Treatment for Geriatric Traumatic Brain Injury: A Nationwide Cohort Study

Running title: Intensive treatment in geriatric TBI

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Abstract

Background: Due to aging of the Japanese population, traumatic brain injuries (TBI) in elderly individuals have increased. However, the effectiveness and prognosis of intensive treatment in geriatric TBI have not yet been determined. Thus, we analyzed the prognostic factors of intensive and aggressive treatments using nationwide data from Japan Neurotrauma Data Bank (JNTDB) projects.

Methods: We analyzed 1,879 geriatric TBI cases (≥65 years old) registered in four JNTDB projects, Project 1998 (P1998) to Project 2015 (P2015). Clinical features, aggressive treatment usage, and 6-month outcomes on the Glasgow Outcome Scale (GOS) were compared among study projects. Logistic regression was performed to clarify prognostic factors in aggressively-treated patients.

Results: The percentage of geriatric TBI cases significantly increased across time (P1998: 30.1%, Project 2004 (P2004): 34.6%, Project 2009 (P2009): 43.9%, P2015: 53.6%, p<0.0001). Aggressive treatment usage also significantly increased, from 67.0% in P1998 to 69.3% in P2015 (p<0.0001). Less invasive methods, such as trepanation and normothermic targeted temperature management, were more often chosen for geriatric patients. These efforts resulted in a significant decrease in the 6-month mortality rate, from 76.2% in P1998...
to 63.1% in P2015 (p=0.0003), although the percentage of severely disabled patients
increased, from 8.9% in P1998 to 11.1% in P2015 (p = 0.0003). Intraventricular hemorrhage
was the most unfavorable prognostic factor for the 6-month outcome (OR 3.79, 95% CI 1.78–
8.06, p<0.0001).

Conclusions: Less invasive treatments reduce mortality in geriatric TBI but do not improve
functional outcomes. The patients’ age does not seem to be the strongest prognostic factor;
thus, physicians should not adhere to only age.

Key words: traumatic brain injury, Glasgow Outcome Scale, intraventricular hemorrhage,
intracranial pressure
Introduction

In Japan, the age distribution of traumatic brain injury (TBI) is rapidly changing. In past reports from the Japan Neurotrauma Data Bank (JNTDB), the ratio of TBIs in young people as a proportion of the whole was shown to decrease, whereas the ratio of TBIs in the elderly was shown to increase. The number of geriatric TBIs is expected to continue to increase as the aging society progresses, and it is expected to have a significant effect on society, including medical economics.

In this current situation, there is an urgent need for measures to deal with geriatric brain injury, but there is still no specific treatment strategy. Thus, it is considered extremely important to determine and discuss the kind of medical interventions adopted by neurotrauma surgeons and how these measures are reflected in patient outcomes.

The aim of this study was, thus, to analyze the prognostic factors of intensive and aggressive treatments in these patients using nationwide data from JNTDB projects. We examined and discuss cases registered in the JNTDB projects (P1998, P2004, P2009, and P2015) regarding the treatment provided for geriatric TBI cases in Japan, as well as patient outcomes. Furthermore, we also examined and discuss how aggressive treatments like surgery, intracranial pressure (ICP) monitoring, and active thermoregulation have been
Materials and Methods

The Japan Neurotrauma Data Bank (JNTDB)

The JNTDB is a Japanese nationwide registry designed to collect and report data on patients with TBI in Japan. This project was initiated by the Japan Society of Neurotraumatology in 1997. The data sheet of the JNTDB was composed of 392 items, containing information regarding characteristics of the injury, diagnosis, treatment, and complications with respect to the outcome of therapies given. After conducting a pilot study in 1997, a three-year nationwide investigation was performed from 1998 (P1998). The inclusion criteria required subjects to be severe TBI patients 1) whose initial Glasgow Coma Scale (GCS) score was less than eight, or 2) whose GCS score decreased within 48 hours of injury onset and commencement of treatment. In P1998, data were collected from 1,002 prospective TBI cases. Subsequently, P2004 was performed from January 2004. In P2004, patients of all ages were included, and data were collected from 1,101 prospective cases. P2009 commenced in January 2009, was completed in 2012, and included 1091 cases. More recently, P2015 was completed in 2018. The P2015
study included data taken from 32 level-one emergency medical centers, and 1,345 patients were added to the database over its duration. All study projects were submitted and approved by the institutional review board within each participating institute. Patients or patient relatives were fully informed about this study with a letter and WEB page of each institute, and the chance of opting-out was provided to all participants.

