birth rate and aging population.[11,12] To date, no study has evaluated the validity of the definition of severe injury in a Japanese cohort using a detailed classification of the definition cutoff values and age groups. We hypothesized that there would be differences in in-hospital mortality rate and risk among Japanese injured patients by age and anatomical severity. Therefore, this study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with an ISS ≥16, ISS ≥18, and ISS ≥26 as the commonly used anatomical injury definitions by age group [2].

2. MATERIALS AND METHODS

2.1. Study setting and population

This retrospective observational nationwide study was conducted based on data obtained from the Japan Trauma Data Bank (JTDB), which registers data of patients with an injury and/or burn, and records prehospitalization- and hospital-related information. The JTDB includes data on demographic characteristics, comorbidities, injury types, mechanism of injury, means of transportation, vital signs, AIS score, prehospital/in-hospital procedures, injury diagnosis as indicated by the AIS, and clinical outcomes. In most cases, physicians trained in AIS coding record the online registration of individual patient data. There were 280 participating hospitals in all 47 prefectures in Japan, including 92% of the Japanese government-approved tertiary emergency medical centers in March 2019. The Japan Association for the Surgery of Trauma permits open access and updating of existing medical information, and the Japan Correlation for Acute Medicine evaluates the submitted data.

In this study, we used the JTDB dataset that included information from January 1, 2014 to December 31, 2018, which initially yielded the data of 181,971 patients. The inclusion criterion for this study was injured patients who were transferred from the scene of injury by ambulance and/or physician. Patients with cardiac arrest on hospital arrival or with missing key data such as mechanism, age, ISS, and/or survival outcome were excluded from this study. Figure 1 presents a flow diagram of the patient selection process in this study.

2.2. Data collection

We collected information from the JTDB, including the following variables: demographic characteristics (age [years], sex, injury mechanism, transportation type, transfer process), and clinical parameters (AIS of the injured region, ISS). In the JTDB, a patient with an AIS of the injured region ≥3 was defined as a case of a severely injured region.

2.4. Ethics statement

This study was approved by the hospital ethics committee of Yokohama City University Medical Center (approval no. B170900003). The approval authority for data access was provided by the Japanese Association for the Surgery of Trauma (Trauma Registry Committee). The requirement for informed consent from the patients was waived owing to the observational nature of the study.

2.5. Statistical analysis

The outcomes were as follows: prevalence, in-hospital mortality, and OR for mortality with respect to age group (0−4, 5−14, 15−24, 25−34, 35−44, 45−54, 55−64, 65−74, ≥75 years) and injury severity (ISS ≥16, ISS ≥18, and ISS ≥26; the ISSs of these groups were used as the definitions of anatomical injury in a previous review article.[2]

Continuous variables are presented as medians with interquartile range (IQR, Q1–Q3), and categorical variables are presented as the number and percentage of patients. The Mann–Whitney U test and Wilcoxon's rank-sum test were used to analyze continuous variables, whereas the chi-square test was used to analyze categorical variables. OR (95% confidence intervals, CI) for mortality was calculated using a logistic regression model. All statistical analyses were performed using STATA/SE software (version 17.0; StataCorp; College Station, Texas, USA). Statistical significance was defined as a two-tailed P-value of <0.05.

2.6. Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. We will not directly disseminate our findings to involved participants but plan to disseminate them through publication of this study.

3. RESULTS

During the 5-year study period, we analyzed the data of 117,199 injured patients transferred from the scene of injury; 113,435 (97%) of them had blunt trauma (Figure 1) (Table 1). The median age and ISS score were 64 years (IQR, 41–78) and 10 (IQR, 9–19), respectively. The overall in-hospital mortality rate was 6.1%.

Table 1 shows the characteristics by age group and injury severity group during the 5-year study period. The number of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 48,028 (41% of all the patients), 32,225 (28%), and 15,343 (13%), respectively.

Table 2 shows in-hospital mortality and OR for mortality with respect to age group and injury severity. In all age categories, the in-hospital mortality of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 13.3%, 17.4%, and 23.5%, respectively. In each age category, the in-hospital mortality for patients aged > 55 years was higher than that for younger age groups, and that of patients aged > 75 years was higher (by more than 20%) than that of all patient groups for each level of injury severity. In-hospital mortality for the 5–14 years age group was 4.0–10.9% and lower than that for the other age groups.

In all age categories, the OR for mortality by patient group was 12.8 (11.9–13.8), 11.0 (10.4–11.6), and 8.4 (8.0–8.8), respectively, for the three levels of injury severity, and the OR in patients with ISS ≥16 or ISS ≥18 was higher than that in patients group ISS ≥26.

Table 1. Characteristics by the nine age groups and three levels of injury severity groups.

Variables	Overall n = 117,199	Age 0−4 n = 1095	Age 5−14 n = 4079	Age 15−24 n = 10,743	Age 25−34 n = 7919	Age 35−44 n = 9952	Age 45−54 n = 1[illegible],188	Age 55−64 n = 13,931	Age 65−74 n = 20,044	Age ≥ 75 n = 36,248
Age, years	64 (41–78)	2 (1–3)	10 (7–12)	20 (17–22)	29 (27–32)	40 (38–42)	49 (4[illegible]–52)	60 (57–62)	69 (67–72)	83 (79–87)
Male	16,317 (44)	675 (62)	2985 (73)	8095 (75)	6008 (75)	7710 (77)	[illegible] (76)	10017 (72)	12662 (63)	16317 (44)
Mechanism of injury										
Blunt	113,435 (97)	1073 (98)	4020 (99)	10,477 (98)	7508 (95)	9361 (94)	[illegible] (94)	13,383 (96)	19,433 (97)	36,705 (99)
Injury region										
Head injury with AIS ≥ 3	36,244 (31)	439 (40)	1213 (30)	2798 (26)	1933 (24)	2527 (25)	3363 (28)	4451 (32)	7384 (37)	12,136 (33)
Facial injury with AIS ≥ 3	940 (0.8)	4 (0.4)	33 (0.8)	150 (1.4)	109 (1.4)	128 (1.3)	124 ([illegible].0)	123 (0.9)	133 (0.7)	136 (0.4)
Neck injury with AIS ≥ 3	478 (0.4)	6 (0.6)	2 (0.1)	27 (0.3)	39 (0.5)	55 (0.6)	70 (0.[illegible])	77 (0.6)	110 (0.6)	92 (0.3)
Chest injury with AIS ≥ 3	25,723 (22)	148 (14)	622 (15)	2831 (26)	2110 (27)	2759 (28)	3485 (29)	3726 (27)	4594 (23)	5448 (15)
Abdominal and pelvic injury with AIS ≥ 3	5407 (5)	27 (2)	185 (5)	805 (7)	591 (7)	682 (7)	709 ([illegible])	684 (5)	831 (4)	893 (2)
Spinal injury with AIS ≥ 3	13,146 (10)	12 (1)	128 (3)	861 (8)	788 (10)	1120 (11)	1530 (13)	2106 (15)	3053 (15)	3548 (10)
Upper extremity injury with AIS ≥ 3	6562 (6)	57 (5)	590 (14)	581 (5)	522 (7)	711 (7)	[illegible]49 ([illegible])	798 (6)	1026 (5)	1428 (4)
Lower extremity injury with AIS ≥ 3	31,526 (27)	124 (11)	634 (16)	2143 (20)	1660 (21)	2055 (21)	2404 (20)	2691 (19)	4358 (22)	15,457 (42)
Injury Severity Score	10 (9–19)	9 (4–16)	9 (5–16)	10 (5–19)	10 (6–20)	13 (9–20)	13 (9–21)	14 (9–21)	14 (9–21)	9 (9–17)
Actual in-hospital mortality	7201 (6.1)	23 (2.1)	48 (1.2)	354 (3.3)	310 (3.9)	372 (3.7)	533 (4.4)	762 (5.5)	1438 (7.2)	3361 (9.0)
Injury Severity Score ≥ 16	48,028 (41)	376 (34)	1166 (29)	3878 (36)	3043 (38)	4076 (41)	5297 (43)	6541 (47)	9711 (48)	13,940 (37)
Injury Severity Score ≥ 18	32,225 (28)	187 (17)	747 (18)	2954 (28)	2305 (29)	2985 (30)	3793 (31)	4372 (31)	6256 (31)	8626 (23)
Injury Severity Score ≥ 26	15,343 (13)	62 (6)	367 (9)	1595 (15)	1129 (14)	1481 (15)	1823 (15)	2038 (15)	2910 (15)	3938 (11)

Data are presented as number (percentage) or median (interquartile range Q1–Q3); AIS, Abbreviated Injury Scale

Table 2. In-hospital mortality and odds ratio for mortality of patient groups with ISS ≥ 16, ISS ≥ 18, and ISS ≥ 26.

