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Assessment of the interaction effect between injury regions in multiple injuries: A nationwide cohort study in Japan

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BACKGROUND: There have been no clinical studies to sufficiently reveal the interaction effect generated by combinations of injury regions of multiple injuries. We hypothesized that certain combinations of trauma regions might lead to increased risk of traumatic death and aimed to verify this hypothesis using a nationwide trauma registry in Japan.

MATERIALS AND METHODS: This was a retrospective study of trauma patients registered in the Japan Trauma Data Bank between 2004 and 2017. We included patients who suffered blunt trauma with an Injury Severity Score of 16 or more. The trauma was classified into four regions (head, chest, abdomen, and extremities), and a multivariable logistic regression analysis was performed that included interaction terms derived from the combination of two regions as covariates.

RESULTS: We included 78,280 trauma patients in this study. Among them, 16,100 (20.6%) patients were discharged to death. Multivariable logistic regression showed the odds ratio (OR) of in-hospital death compared with patients without injury of an Abbreviated Injury Scale score of 3 or more in each injured region as follows: head score, 2.31 (95% confidence interval [CI], 2.13–2.51); chest score, 2.28 (95% CI, 2.17–2.39); abdomen score, 1.68 (95% CI, 1.56–1.82); and extremities score, 1.84 (95% CI, 1.76–1.93), respectively. In addition, the ORs of the statistically significant interaction terms were as follows: head-chest 1.29 (95% CI, 1.13–1.48), chest-abdomen 0.77 (95% CI, 0.67–0.88), chest-extremities 1.95 (95% CI, 1.77–2.14), and abdomen-extremities 0.70 (95% CI, 0.62–0.79), respectively.

CONCLUSION: In this population, among patients with multiple injuries, a combination of head-chest trauma and chest-extremities trauma was shown to increase the risk of traumatic death. (*J Trauma Acute Care Surg.* 2021;90: 185–190. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health on behalf of the American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Prognostic, Level III.

KEY WORDS: Multiple injuries; interaction effect; blunt injury; mortality; nationwide cohort.

T rauma is a leading cause of mortality worldwide. More than 5 million people die each year as a result of injuries, which accounts for 9% of the world's deaths. Trauma death is predicted to continue to increase as a leading cause of death until 2030.[1] Especially, treatment of multiple injuries is an important factor related to decreasing total deaths from trauma. Even today, the treatments of patients with multiple injuries remain challenging because of the heterogeneous injury patterns and complex pathophysiology.

Trauma surgeons have learned from experience that the treatment for multiple injuries is not just a combination of individual injury treatments in clinical settings. According to Mattox,[2] the mortality of multiple injuries may not be described simply as an additive combination of each single trauma. The treatment of trauma should be determined on the basis of pathophysiological mechanisms and not just anatomical damage. Some basic experimental studies found that the complex reactions between damaged organs, rather than being simply the combination of each constituent trauma, were the predominant pathophysiology in multiple injuries.[3,4]

However, no sufficient clinical studies have revealed the interaction effect generated by combinations of injury regions in multiple injuries. We hypothesized that certain combinations of trauma regions might lead to an increased risk of traumatic death. The purpose of this study was to examine the interaction effects with combinations of injured regions in patients with blunt trauma by use of a nationwide trauma registry in Japan.

PATIENTS AND METHODS

Study Design and Data Collection

We conducted a retrospective analysis of registered data from the Japan Trauma Data Bank (JTDB) to clarify the effect of the combination of trauma regions on in-hospital mortality.

294,275 patients registered in the Japan Trauma Data Bank

24,810 patients were excluded, with reasons :
  Penetrating injury   n=10,365
  Burns   n=7,391
  Others   n=7,054

269,465 blunt trauma patients

164,628 patients were excluded, with reasons :
  ISS < 16, ISS =75

104,837 trauma patient with ISS ≥ 16

26,557 patients were excluded, with reasons :
  Non-direct transportation   n=17,628
  Cardio pulmonary arrest on arrival   n=7,234
  Isolated face and external trauma   n=77
  Pregnancy   n=33
  Missing data   n=1,585