Study procedure

This was a retrospective cohort study of data in JNTDB. For our analysis of cases registered in the JNTDB database (P1998: 1998-2001, 10 facilities, 1002 cases; P2004: 2004-2006, 19 facilities, 1101 cases; P2009: 2009-2011, 22 facilities, 1091 cases; P2015: 2015-2017, 32 facilities, 1345 cases), the geriatric group included patients aged 65 years or older. We compared the aging rate, age, gender, ratio of diffuse brain injury and focal brain injury, the GCS score at initial consultation, Injury Severity Score (ISS), length of hospital stay, vital signs, blood gas findings, pupil findings, and computed tomography (CT) findings. In CT findings, we examined the presence of vault fractures, basilar skull fractures, pneumocephalus, traumatic subarachnoid hemorrhage, and intraventricular hemorrhage, and compared the proportion of patients with diffuse injury, based on the Traumatic Coma Data
Bank (TCDB) classification Diffuse injury I - IV, and the proportion of those with focal injury, based on the presence of an evacuated and non-evacuated mass.

We also compared the proportion of patients managed with different types of treatment, including craniotomy, trepanation, trepanation following craniotomy, barbiturate therapy, active thermoregulation (therapeutic hypothermia, intentional normothermia), and ICP monitoring, to examine transitions in treatment. We compared aggressive treatment (cases treated with any type of treatment involving craniotomy, trepanation, active thermoregulation, barbiturate therapy, or ICP monitoring) and non-aggressive forms of treatment. The length of hospital stay and Glasgow Outcome Scale (GOS) score at 6 months after injury were compared among projects as patient outcomes.

The data obtained from P1998, P2004, P2009, and P2015 were examined retrospectively using univariate analysis to clarify the characteristics of patients with poor outcome (severe disability, vegetative state, and death) in geriatric brain injury, and poor prognostic factors were examined using multiple logistic regression analysis.

The mean value of each item is displayed as mean ± standard deviation, and t-tests were used for two-group comparisons. The chi-square test was used for comparison of categorical data. Analysis of variance was used for four-group comparisons. An alpha
criterion value of $p < 0.05$ was deemed to represent a significant difference.

Results

Study population

With the criterion of our study, 1,879 cases were extracted from the dataset of JNTDB, which was collected over 20 years. The 6-month outcome data was missing in 421 cases. Therefore, logistic analysis was performed to detect the 6-month prognostic factor using the data of 1,458 cases (Figure 1).

[Figure 1 here]

Transition in age composition and changes in aging rate in each project

A graph displaying the age composition of patients in each project is shown in Figure 2. In P1998, the inclusion criterion for data registration was cases aged 6 years and older, so, in Figure 2, the 0-9-years category in P1998 was limited to 6-9 years. P1998 had a bimodal distribution with two clear peaks at 20-29 years and 60-69 years, but, from P2004, the 20-29-year-old peak decreased and the 60-69-year-old peak increased, changing to a monomodal tendency. Furthermore, in P2015, the number of patients in the 60-years-and-older age group
continued to increase, with the age distribution peak shifting to 70-79 years, changing to a
shape with a gentle downward slope towards the younger age groups.