	Overall			Age 0–4			Age 5–14			Age 15–24			Age 25–34		
	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)
ISS ≥ 16	48,028	13.3 (6383)	12.8 (11.9–13.8)	376	5.9 (22)	44.6 (6.0–332.4)	1166	4.0 (46)	59.8 (14.5–246.7)	3878	8.6 (335)	34.1 (21.4–54.2)	3043	9.8 (299)	48.2 (26.4–88.1)
ISS ≥ 18	32,225	17.4 (5602)	11.0 (10.4–11.6)	187	11.2 (21)	57.3 (13.3–246.7)	747	5.8 (43)	40.6 (16.0–103.0)	2954	11.0 (325)	33.1 (22.6–48.5)	2305	12.2 (280)	25.7 (17.6–37.6)
ISS ≥ 26	15,343	23.5 (3605)	8.4 (8.0–8.8)	62	17.7 (11)	18.4 (7.7–43.6)	367	10.9 (40)	56.6 (26.3–122.0)	1595	16.1 (257)	17.9 (14.1–22.8)	1129	19.9 (225)	19.6 (15.2–25.4)

Age 35–44			Age 45–54			Age 55–64			Age 65–74			Age ≥ 75		
No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)	No. of patients	Mortality, % (n)	OR (95%CI)
4076	8.7 (353)	29.2 (18.4–46.5)	5297	9.3 (492)	17.1 (12.4–23.6)	6541	10.8 (707)	16.2 (12.3–21.3)	9711	13.6 (1317)	13.2 (11.0–16.0)	13940	20.2 (2812)	10.5 (9.5–11.5)
2985	11.2 (335)	23.7 (16.8–33.4)	3793	11.7 (442)	12.0 (9.6–15.1)	4372	14.4 (629)	11.9 (9.8–14.4)	6256	18.6 (1163)	11.2 (9.8–12.9)	8626	27.4 (2364)	10.5 (9.7–11.3)
1481	18.2 (270)	18.3 (14.5–23.2)	1823	17.7 (322)	10.3 (8.6–12.4)	2038	20.9 (426)	9.1 (7.8–10.6)	2910	24.6 (716)	7.4 (6.6–8.3)	3938	34.0 (1338)	8.0 (7.3–8.6)

ISS, Injury Severity Score; OR, odds ratio; CI, confidence interval.

4. DISCUSSION

To the best of our knowledge, this is the first nationwide study in Japan to evaluate in-hospital mortality and OR for mortality in patients with severe injury according to age. Our study showed that in all three groups with ISS ≥16, ISS ≥18, and ISS ≥26, which are the commonly used anatomical injury definitions, in-hospital mortality for patients aged < 55 years was between 4.0% and 17.7% for each level of injury severity. Moreover, after evaluating the validity of the definition for severely injured patients in a Japanese cohort via the detailed classification of the definition cutoff values and age groups, there was no acceptable definition, with not only a high in-hospital mortality but also a high OR for mortality for all age groups.

Previous studies demonstrated that in 1990 when severe injury was defined as an ISS cutoff of ≥16 points, the mortality of patients with an ISS ≥16 was more than 20%; however, the mortality of these patients decreased; therefore, an ISS cutoff of ≥18 or 26 might be suitable for defining severely injured patients with a high mortality rate.[1–3,8] This study also showed that patients with ISS ≥26 had the highest in-hospital mortality in all age categories. However, the OR for mortality in patients with ISS ≥26 was lower than that in patients with ISS ≥16 and ISS ≥18. There are possible explanations for the lack of an accepted definition with a high in-hospital mortality and high OR for mortality in a Japanese cohort.

First, there are differences in the study era and/or cohorts at the time of development.[1] A previous 10-year nationwide study using the JTDB dataset from 2004 to 2013 demonstrated that the in-hospital mortality of patients with ISS ≥16 decreased from 28.5% to 15.7% due to improvements in trauma care and medical ambulance services.[9] Moreover, in the Japanese cohort, unlike the aging population in the rest of the world, the characteristics and survival outcome of severely injured patients varied widely according to age, and the mortality risk of elderly patients with severe injury was higher than that of the other age groups.[12] A previous Japanese nationwide study showed that the incidence rate of severe traumatic brain injury among severely injured patients aged > 65 years was high (40.7%).[13] Moreover, the in-hospital mortality of these patients was higher than that of the other age-groups.[13] These results suggest that the elderly patient groups had a higher mortality because of the high proportion and mortality of severe traumatic head injury. This study also showed that the prevalence and in-hospital mortality of severely injured patients aged 55–64, 65–75, and ≥75 years increased stepwise. On the other hand, previous studies suggested that the ISS cutoff of ≥16 in adult patients was equivalent to a cut-off ≥26 in pediatric patients aged <16 years.[14,15] This study showed different results from those of a previous study [15], wherein the in-hospital mortality of pediatric patients aged 0–4 years with an ISS ≥26 was high (17.7%) and that of pediatric patients aged 5–14 years with an ISS ≥26 was low (10.9%), as shown in Table 2. Moreover, a previous study showed that there was a difference in the optimal cut off value of ISS in predicting severely injury mortality risk by region and/or mechanism of injury among pediatric patients. Therefore, it is important to develop an acceptable definition of severe injury by considering the age-related characteristics and mortality risks in a Japanese cohort. Moreover, this study showed that the mortality rate and mortality risk of injured patients in Japan differed by age groups and did not have a linear correlation with age in years. For a better predictive accuracy in mortality, it may be effective to add age categories as a predictive variable for mortality and to calculate the coefficient for coded value according to mortality risk by each age group, as shown in the Trauma and injury Severity Score methodology [16].

Second, there was a limitation in evaluating only anatomical severity as a definition of severe injury. A more recent approach suggests that the addition of other physiological variables to the anatomical severity score has the advantage of identifying severely injured patients with a high mortality risk.[2,17,18] Although the mortality of patients with ISS ≥16 was 18.7%, that of patients with ISS ≥16 in addition to one other physiological parameter increased from 35% to 38%.[2] Moreover, patients with an increasing number of the physiological variable, such as the Glasgow coma scale, hypotension, and laboratory values (e.g., acidosis and/or coagulopathy), may have an increased risk of mortality.[17–19] However, we could not evaluate the variables according to physiological parameters and findings of blood tests. Therefore, it seems important to evaluate these parameters together with the anatomical severity used in this study to develop a well-validated definition of severely injured patients.