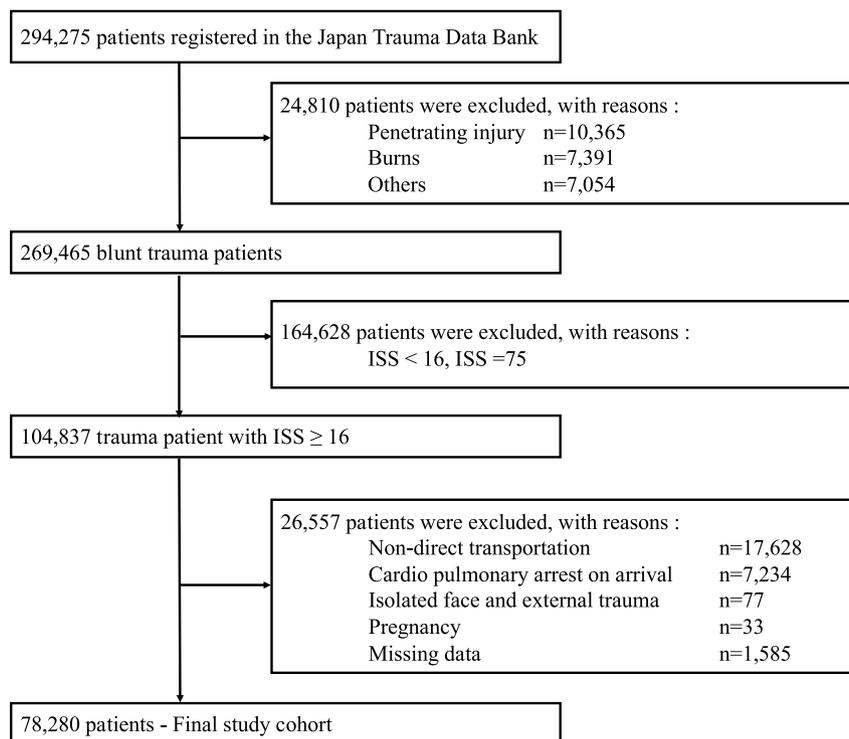78,280 patients - Final study cohort

Figure 1. Patient flow diagram for the 78,280 analyzed patients.

The JTDB from 2004 to 2017 was retrospectively reviewed to select data for this study.

Patients included in the analysis had suffered blunt trauma with an Injury Severity Score (ISS) of 16 or more. We excluded those patients with any missing data for age, sex, respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), or Glasgow Coma Scale score[5,6] on admission or hospital mortality. We also excluded patients with nondirect transportation, cardiopulmonary arrest (with data, such as RR = 0, HR = 0, SBP = 0) on arrival, patients with ISS of 75, and pregnancy. Patients with isolated injury to the facial region were also excluded from further analysis because of the limited number of individuals in this group. Similarly, some patients with isolated external trauma were also excluded.

Japan Trauma Data Bank

The JTDB is a nationwide trauma registry introduced in Japan in 2003 that currently contains data from 272 hospitals as of March 2018. The JTDB was established by the Japanese Association for the Surgery of Trauma (Trauma Registry Committee) and the Japanese Association for Acute Medicine (Committee for Clinical Care Evaluation) to improve and assure the quality of trauma care in Japan. Data are continuously recorded via the Internet and stored on a data server at the Association for Japan Trauma Care and Research. Patients suspected of having an injury with an Abbreviated Injury Scale (AIS) score of 3 or greater are registered mainly from tertiary care and emergency centers. The annual report summarizing the last 5 years of demographic data is available on the website of the Japan Trauma Care and Research.[7] The database contains patient demographic data on age, sex, mechanism of injury, onset-to-arrival time,

preexisting comorbidities, vital signs on arrival, AIS codes recorded using AIS 90 Update 98,[8] ISS,[9] Revised Trauma Score (RTS),[10] and Trauma and Injury Severity Score (TRISS),[11] medical treatment including interventional radiology and surgical operations, 24-hour transfusion record, the time to death from

TABLE 1. Characteristics of the Patients at Baseline

Parameters	N = 78,280
Age (y)	60 [37–74]
Male patients, n (%)	55,151 (70.5)
Vital signs on admission	
HR (bpm)	83 [70–100]
SBP (mm Hg)	130 [104–154]
RR (/min)	20 [16–25]
Glasgow Coma Scale score	14 [8–15]
RTS	7.6 [6.0–7.8]
ISS	24 [17–29]
TRISS (probability of survival)	0.91 [0.67–0.95]
24-h blood transfusion, n (%)	19,003 (24.3)
Surgery	
Craniotomy or craterization, n (%)	8,430 (10.8)
Thoracotomy, n (%)	2,204 (2.8)
Laparotomy, n (%)	3,221 (4.1)
Bone fixation, n (%)	12,828 (16.4)
Transarterial embolization, n (%)	4,441 (5.7)
Time to death from injury (h)	4.3 [1.6–46.7]
In-hospital death, n (%)	16,100 (20.6)

Data are number (%) or median [IQR], unless otherwise indicated.