[Figure 2 here]

The aging rate (percentage of patients aged 65 years and older) increased
significantly across projects (Figure 3), from 30.1% in P1998 to 34.6% in P2004, 43.9% in
P2009, and 53.6% in P2015 ($p<0.0001$). There was also a significant increase in the
percentage of elderly-elder (aged 75 years and older) among the elderly population (P1998:
14.6%, P2015: 33.3%, $p<0.0001$, Figure 3).

[Figure 3 here]

Transition in the physiology and anatomical severity of geriatric TBI patients

The general clinical features of geriatric patients with TBI in the four projects are
presented in Table 1. In P1998, the ratio of males was larger (63.4%), but that ratio
significantly declined to reach 52.1% in P2015. There was also a significant increase in the
average age of cases in the elderly group (P1998: 75.3 ± 7.4 years, P2015: 77.5 ± 7.6 years,
$p<0.0001$). The median GCS score upon hospital arrival was 5.0 in P1998, which
significantly increased to a mean of 6.0 in P2015. The results suggested that the significant increase observed in the motor score in particular may have affected this outcome.

There were no significant differences in heart rate, respiratory rate, body temperature, or pupil findings among patients in the four projects, but there was a significant increase in systolic blood pressure, PaO₂, and PaCO₂ upon hospital arrival. There was a reduction in ISS, which shows the anatomical severity of the condition (Median (IQR): P1998: 25.0 (25.0-27.0), P2015: 25.0 (17.0-27.0), p = 0.035), and, based on the detailed findings of the initial CT, there was significant reduction in vault fractures and a significant increase in basilar skull fracture and pneumocephalus, traumatic subarachnoid hemorrhage, and intraventricular hemorrhage (IVH) (p<0.0001, chi-square test).

A comparison of the ratio of diffuse/focal injury showed an increase in focal injuries and a decline in diffuse injuries over time (p = 0.0007).

Transition in treatment of geriatric TBI patients

A comparison of the four project groups showed an increase in trepanations and a decrease in craniotomies (Table 2). In P2015, ICP monitoring accounted for 36.6% of
intensive care treatment as a whole, while active thermoregulation (cerebral hypothermia, active normothermia) was implemented for 22.6% of all cases. In P2015, the percentage of cases using aggressive treatment significantly increased to 69.3%.

Table 2 here

Transition in the outcomes of geriatric TBI patients

A comparison of the length of hospital stay showed a significant decline across time, with a mean length of stay of 26.9 days in P2015 (Table 3). A comparison of GOS score on discharge after injury showed a significant reduction in mortality (62.8% in P1998 to 44.7% in P2015; Table 3). However, in the analysis of the 6-month GOS score, there was a significant increase in the percentage of patients who were severely disabled or in a vegetative state within the dependent survivor group, for whom assistance and nursing is regarded to be necessary for daily living, increasing from 11.3% to 19.1% of the whole (p<0.0001; Table 4).

Table 3 and 4 here

Characteristics of the functionally poor outcome group among geriatric TBI patients
We examined differences in the 6-month good outcome group (good recovery and moderate disability) and poor outcome group (severely disabled, vegetative state, and dead) from P1998-P2015 to ascertain the factors involved in functional outcomes in geriatric patients with TBI (Table 5).

There were significant differences between the good and the poor outcome groups in age, body temperature, blood sugar, ISS, GCS score, pupil abnormality, presence of fracture, percentage of traumatic subarachnoid hemorrhage cases, and percentage of IVH cases. When we conducted logistic regression analysis with items that were $p<0.1$ set as the independent variables and poor outcome as the dependent variable, we found that age of 75 years and older, ISS $\geq 25$, GCS score $\leq 8$, presence of traumatic subarachnoid hemorrhage, and presence of IVH were all factors associated with poor outcomes. The presence of an IVH was the strongest predictive factor (OR 3.79, 95%CI 1.78–8.06, $p<0.0001$; Table 6).