Our study had some limitations. First, there was selection bias because not all Japanese hospitals that treat severely injured patients are registered in the JTDB. The 280 tertiary centers equivalent to Level I trauma centers in the United States participated, including 92% of the Japanese government-approved tertiary emergency medical centers in March 2019. Therefore, the JTDB is not a population-based sample of injured patients and the data are registered voluntarily. Moreover, the JTDB dataset has missing data, especially for pediatric patients.[**20**] The number of pediatric patients were lower than that of adult patients. Therefore, missing data may have a more significant influence on the analysis of the pediatric patients' data than that of the adult patients' data. A high-quality Japanese nationwide dataset with less missing data should be constructed to improve the accuracy of predicting the survival of injured patients in the data analysis for all age categories. Second, because the number of patients aged 0−4 and 5−14 years was small (0.9% and 3.5% of all the patients, respectively), it is possible that the ORs of these patient groups with small sample sizes were overestimated. In addition, the number of participating hospitals differed across the study period. Furthermore, the JTDB used AIS 90 until 2018 and is now using the AIS 2005 updated 2008 coding scale. Similar studies need to be conducted using the newest measure to verify our results.

5. CONCLUSIONS

This is the first nationwide study in Japan to evaluate the prevalence, in-hospital mortality, and OR for mortality in patients with severe injury according to age categories. This study showed that there were differences in in-hospital mortality rate and risk among Japanese injured patients by age and anatomical severity; therefore, the use of correlation between mortality and injury severity score such as the ISS may be hardly justified in the definition of severely injured patients in all age categories. In the future, it will be important to evaluate the other parameters such as age, physiological variables, and laboratory variables together with the anatomical severity by using the population-based database to develop a well-validated definition of severely injured patients.

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Informed Consent Statement: The requirement for informed consent from the patients was waived due to the observational nature of the study design.

Data Availability Statement: The approving authority for data access was the Japanese Association for the Surgery of Trauma (Trauma Registry Committee).

Acknowledgments: None.

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References

1 Champion HR, Copes WS, Sacco WJ et al. The major trauma outcome study: Establishing national norms for trauma care. *J Trauma* **1990**;30:1356–65. DOI:10.1097/00005373-199011000-00008.

2 Butcher N, Balogh ZJ. The definition of polytrauma: The need for international consensus. *Injury* **2009**;40;Supplement 4:S12–22. DOI:10.1016/j.injury.2009.10.032.

3 Butcher N, Balogh ZJ. AIS > 2 in at least two body regions: A potential new anatomical definition of polytrauma. *Injury* **2012**;43:196–9. DOI:10.1016/j.injury.2011.06.029.

4 Rosoff L, Berne CJ. Management of acute hemodynamic and respiratory disturbances in the severely injured patient. *Surg Clin North Am* **1968**;48:1187–96. DOI:10.1016/s0039-6109(16)38679-0.

5 Mahoney JW. Evaluation and diagnosis in the multiply injured patient. *Clin Orthop Relat Res* **1968**;60:227–30. DOI:10.1097/00003086-196809000-00029.

6 Baker SP, O'Neill B, Haddon W Jr. et al. The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* **1974**;14:187–96. DOI:10.1097/00005373-197403000-00001.

7 Association for the Advancement of Automotive Medicine. The abbreviated injury scale. *Revision updated 1998*. https://www.tarn.ac.uk/content/downloads/72/coding.pdf 1990.

8 Wong TH, Lumsdaine W, Hardy BM et al. The impact of specialist Trauma Service on Major Trauma Mortality. *J Trauma Acute Care Surg* **2013**;74:780–4. DOI:10.1097/TA.0b013e3182826d5f.

9 Nagata I, Abe T, Uchida M et al. Ten-year inhospital Mortality trends for patients with trauma in Japan: A multicentre observational study. *BMJ Open* **2018**;8:e018635. DOI:10.1136/bmjopen-2017-018635.

10 Hondo K, Shiraishi A, Fujie S et al. In-hospital trauma mortality has decreased in Japan possibly due to trauma education. *J Am Coll Surg* **2013**;217:850–7.e1. DOI:10.1016/j.jamcollsurg.2013.05.026.

11 Toida C, Muguruma T, Gakumazawa M et al. Ten-year in-hospital mortality trends among paediatric injured patients in Japan: A nationwide observational study. *J Clin Med* **2020**;9:3273. DOI:10.3390/jcm9103273.

12 Kojima M, Endo A, Shiraishi A et al. Age-related characteristics and outcomes for patients with severe trauma: Analysis of Japan's nationwide trauma registry. *Ann Emerg Med* **2019**;73:281–90. DOI:10.1016/j.annemergmed.2018.09.034.

13 Toida C, Muguruma T, Gakumazawa M et al. Age- and Severity-Related In-Hospital Mortality Trends and Risks of Severe Traumatic Brain Injury in Japan: A Nationwide 10-Year Retrospective Study. *J Clin Med* **2021**;10:1072. DOI:10.3390/jcm10051072.

14 Keskey EC, Hampton DA, Bierman H et al. Novel trauma composite score in a more reliable predicator of mortality than injury severity score in pediatric trauma. *J Trauma Acute Care Surg* **2021**;19:599–604.

15 Brown JB, Gestring ML. Leeper CM, et al. The value of the injury severity score in pediatric trauma: Time for a new definition of severe injury. *J Trauma Acute Care Surg* **2017**;82:995–1001.

16 Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma score and the injury severity score. *J Trauma* **1987**;27:370–8.

17 Pape HC, Lefering R, Butcher N; et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg* **2014**;77:780–6. DOI:10.1097/TA.0000000000000453.

18 Driessen MLS, Sturms LM, van Zwet EW; et al. Evaluation of the Berlin polytrauma definition: A Dutch nationwide observational study. *J Trauma Acute Care Surg* **2021**;90:694–9. DOI:10.1097/TA.0000000000003071.

19 Brockamp T, Maegele M, Gaarder C; et al. Comparison of the predictive performance of the BIG, TRISS, and PS09 score in an adult trauma population derived from multiple international trauma registries. *Crit Care* **2013**;17:R134. DOI:10.1186/cc12813.

20 Toida C, Muguruma T, Gakumazawa M et al. Validation of age-specific survival prediction in pediatric patients with blunt trauma using trauma and injury severity score methodology: A ten-year nationwide observational study. *BMC Emerg Med* **2020**;20:91. DOI:10.1186/s12873-020-00385-0.

Figure Legend

Figure 1. Flow diagram of the patient selection process.

JTDB, Japanese Trauma Data Bank.