RESULTS

Study Participants and Baseline Characteristics

The patient flow diagram is shown in Figure 1. In total, 294,275 patients were registered in the JTDB for the period 2004 to 2017. Of these patients, 269,465 suffered blunt trauma, and we included 104,837 patients with an ISS of 16 or more at the time of hospital arrival. We excluded 26,557 patients with nondirect transportation, cardiopulmonary arrest on arrival, isolated facial/external trauma, pregnancy, and missing data. We thus analyzed 78,280 patients as the final study cohort.

Table 1 shows the characteristics of the patients in this study. Their median age was 60 years (IQR, 37–74 years), and 55,151 patients (70.5%) were men. The median RTS was 7.6

TABLE 2. Number of Patients and Mortality in Each Trauma Region

	No. Deaths/No. Patients	Mortality (%)
Trauma region with AIS score, ≥ 3		
Head only	5,313/32,798	16.2
Chest only	1,245/10,159	12.3
Abd only	210/1,464	14.3
Ext only	270/2,265	11.9
Head + Chest	2,902/10,691	27.1
Head + Abd	167/639	26.1
Head + Ext	799/3,970	20.1
Chest + Abd	431/2,585	16.7
Chest + Ext	1,433/5,320	26.9
Abd + Ext	126/1,102	11.4
Head + Chest + Abd	395/1,065	37.1
Head + Chest + Ext	1,992/3,956	50.4
Head + Abd + Ext	107/331	32.3
Chest + Abd + Ext	411/1,293	31.8
Head + Chest + Abd + Ext	299/642	46.6
Total	16,100/78,280	20.6

Abd abdomen, Ext extremities.

injury, and in-hospital death, and we obtained these data to perform this study.

Primary Outcome

The primary outcome of this study was in-hospital death.

Statistical Analysis

Summary statistics of the patient demographic characteristics are presented as number, percent and median with interquartile range (IQR) as appropriate. To investigate the interaction effect with the combination of trauma regions, we performed multivariable logistic regression analysis with the dependent variable set as in-hospital death, and odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. In the definition of explanatory variables, we classified the trauma region into four regions; head, chest, abdomen, and extremities, and an injury of AIS score of 3 or more in each region was regarded as positive. According to the ISS calculations, cervical injuries are included in head injuries and pelvic injuries in extremities trauma. Then, six interaction terms were created with two combinations of the four regions ($_4C_2$): head-chest, head-abdomen, head-extremities, chest-abdomen, chest-extremities, and abdomen-extremities. We included four variables describing trauma regions and 6 interaction terms in the logistic regression model. To control for possible confounding, the model included age and sex.

The two-sided significance level for all tests was p less than 0.05. Statistical analysis was conducted with the use of JMP Pro statistical software (version 14.3.0 for Windows; SAS Institute Inc., Cary, NC) and R software (version 3.3.1; R Development Core Team, Vienna, Austria). This study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of the Osaka University Graduate School of Medicine (approval no. 16260). This article was written based on the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the reporting of cohort and cross-sectional studies.[12]

TABLE 3. Multivariable Regression Analysis for Trauma Region and Interaction

Variables	Adjusted OR for in-Hospital Death	95% CI	p
Combination of head and chest trauma			
Head (−) and chest (−)	Reference	—	—
Head (+) only	2.31	2.13–2.51	<0.001
Chest (+) only	2.28	2.17–2.39	<0.001
Interaction between head (+) and chest (+)	1.29	1.13–1.48	<0.001
Combination of head and abdominal trauma			
Head (−) and abdomen (−)	Reference	—	—
Head (+) only	2.31	2.13–2.51	<0.001
Abdomen (+) only	1.68	1.56–1.82	<0.001
Interaction between head (+) and abdomen (+)	0.98	0.87–1.10	0.725
Combination of head and extremities trauma			
Head (−) and extremities (−)	Reference	—	—
Head (+) only	2.31	2.13–2.51	<0.001
Extremities (+) only	1.84	1.76–1.93	<0.001
Interaction between Head (+) and Extremities (+)	0.97	0.88–1.06	0.476
Combination of chest and abdominal trauma			
Chest (−) and abdomen (−)	Reference	—	—
Chest (+) only	2.28	2.17–2.39	<0.001
Abdomen (+) only	1.68	1.56–1.82	<0.001
Interaction between chest (+) and abdomen (+)	0.77	0.67–0.88	<0.001
Combination of chest and extremities trauma			
Chest (−) and extremities (−)	Reference	—	—
Chest (+) only	2.28	2.17–2.39	<0.001
Extremities (+) only	1.84	1.76–1.93	<0.001
Interaction between chest (+) and extremities (+)	1.95	1.77–2.14	<0.001
Combination of abdomen and extremities trauma			
Abdomen (−) and extremities (−)	Reference	—	—
Abdomen (+) only	1.68	1.56–1.82	<0.001
Extremities (+) only	1.84	1.76–1.93	<0.001
Interaction between abdomen (+) and extremities (+)	0.70	0.62–0.79	<0.001