[Table 6 here]
Discussion

Our analyses showed that less invasive treatments might reduce mortality in geriatric patients with TBI. However, intensive treatments did not improve functional outcomes. The strongest prognostic factor that impeded aggressive treatment was the pathophysiology of IVH, and the patients’ age itself was not the sole strongest prognostic factor. So far, this study is the first study that analyzed the efficacy and trends of treatment for geriatric traumatic brain injury with nationwide patient cohort.

Aging of geriatric TBI is progressing with “super-aging” of patients

There has been a steep increase in the super-aged population in Japan with the recent advances in medicine. As of 2017, the elderly population in Japan reached its highest point ever, at 35,140,000 people, with people aged 65 years and older accounting for 27.7% of the total population (aging rate); thus, almost 1 in 4 people in Japan are now elderly. Also, the population of 90 years and older exceeded 2 million for the first time, indicating Japan’s shift to a super-aging society. While Japan’s total population has declined by 210,000 people, the elderly population has increased by 570,000 people. Thus, Japan is predicted to enter the process of long-term population decline associated with the continuously declining birth rate.
However, as the so-called “baby boom generation” enters old age, the elderly population is estimated to increase even more. By 2035, it is predicted that 1 in 3 Japanese people will be 65 years and older, which is predicted to increase to 1 in 2.5 people by 2060, with Japan expected to become an unprecedented aging society. In fact, the elderly population was increased as 1.5 times, from 1998 (2.2 million) to 2015 (3.3 million). The percentage of geriatric TBIs in Japan is also increasing with the changes in population composition. The results of our study demonstrate that there is a much more marked increase in aging above what was reported previously.

Conversely, it should also be noted that, while the number of head trauma patients between the ages of 10 and 20 and between 20 and 30 was decreasing up to P2009, in 2015, this trend was reversed, and there was a slight increase in these age groups. The cause of this change is unclear, but it highlights the importance of being prepared for high-energy trauma caused by sports, traffic injuries, and falls. Continuing to enlighten young people on the risks of head trauma is indispensable to prevent a reduction in the population of young people who are able to support the aging society in the future. On the other hand, in the elderly category, this study clarified that the number of head traumas in the elderly-elder group aged 75 years and older are increasing year-to-year. It has been reported that the increase in elderly-elder
TBI patients is causing new medical economic problems.

A US report claimed that the frequency of CT and magnetic resonance imaging scans in the elderly (aged 65 years and older) population is three-times higher than that in the younger age group, and the admission rate of intensive care unit is four times higher. The annual medical cost per person has increased from 73,000 to 78,000 United States Dollars, and the rehospitalization rate is also reportedly higher. The number of head trauma patients aged 75 years and older is expected to also increase in Japan; thus, the importance of medical economics in this field cannot be overlooked.

Overview of the transition in geriatric TBI patients

As shown in Table 1, the increase in GCS score, particularly in the motor score, is a noteworthy result. The cause is unknown, but the increase in focal injuries associated with aging resulted in an increase in the Talk and Deteriorate group, so it is presumed that the GCS score at initial consultation may have also increased. To confirm this information, we found that the proportion of patients in the Talk and Deteriorate group had increased significantly among those in the focal injury group (diffuse injury group 11.3%, focal injury group 24.1%, $p \leq 0.0001$).
Further, while the incidence of vault fracture decreased, the incidence of basilar skull fracture and pneumocephalus, traumatic subarachnoid hemorrhage, and IVH increased. The incidence of traumatic subarachnoid hemorrhage in particular was seen in 72.7% of elderly patients in P2015. It was previously noted that geriatric TBI patients have a specific pathophysiology associated with aging prior to sustaining the injury, including coagulopathy, common use of aspirin and anticoagulants, and increased fragility of blood vessels associated with arteriosclerosis and amyloid angiopathy; thus, the incidence of traumatic subarachnoid hemorrhage in geriatric TBI patients may have increased with the increased age of the affected population.

Reports have suggested that traumatic subarachnoid hemorrhage may be a delayed cerebral vascular disorder caused by cerebral vasospasm, and that the mortality rate doubles in patients with a traumatic subarachnoid hemorrhage compared to those without. Therefore, this may be an important finding as an outcome prognosticator in geriatric TBI patients.