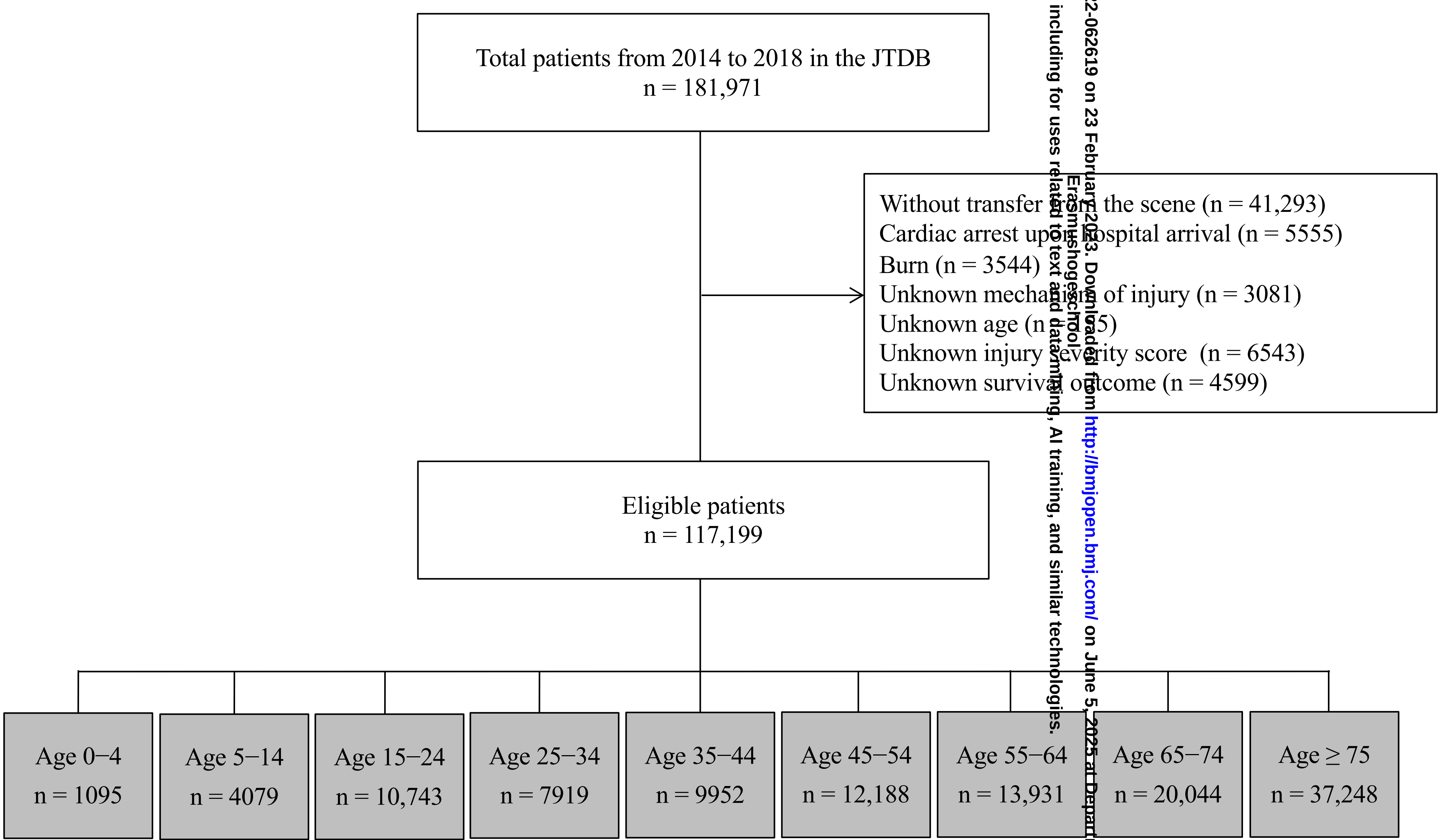

Figure 1. Flow diagram of the patient selection process.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	2,3
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3,4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	4,5
		(*c*) Explain how missing data were addressed	3,4
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3,4,5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3,4,5
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) Summarise follow-up time (eg, average and total amount)	3
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,7,8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,7,8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Article

Evaluating the definition of Severely Injured Patients: A Japanese Nationwide 5-Year Retrospective Study

Chiaki Toida [1,2]*, Takashi Muguruma [2], Masayasu Gakumazawa [2], Mafumi Shinohara [2], Takeru Abe [2], Ichiro Takeuchi [2]

1 Department of Emergency Medicine, Teikyo University School of Medicine Graduate School of Medicine, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8606, Japan; toida-ygc@umin.ac.jp

2 Department of Emergency Medicine, Yokohama City University Graduate School of Medicine, 4-57 Urafunecho, Minami-ku, Yokohama 232-0024, Japan; mgrmtks@gmail.com (T.M.); gakumazawa-tuk@umin.ac.jp (M.G.); s_mafumi@yokohama-cu.ac.jp (M.S.); abet@yokohama-cu.ac.jp (T.A.); takeqq@yokohama-cu.ac.jp (I.T.)

* Correspondence: toida-ygc@umin.ac.jp; Tel: +81-3-3815-5411

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Abstract:

Objectives: The definition of severely injured patients lacks universal consensus based on quantitative measures. The most widely used definition of severe injury is based on the Injury Severity Score (ISS), which is calculated using the Abbreviated Injury Scale in Japan. This study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with ISS ≥16, ISS ≥18, and ISS ≥26 by age groups.

Design: Retrospective cohort study.

Setting: Japan Trauma Data Bank, which is a nationwide trauma registry with data from 280 hospitals.

Participants: We utilized data of 117,199 injured patients from a national database. We included injured patients who were transferred from the scene of injury by ambulance and/or physician.

Primary and secondary outcome measures: Prevalence, in-hospital mortality, and OR for mortality with respect to age and injury level (ISS group).

Results: In all age categories, the in-hospital mortality of patient groups with an ISS≥16, ISS≥18, and ISS≥26 was 13.3%, 17.4%, and 23.5%, respectively. The in-hospital mortality for patients aged > 75 years was the highest (20% greater than that of the other age groups). Moreover, in-hospital mortality for age group 5–14 years was the lowest (4.0–10.9%). In all the age groups, the OR for mortality for patients with ISS≥16, ISS≥18, and ISS≥26 was 12.8, 11.0, and 8.4, respectively.

Conclusions: Our results revealed the lack of an acceptable definition, with a high in-hospital mortality and high OR for mortality for all age groups.

Keywords: severely injured patient; trauma scoring system; anatomical injury severity; mortality risk; Japan Trauma Data Bank

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Strengths and limitations of this study

- We used data from a large nationwide Japanese trauma registry to evaluate in-hospital mortality and odds ratio (OR) for mortality in patients with severe injury according to age.
- This is the first study to reveal that no definition of severe injury was acceptable, with not only high in-hospital mortality but also a high OR for mortality for all age groups.
- The Japanese nationwide dataset with more missing data may have led to selection bias.

1. INTRODUCTION

The terminology used to quantify anatomical injury severity has been vaguely described for many decades using various phrases, such as severely injured and major trauma.[1–5] Although the most widely used definitions continue to rely on patients who have a high mortality and morbidity risk and require intense medical resources, such as massive resuscitation, multiple surgical operations, intensive care, and complex rehabilitation programs,[4,5] the definition lacks a universal consensus with quantitative measures.[2,3]

The most widely used definition of severely injured patients is the Injury Severity Score (ISS),[6] which is calculated using the Abbreviated Injury Scale (AIS).[7] Thirty years ago, an ISS cutoff value of ≥16 was defined as “severely injured” because patients with an ISS ≥16 had an expected mortality rate of > 20%.[1] However, the mortality of patients with an ISS ≥16 and ISS ≥26 decreased from 12.4% to 9.3% and from 25.4% to 20.3%, respectively, during the 10-year study period, due to a reduction in mortality and/or morbidity associated with organized trauma systems.[8]

Research based on the Japanese nationwide trauma registry has also shown that the in-hospital mortality trend has decreased in injured patients.[9–11] Moreover, there are more age-related differences in the mortality of severely injured patients in Japan than that in the other developed countries because Japan has faced issues with the declining birth rate and aging population.[11,12] To date, no study has evaluated the validity of the definition of severe injury in a Japanese cohort using a detailed classification of the definition cutoff values and age groups. We hypothesized that there would be differences in in-hospital mortality rate and risk among Japanese injured patients by age and anatomical injury severity. Therefore, this study aimed to compare the prevalence, in-hospital mortality, and odds ratio (OR) for mortality in patients with an ISS ≥16, ISS ≥18, and ISS ≥26 as the commonly used anatomical injury definitions by age group [2].