The multivariable regression analysis was adjusted for age and sex. Positive (+) indicates the presence of the trauma with AIS score ≥3 in each trauma region. Negative (−) indicates the presence of the trauma with AIS score of <3 or none in each trauma region.

(IQR, 6.0–7.8), the median ISS was 24 (IQR, 17–29), and the median TRISS was 0.91 (IQR, 0.67–0.95). In-hospital mortality was 20.6% (16,100/78,280), and the time to death from injury was 4.3 hours (IQR, 1.6–46.7 hours).

Table 2 shows the number of patients and mortality in each trauma region. In this table, a trauma combination with AIS score of 3 or more is described in a nonoverlapping manner. The percentage of patients with head trauma was 41.9% (32,798/78,280), which was the highest combination of the injury regions. The second combination was head + chest at 13.7% (10,691/78,280), and the third was chest alone at 13.0% (10,159/78,280). Generally, mortality tended to increase as the more damaged region was added. The combination with the highest mortality rate was head + chest + extremities at 50.4%. The second highest mortality rate was head + chest + abdomen + extremities at 46.6%, and the third was head + chest + abdomen at 37.1%.

Evaluation for Interaction of the Combination With Trauma Region

Table 3 shows the results of multivariable regression analysis for trauma regions and interaction terms. Multivariable logistic regression showed the ORs of in-hospital death compared with those without injury of AIS score of 3 or more in each injured region. Each of the four traumatic regions was associated with increased in-hospital death as an independent factor. The adjusted ORs of head, chest, abdomen, and extremities were as follows: head, 2.31 (95% CI, 2.13–2.51); chest, 2.28 (95% CI, 2.17–2.39); abdomen, 1.68 (95% CI, 1.56–1.82); and extremities, 1.84 (95% CI, 1.76–1.93). In addition, the adjusted ORs of the interaction term were as follows: head-chest 1.29 (95% CI, 1.13–1.48), chest-abdomen 0.77 (95% CI, 0.67–0.88), chest-extremities 1.95 (95% CI, 1.77–2.14), and abdomen-extremities 0.70 (95% CI, 0.62–0.79).

Figure 2 shows the increase in ORs for trauma death associated with the combination of trauma regions. There was a positive interaction with mortality in chest trauma as follows: head-chest, 29% and chest-extremities, 95%. However, certain combinations showed a negative interaction for trauma death as follows: chest-abdomen, 23% and abdomen-extremities, 30%.

DISCUSSION

In this study, the injury regions were classified into four parts: head, chest, abdomen, and extremities, and the combined interaction of trauma of AIS score of 3 or higher was evaluated. We found a positive interaction effect in the combinations involving the chest (chest-head and chest-extremities), suggesting that the combinations of these injury regions were associated with a super-additive increased risk of death. However, we also found a negative interaction effect in the combinations with chest-abdomen and abdomen-extremities.