2. MATERIALS AND METHODS

2.1. Study setting and population

This retrospective observational nationwide study was conducted based on data obtained from the Japan Trauma Data Bank (JTDB), which registers data of patients with an injury and/or burn, and records prehospitalization- and hospital-related information. The JTDB includes data on demographic characteristics, comorbidities, injury types, mechanism of injury, means of transportation, vital signs, AIS score, prehospital/in-hospital procedures, injury diagnosis as indicated by the AIS, and clinical outcomes. In most cases, physicians trained in AIS coding record the online registration of individual patient data. There were 280 participating hospitals in all 47 prefectures in Japan, including 92% of the Japanese government-approved tertiary emergency medical centers in March 2019. The Japan Association for the Surgery of Trauma permits open access and updating of existing medical information, and the Japan Correlation for Acute Medicine evaluates the submitted data.

In this study, we used the JTDB dataset that included information from January 1, 2014 to December 31, 2018, which initially yielded the data of 181,971 patients. The inclusion criterion for this study was injured patients who were transferred from the scene of injury by ambulance and/or physician. Patients with cardiac arrest on hospital arrival or with missing key data, such as mechanism, age, ISS, and/or survival outcome, were excluded from this study. Figure 1 presents a flow diagram of the patient selection process in this study.

2.2. Data collection

We collected information from the JTDB, including the following variables: demographic characteristics (age [years], sex, injury mechanism, transportation type, and transfer process) and clinical parameters (AIS of the injured region and ISS). In the JTDB, a patient with an AIS of the injured region ≥3 was defined as a case of a severely injured region.

2.3. Ethics statement

This study was approved by the hospital ethics committee of Yokohama City University Medical Center (approval no. B170900003). The approval authority for data access was provided by the Japanese Association for the Surgery of Trauma (Trauma Registry Committee). The requirement for informed consent from the patients was waived owing to the observational nature of the study.

2.4. Statistical analysis

The outcomes were as follows: prevalence, in-hospital mortality, and OR for mortality with respect to age group (0−4, 5−14, 15−24, 25−34, 35−44, 45−54, 55−64, 65−74, and ≥75 years) and injury severity (ISS ≥16, ISS ≥18, and ISS ≥26); the ISSs of these groups were used as the definitions of anatomical injury in a previous review article.[2]

Continuous variables are presented as medians with interquartile range (IQR, Q1–Q3), and categorical variables are presented as the number and percentage of patients. The Mann–Whitney U test and Wilcoxon's rank-sum test were used to analyze continuous variables, whereas the chi-square test was used to analyze categorical variables. OR (95% confidence intervals, CI) for mortality was calculated using a logistic regression model. All statistical analyses were performed using STATA/SE software (version 17.0; StataCorp; College Station, Texas, USA). Statistical significance was defined as a two-tailed P-value of <0.05.

2.5. Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of this research. We will not directly disseminate our findings to involved participants. However, we plan to disseminate them through the publication of an article.

3. RESULTS

During the 5-year study period, we analyzed the data of 117,199 injured patients transferred from the scene of injury; 113,435 (97%) of them had blunt trauma (Figure 1) (Table 1). The median age and ISS score were 64 years (IQR, 41–78) and 10 (IQR, 9–19), respectively. The overall in-hospital mortality rate was 6.1%.

Table 1 shows the characteristics by age group and injury severity group during the 5-year study period. The number of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 48,028 (41% of all the patients), 32,225 (28%), and 15,343 (13%), respectively.

Figure 2 shows in-hospital mortality and OR for mortality with respect to age group and injury severity. In all age categories, the in-hospital mortality of patients with ISS ≥16, ISS ≥18, and ISS ≥26 was 13.3%, 17.4%, and 23.5%, respectively. In each age category, the in-hospital mortality for patients aged > 55 years was higher than that for younger age groups, and that of patients aged > 75 years was higher (by more than 20%) than that of all patient groups for each level of injury severity. In-hospital mortality for the 5–14 years age group was 4.0–10.9% and lower than that for the other age groups.

In all age categories, the OR for mortality by patient group was 12.8 (11.9–13.8), 11.0 (10.4–11.6), and 8.4 (8.0–8.8), respectively, for the three levels of injury severity, and the OR in patients with ISS ≥16 or ISS ≥18 was higher than that in patients group ISS ≥26.

Table 1. Characteristics by the nine age groups and three levels of injury severity groups.

Variables	Overall n = 117,199	Age 0–4 n = 1095	Age 5–14 n = 4079	Age 15–24 n = 10,743	Age 25–34 n = 7919	Age 35–44 n = 9952	Age 45–54 n = 12,188	Age 55–64 n = 13,931	Age 65–74 n = 20,044	Age ≥ 75 n = 36,248
Age, years	64 (41–78)	2 (1–3)	10 (7–12)	20 (17–22)	29 (27–32)	40 (38–42)	49 (47–52)	60 (57–62)	69 (67–72)	83 (79–87)
Male	73,680 (63)	675 (62)	2985 (73)	8095 (75)	6008 (75)	7710 (77)	9211 (76)	10017 (72)	12662 (63)	16317 (44)
Mechanism of injury										
Blunt	113,435 (97)	1073 (98)	4020 (99)	10,477 (98)	7508 (95)	9361 (94)	11,475 (94)	13,383 (96)	19,433 (97)	36,705 (99)
Injury region										
Head injury with AIS ≥ 3	36,244 (31)	439 (40)	1213 (30)	2798 (26)	1933 (24)	2527 (25)	3363 (28)	4451 (32)	7384 (37)	12,136 (33)
Facial injury with AIS ≥ 3	940 (0.8)	4 (0.4)	33 (0.8)	150 (1.4)	109 (1.4)	128 (1.3)	124 (1.0)	123 (0.9)	133 (0.7)	136 (0.4)
Neck injury with AIS ≥ 3	478 (0.4)	6 (0.6)	2 (0.1)	27 (0.3)	39 (0.5)	55 (0.6)	70 (0.6)	77 (0.6)	110 (0.6)	92 (0.3)
Chest injury with AIS ≥ 3	25,723 (22)	148 (14)	622 (15)	2831 (26)	2110 (27)	2759 (28)	3485 (29)	3726 (27)	4594 (23)	5448 (15)
Abdominal and pelvic injury with AIS ≥ 3	5407 (5)	27 (2)	185 (5)	805 (7)	591 (7)	682 (7)	709 (6)	684 (5)	831 (4)	893 (2)
Spinal injury with AIS ≥ 3	13,146 (10)	12 (1)	128 (3)	861 (8)	788 (10)	1120 (11)	1530 (13)	2106 (15)	3053 (15)	3548 (10)
Upper extremity injury with AIS ≥ 3	6562 (6)	57 (5)	590 (14)	581 (5)	522 (7)	711 (7)	849 (7)	798 (6)	1026 (5)	1428 (4)
Lower extremity injury with AIS ≥ 3	31,526 (27)	124 (11)	634 (16)	2143 (20)	1660 (21)	2055 (21)	2404 (20)	2691 (19)	4358 (22)	15,457 (42)
Injury Severity Score	10 (9–19)	9 (4–16)	9 (5–16)	10 (5–19)	10 (6–20)	13 (9–20)	13 (9–21)	14 (9–21)	14 (9–21)	9 (9–17)
Actual in-hospital mortality	7201 (6.1)	23 (2.1)	48 (1.2)	354 (3.3)	310 (3.9)	372 (3.7)	533 (4.4)	762 (5.5)	1438 (7.2)	3361 (9.0)
Injury Severity Score ≥ 16	48,028 (41)	376 (34)	1166 (29)	3878 (36)	3043 (38)	4076 (41)	5297 (43)	6541 (47)	9711 (48)	13,940 (37)
Injury Severity Score ≥ 18	32,225 (28)	187 (17)	747 (18)	2954 (28)	2305 (29)	2985 (30)	3793 (31)	4372 (31)	6256 (31)	8626 (23)
Injury Severity Score ≥ 26	15,343 (13)	62 (6)	367 (9)	1595 (15)	1129 (14)	1481 (15)	1823 (15)	2038 (15)	2910 (15)	3938 (11)

Data are presented as number (percentage) or median (interquartile range Q1–Q3); AIS, Abbreviated Injury Scale

4. DISCUSSION

To the best of our knowledge, this is the first nationwide study in Japan to evaluate in-hospital mortality and OR for mortality in patients with severe injury according to age. Our study showed that in all three groups with ISS ≥16, ISS ≥18, and ISS ≥26, which are the commonly used anatomical injury definitions, in-hospital mortality for patients aged < 55 years was between 4.0% and 17.7% for each level of injury severity. Moreover, after evaluating the validity of the definition for severely injured patients in a Japanese cohort via the detailed classification of the definition cutoff values and age groups, there was no acceptable definition, with not only a high in-hospital mortality, but also a high OR for mortality for all age groups.

Previous studies demonstrated that in 1990 when severe injury was defined as an ISS cutoff of ≥16 points, the mortality of patients with an ISS ≥16 was more than 20%; however, the mortality of these patients decreased; therefore, an ISS cutoff of ≥18 or 26 might be suitable for defining severely injured patients with a high mortality rate.[1–3,8] This study also showed that patients with ISS ≥26 had the highest in-hospital mortality in all age categories. However, the OR for mortality in patients with ISS ≥26 was lower than that in patients with ISS ≥16 and ISS ≥18. There are possible explanations for the lack of an accepted definition with a high in-hospital mortality and high OR for mortality in a Japanese cohort.

First, there are differences in the study era and/or cohorts at the time of development.[1] A previous 10-year nationwide study using the JTDB dataset from 2004 to 2013 demonstrated that the in-hospital mortality of patients with ISS ≥16 decreased from 28.5% to 15.7% owning to improvements in trauma care and medical ambulance services.[9] Moreover, in the Japanese cohort, unlike the aging population in the rest of the world, the characteristics and survival outcome of severely injured patients varied widely according to age, and the mortality risk of elderly patients with severe injury was higher than that of the other age groups.[12] A previous Japanese nationwide study showed that the incidence rate of severe traumatic brain injury among severely injured patients aged > 65 years was high (40.7%).[13] Moreover, the in-hospital mortality of these patients was higher than that of the other age groups.[13] These results suggest that the elderly patient groups had a higher mortality because of the high proportion and mortality of severe traumatic head injury. This study also showed that the prevalence and in-hospital mortality of severely injured patients aged 55–64, 65–75, and ≥75 years increased stepwise. On the other hand, previous studies suggested that the ISS cutoff of ≥16 in adult patients was equivalent to a cutoff of ≥26 in pediatric patients aged <16 years.[14,15] This study showed different results from those of a previous study [15], wherein the in-hospital mortality of pediatric patients aged 0–4 years with an ISS ≥26 was high (17.7%) and that of pediatric patients aged 5–14 years with an ISS ≥26 was low (10.9%), as shown in Figure 2. Moreover, a previous study showed that there was a difference in the optimal cut off value of ISS in predicting severely injury mortality risk by region and/or mechanism of injury among pediatric patients. Therefore, it is important to develop an acceptable definition of severe injury by considering the age-related characteristics and mortality risks in a Japanese cohort. Moreover, this study showed that the mortality rate and risk of injured patients in Japan differed by age groups and did not have a linear correlation with age in years. For a better predictive accuracy in mortality, it may be effective to add age categories as a predictive variable for mortality and to calculate the coefficient for coded value according to mortality risk by each age group, as shown in the Trauma and Injury Severity Score methodology [16]. Second, there was a limitation in evaluating only anatomical injury severity as a definition of severe injury. A more recent approach suggests that the addition of other physiological variables to the anatomical injury severity score has the advantage of identifying severely injured patients with a high mortality risk.[2,17,18] Although the mortality of patients with ISS ≥16 was 18.7%, that of patients with ISS ≥16 in addition to one other physiological parameter increased from 35% to 38%.[2] Moreover, patients with an increasing number of the physiological variable, such as the Glasgow Coma Scale, hypotension, and laboratory values (e.g., acidosis and/or coagulopathy), may have an increased risk of mortality.[17–19] However, we could not evaluate the variables according to physiological parameters and findings of blood tests. Therefore, it seems important to evaluate these parameters together with the anatomical injury severity used in this study to develop a well-validated definition of severely injured patients.

Our study had some limitations. First, there was selection bias because not all Japanese hospitals that treat severely injured patients are registered in the JTDB. The 280 tertiary centers equivalent to Level I trauma centers in the United States participated, including 92% of the Japanese government-approved tertiary emergency medical centers in March 2019. Therefore, the JTDB is not a population-based sample of injured patients and the data are registered voluntarily.

Moreover, the JTDB dataset has missing data, especially for pediatric patients.[20] The number of pediatric patients were lower than that of adult patients. Therefore, missing data may have a more significant influence on the analysis of the pediatric patients' data than that of the adult patients' data. A high-quality Japanese nationwide dataset with less missing data should be constructed to improve the accuracy of predicting the survival of injured patients in the data analysis for all age categories. Second, because the number of patients aged 0−4 and 5−14 years was small (0.9% and 3.5% of all the patients, respectively), it is possible that the ORs of these patient groups with small sample sizes were overestimated. In addition, the number of participating hospitals differed across the study period. Furthermore, the JTDB used AIS 90 until 2018 and is now using the AIS 2005 updated 2008 coding scale. Similar studies need to be conducted using the newest measure to verify our results. Last, we did not evaluate which definition would be effective for each age group. A recent study showed significant discrepancies in the mortality risk of severely injured patients by each injury region.[21] We intend to calculate the coefficient for the coded value according to mortality risk by age group and injury region for a better mortality estimate.

5. CONCLUSIONS

This is the first nationwide study in Japan to evaluate the prevalence, in-hospital mortality, and OR for mortality in patients with severe injury according to age categories. This study showed that there were differences in in-hospital mortality rate and risk among Japanese injured patients by age and anatomical injury severity; therefore, the use of correlation between mortality and injury severity score, such as the ISS, may be hardly justified in the definition of severely injured patients in all age categories. In the future, it will be important to evaluate the other parameters, such as age, physiological variables, and laboratory variables, together with the anatomical injury severity by using the population-based database to develop a well-validated definition of severely injured patients.

Author Contributions: Conceptualization, CT and TM; methodology, CT; software, CT and TA; validation, CT, TM, TA, MG, and MS; formal analysis, CT; investigation, CT, TM, MS, MG, and TA; resources, CT and TA; data curation, CT and TA; writing—original draft preparation, CT;

writing—review and editing, CT, TM, MS, MG, TA, and IT; visualization, CT; supervision, IT; project administration and funding acquisition, CT All authors have read and agreed to the published version of the manuscript.

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Ethical Approval Statement: This study was approved by the institutional ethics committees of Yokohama City University Medical Centre (approval no. B170900003).

Informed Consent Statement: The requirement for informed consent from the patients was waived owning to the observational nature of the study design.

Data Availability Statement: No additional data available.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

References

1 Champion HR, Copes WS, Sacco WJ, et al. The major trauma outcome study: Establishing national norms for trauma care. *J Trauma* **1990**;30:1356–65. DOI:10.1097/00005373-199011000-00008.

2 Butcher N, Balogh ZJ. The definition of polytrauma: The need for international consensus. *Injury* **2009**;40 Suppl 4:S12–22. DOI:10.1016/j.injury.2009.10.032.

3 Butcher N, Balogh ZJ. AIS>2 in at least two body regions: A potential new anatomical definition of polytrauma. *Injury* **2012**;43:196–9. DOI:10.1016/j.injury.2011.06.029.