It is reasonable that positive interactions with traumatic death were observed in combinations between 'chest' and 'head or extremities'. This may be explained by the biologically plausible reason that immune responses and coagulation/fibrinolysis reactions are likely to be activated in severe trauma, and hypoxemia caused by chest trauma affects other organs. The effect of local damage on remote organs can be explained by the so-called remote organ damage or ROD concept,[3] in which the initial tissue damage, blood loss, and secondary tissue damage lead to the release of endogenous mediators acting as damage-associated molecular patterns (DAMPs).[13–15] It is considered that complications, such as pneumonia after trauma, the development of acute respiratory distress syndrome,[16] and multiple organ dysfunction syndromes, are closely related to the release of DAMPs by injured tissue.[4,17] When trauma induces the release of DAMPs throughout the body, damage to remote organs indirectly affects the lungs,[18] and damage to the lungs affects remote organs in the process of the clearance of DAMPs.[19] In clinical studies, it is also shown that trauma causes the subsequent release of cytokines and activation of the complement system, resulting in an excessive inflammatory reaction thereafter.[20–26] Patients with multiple injuries combined with chest trauma suffer high mortality,[27–30] and that may be associated with these post-traumatic immune responses.[31,32] From the viewpoint of the blood coagulation system, lung microvascular injury causes the release of tissue factor, activation of the extrinsic coagulation pathway, deposition of fibrinogen, platelet activation, and the release of proinflammatory mediators. Then, it induces the formation of microvascular thrombi, thereby further deteriorating tissue damage and the consumption of clotting factors, which leads to bleeding, additional organ injury, and hypoxemia.[33]

	Head AIS ≥ 3	Chest AIS ≥ 3	Abdomen AIS ≥ 3	Extremities AIS ≥ 3
Head AIS ≥ 3		29%* ↑	—	—
Chest AIS ≥ 3			23%* ↓	95%* ↑
Abdomen AIS ≥ 3				30%* ↓
Extremities AIS ≥ 3				

Figure 2. Interaction matrix with the increase of odds by combination of trauma region. Asterisks indicate statistical significance (*p* < 0.05). Bar indicates no statistically significant difference.

In head trauma combined with chest trauma, the posttraumatic course and outcomes may be significantly influenced by the chest trauma, which can account for up to 25% of trauma-related deaths.[27,34] The effect of head injury on the lungs has been shown in a rat model, in which traumatic brain injury caused the release of tissue factor and the activation of the coagulation pathways correlated with acute lung injury.[35] In the clinical data, specific biomarkers in head trauma patients with chest trauma increase, and these biomarkers correlate with worse outcomes.[36]

Regarding chest and extremity trauma, there are reports that systemic inflammation induced by chest trauma disturbed the healing of fractures.[37] The effects of extremities trauma on remote organs including the lungs also have been identified in several studies as a potential cause of death.[38–40] Our results were consistent with those of previous reports, in which chest trauma had a positive interaction effect between head trauma and extremities trauma.

However, we observed an unexpected result in that the combinations of chest-abdomen and abdomen-extremities had negative interactions on in-hospital mortality. This finding would be difficult to explain by pathophysiological mechanisms alone. As potential reasons, we consider the influence of a clinically plausible reason, that is, the treatment strategy and treatment system of the medical facility. In terms of treatment strategy, patients with abdominal and pelvic trauma may receive simultaneous interventions for bleeding control, such as transarterial embolization or resuscitative endovascular balloon occlusion of the aorta, so a combination of injuries that allows simultaneous interventions may have a negative interaction. Additionally, in terms of the trauma care system, the magnitude of the interaction caused by the combination of trauma may be different between a facility where simultaneous intervention is possible and a facility where it is difficult. For example, a trauma center rich in manpower would allow simultaneous interventions in treatment, resulting in better outcomes than a facility with insufficient manpower.

The clinical implications of this research are twofold. First, this study showed potentially lethal combinations of multiple injuries. Consideration of such combinations by clinicians may trigger earlier therapeutic intervention. Second, this real-world data may support some of the results of previous basic experiments and other clinical studies related to trauma death. Considering the interaction of multiple injuries as a therapeutic target may be a breakthrough in improving therapeutic outcomes.

Limitations

Our study has some limitations that might be potential sources of bias. First, this was a retrospective study, and the usual limitations inherent to this type of study apply. Unmeasured confounding factors may have influenced the association between multiple injuries and outcome. Second, the patients with cardiopulmonary arrest on hospital arrival were not included in the study, which may have led to selection bias. Third, this study evaluated only the combination of the two trauma regions. A combination of three or more regions requires a high-dimensional calculation and the interpretation of the results becomes complicated, and we could not perform it. Fourth, with AIS coding, only the maximum value is adopted even if there are multiple injuries in the same region. The interaction between organ injuries within the same area was not evaluated.

CONCLUSION

In the present study population, among patients with multiple injuries, a combination of chest-head trauma and chest-extremities trauma was shown to increase the risk of traumatic death. These are clinically important as potentially lethal combinations, and the present findings are believed to increase the robustness of the previous basic experimental data.

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