4 Rosoff L, Berne CJ. Management of acute hemodynamic and respiratory disturbances in the severely injured patient. *Surg Clin North Am* **1968**;48:1187–96. DOI:10.1016/s0039-6109(16)38679-0.

5 Mahoney JW. Evaluation and diagnosis in the multiply injured patient. *Clin Orthop Relat Res* **1968**;60:227–30. DOI:10.1097/00003086-196809000-00029.

6 Baker SP, O'Neill B, Haddon W Jr, et al. The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* **1974**;14:187–96. DOI:10.1097/00005373-197403000-00001.

7 Association for the Advancement of Automotive Medicine. The abbreviated injury scale. *Revision updated 1998*. https://www.tarn.ac.uk/content/downloads/72/coding.pdf 1990.

8 Wong TH, Lumsdaine W, Hardy BM, et al. The impact of specialist trauma service on major trauma mortality. *J Trauma Acute Care Surg* **2013**;74:780–4. DOI:10.1097/TA.0b013e3182826d5f.

9 Nagata I, Abe T, Uchida M, et al. Ten-year inhospital Mortality trends for patients with trauma in Japan: A multicentre observational study. *BMJ Open* **2018**;8:e018635. DOI:10.1136/bmjopen-2017-018635.

10 Hondo K, Shiraishi A, Fujie S, et al. In-hospital trauma mortality has decreased in Japan possibly due to trauma education. *J Am Coll Surg* **2013**;217:850–7.e1. DOI:10.1016/j.jamcollsurg.2013.05.026.

11 Toida C, Muguruma T, Gakumazawa M, et al. Ten-year in-hospital mortality trends among paediatric injured patients in Japan: A nationwide observational study. *J Clin Med* **2020**;9:3273. DOI:10.3390/jcm9103273.

12 Kojima M, Endo A, Shiraishi A, et al. Age-related characteristics and outcomes for patients with severe trauma: Analysis of Japan's nationwide trauma registry. *Ann Emerg Med* **2019**;73:281–90. DOI:10.1016/j.annemergmed.2018.09.034.

13 Toida C, Muguruma T, Gakumazawa M, et al. Age- and severity-related in-hospital mortality trends and risks of severe traumatic brain injury in Japan: A nationwide 10-year retrospective study. *J Clin Med* **2021**;10:1072. DOI:10.3390/jcm10051072.

14 Keskey RC, Hampton DA, Bierman H, et al. Novel trauma composite score in a more reliable predicator of mortality than injury severity score in pediatric trauma. *J Trauma Acute Care Surg* **2021**;91:599–604. DOI:10.1097/TA.0000000000003235.

15 Brown JB, Gestring ML, Leeper CM, et al. The value of the injury severity score in pediatric trauma: Time for a new definition of severe injury. *J Trauma Acute Care Surg* **2017**;82:995–1001. DOI:10.1097/TA.0000000000001440.

16 Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma* **1987**;27:370–8.

17 Pape HC, Lefering R, Butcher N, et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg* **2014**;77:780–6. DOI:10.1097/TA.0000000000000453.

18 Driessen MLS, Sturms LM, van Zwet EW, et al. Evaluation of the Berlin polytrauma definition: A Dutch nationwide observational study. *J Trauma Acute Care Surg* **2021**;90:694–9. DOI:10.1097/TA.0000000000003071.

19 Brockamp T, Maegele M, Gaarder C, et al. Comparison of the predictive performance of the BIG, TRISS, and PS09 score in an adult trauma population derived from multiple international trauma registries. *Crit Care* **2013**;17:R134. DOI:10.1186/cc12813.

20 Toida C, Muguruma T, Gakumazawa M, et al. Validation of age-specific survival prediction in pediatric patients with blunt trauma using trauma and injury severity score methodology: A ten-

year nationwide observational study. *BMC Emerg Med* **2020**;20:91. DOI:10.1186/s12873-020-00385-0.

21 Driessen MLS, de Jongh MAC, Sturms LM, et al. Severe isolated injuries have a high impact on resource use and mortality: a Dutch nationwide observational study. *Eur J Trauma Emerg Surg* **2022**;48:4267-76. doi: 10.1007/s00068-022-01972-5.

Figure Legends

Figure 1. Flow diagram of the patient selection process.

JTDB, Japanese Trauma Data Bank

Figure 2. Association between odds ratio for in-hospital mortality and age groups by patients with Injury Severity Score (ISS) ≥16, ISS ≥18, and ISS ≥26.

In a Japanese cohort, using the detailed definition cutoff values and age groups, there was no acceptable definition, with not only a high in-hospital mortality, but also a high odds ratio for mortality for all age groups.

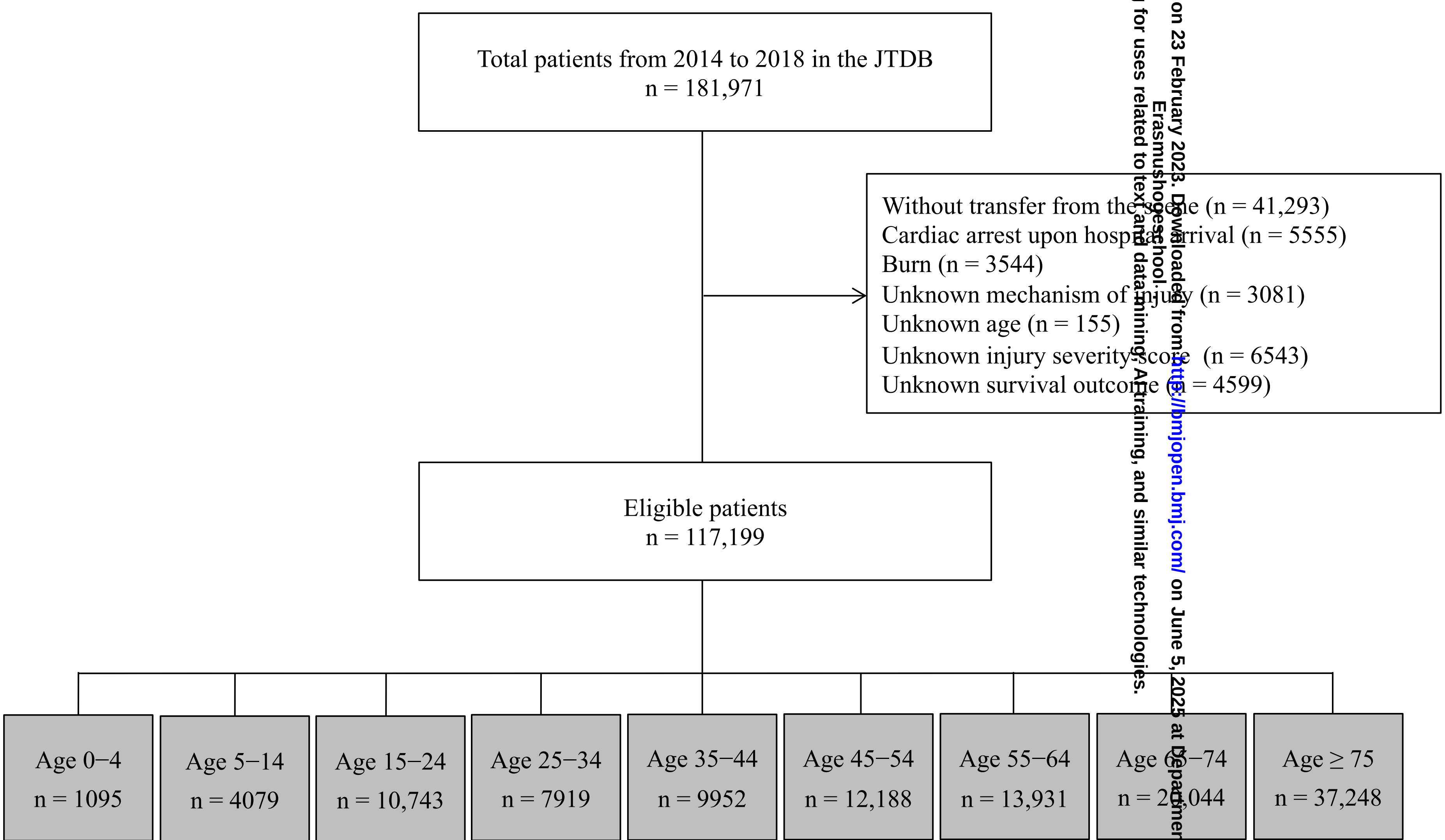

Figure 1. Flow diagram of the patient selection process.

Group	ISS	No. of patients	Mortality,%	OR	95% CI
Overall	ISS ≥ 16	48,028	13.3	12.8	(11.9, 13.8)
	ISS ≥ 18	32,225	17.4	11.0	(10.4, 11.6)
	ISS ≥ 26	15,343	23.5	8.4	(8.4, 8.8)
Age 0 − 4	ISS ≥ 16	376	5.9	44.6	(6.0, 333.4)
	ISS ≥ 18	187	11.2	57.3	(13.3, 246.7)
	ISS ≥ 26	62	17.7	18.4	(7.7, 43.6)
Age 5 − 14	ISS ≥ 16	1166	4.0	59.8	(14.5, 246.7)
	ISS ≥ 18	747	5.8	40.6	(16.0, 103.0)
	ISS ≥ 26	367	10.9	56.6	(26.3, 122.0)
Age 15 − 24	ISS ≥ 16	3878	8.6	34.1	(21.4, 54.2)
	ISS ≥ 18	2954	11.0	33.1	(22.6, 48.5)
	ISS ≥ 26	1595	16.1	17.9	(14.1, 22.8)
Age 25 − 34	ISS ≥ 16	3043	9.8	48.2	(26.4, 88.1)
	ISS ≥ 18	2305	12.2	25.7	(17.6, 37.6)
	ISS ≥ 26	1129	19.9	19.6	(15.2, 25.4)
Age 35 − 44	ISS ≥ 16	4076	8.7	29.2	(18.4, 46.5)
	ISS ≥ 18	2985	11.2	23.7	(16.8, 33.4)
	ISS ≥ 26	1481	18.2	18.3	(14.5, 23.2)
Age 45 − 54	ISS ≥ 16	5297	9.3	17.1	(12.4, 23.6)
	ISS ≥ 18	3793	11.7	12.0	(9.6, 15.1)
	ISS ≥ 26	1823	17.7	10.3	(8.6, 12.4)
Age 55 − 64	ISS ≥ 16	6541	10.8	16.2	(12.3, 21.3)
	ISS ≥ 18	4372	14.4	11.9	(9.8, 14.4)
	ISS ≥ 26	2038	20.9	9.1	(7.8, 10.6)
Age 65 − 74	ISS ≥ 16	9711	13.6	13.2	(11.0, 16.0)
	ISS ≥ 18	6256	18.6	11.2	(9.8 12.9)
	ISS ≥ 26	2910	24.6	7.4	(6.6, 8.3)
Age ≥ 75	ISS ≥ 16	13,940	20.2	10.5	(9.5, 11.5)
	ISS ≥ 18	8626	27.4	10.5	(9.7, 11.3)
	ISS ≥ 26	3938	34.0	8.0	(7.3, 8.6)

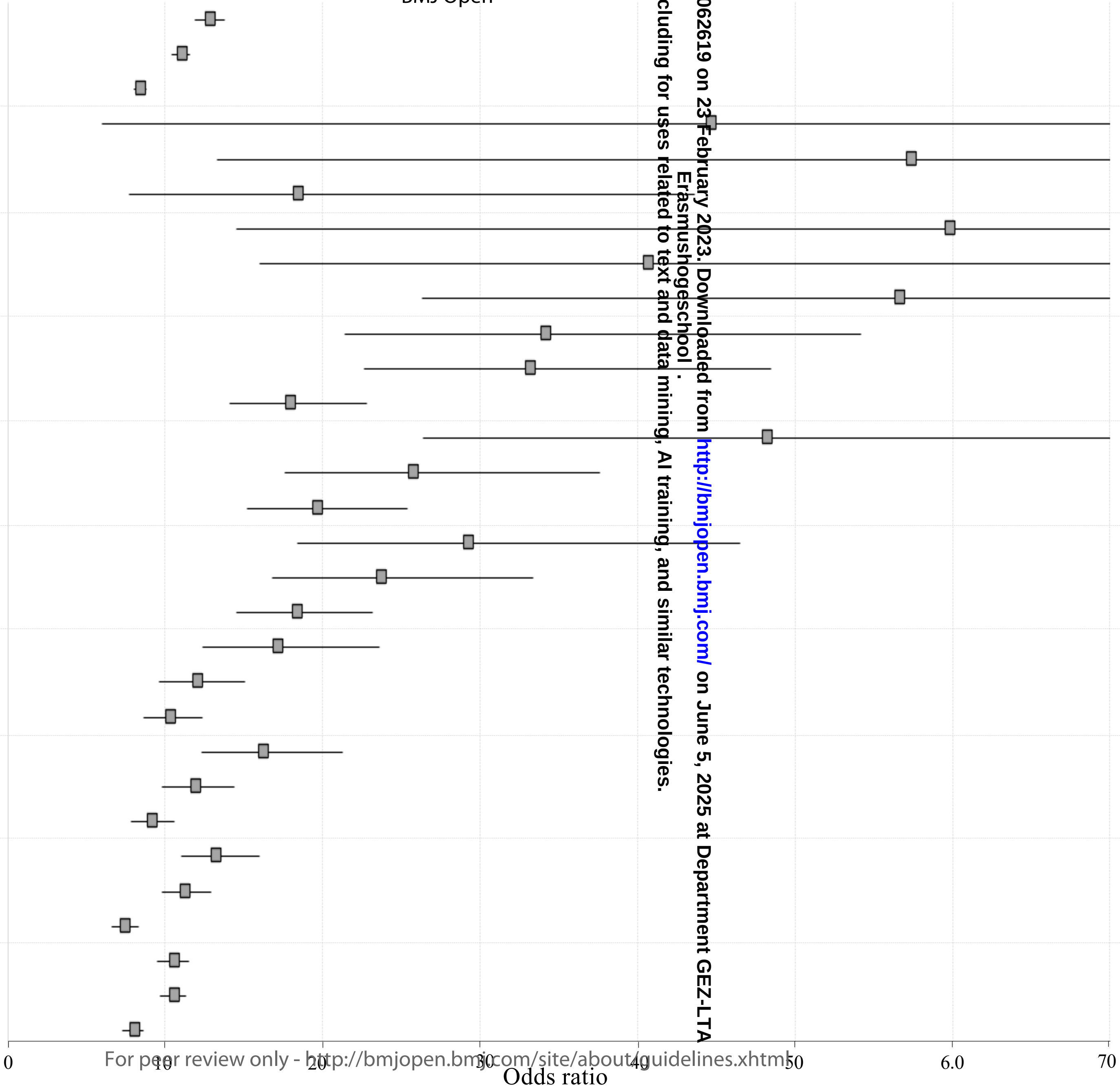

Figure 2. Association between odds ratio for in-hospital mortality and age groups by patients with Injury Severity Score (ISS) ≥16, ISS ≥18, and ISS ≥26.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	2,3
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3,4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	4,5
		(*c*) Explain how missing data were addressed	3,4
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3,4,5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3,4,5
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) Summarise follow-up time (eg, average and total amount)	3
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5,6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5,6,7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5,6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.