Increase of aggressive treatment in geriatric TBI patients

One of the general characteristics of head trauma is that the outcome worsens with age. Due to this, the patient’s age at the time of the injury is also listed as an important
prognosticator.\textsuperscript{9-12} There are several reports concluding that the physiological fragility of the elderly brain tissue is the cause of poorer outcomes.\textsuperscript{8,13} Unfortunately, because the brain tissue and cerebral blood vessels are older, patients often do not improve even with aggressive treatment.\textsuperscript{14} Also, there is currently no specific treatment or guidelines in place for elderly patients based on strong evidence that takes into account pathologies specific to the elderly, which makes it difficult to determine the type of patient for whom aggressive treatment should be used and the extent of that treatment.\textsuperscript{2}

As neurosurgeons, we are faced with difficult decisions about whether or not to treat certain patients, and we often encounter cases where we are concerned about the results our decisions will bring, as well as cases where we suffer from remorse. However, in this study, we clarified that the percentage of geriatric TBI patients undergoing more aggressive forms of treatment is conversely on the rise. In particular, we found an increase in the proportion of patients undergoing trepanation, and a decrease in the percentage of craniotomy cases. This may be the result of doctors considering the physical burden of such procedures on elderly patients and opting for less invasive treatment options.

There has also been a rapid decline in the number of patients treated with therapeutic hypothermia, with most treatments implemented using normothermia and even with active
thermoregulation therapy. In particular, the percentage of elderly patients who had cerebral hypothermia treatment did not exceed 1.5% in P2015. This may have been largely influenced by the results of a multi-center joint study implemented by Clifton et al., which found that, in general, cerebral hypothermia treatment has no efficacy, and, in patients aged 45 years and older, cerebral hypothermia treatment actually increases the chance of poor outcomes.\textsuperscript{15} The target disease differed, but the results of a comparative clinical trial (Targeted Temperature Management [TTM] Trial) on normothermia and cerebral hypothermia treatment in post-cardiac arrest syndrome may have also affected this change in treatment practice.\textsuperscript{16}

On the contrary, the ICP monitoring rate was 30% or less in all three patient groups of P1998, P2004, and P2009, but it increased to 36.6% in P2015. While ICP monitoring is one of the most strongly recommended procedures in the TBI Treatment and Management Guidelines in Japan\textsuperscript{17}, there are no global reports of high evidence-level to support this practice. Also, as cerebrovascular autoregulation is reduced in the elderly compared to that in younger age groups,\textsuperscript{13} further research is needed in geriatric TBI patients to determine the preferred treatment threshold for ICP and cerebral perfusion pressure (CPP) specific to the elderly.
Significantly decreased mortality rate has, but significantly increased poor functional outcomes rate

The mortality rate of geriatric TBI patients decreased significantly since P1998 due to the aggressive treatment efforts of neurosurgeons. However, the percentage of severely disabled patients significantly increased. Moreover, the percentage of dependent survivors (severely disabled and vegetative state/survivor) has been increasing with time, and, in P2015, 19.1% of all cases were dependent survivors. A future issue, in addition to saving the patients’ life, is to consider how to improve the functional outcome of patients, as well as to dedicate more effort into building a comprehensive treatment strategy that includes neuroprotective therapy, rehabilitation medicine, and regenerative medicine.

Factors predicting unfavorable outcomes in geriatric TBI patients

The results of our study suggest that aggressive treatment may improve the life prognosis of geriatric TBI patients, but also that the improvement of functional outcomes should be a future target. However, we frequently experience cases in clinical practice for which it is difficult to improve functional outcomes with any kind of aggressive treatment. When a patient becomes bedridden long-term or falls into a vegetative state, it creates...
enormous psychological and financial burdens for the patient’s family. Therefore, it is extremely difficult to determine the extent to which aggressive treatment should be used on certain types of patients, or if it should simply be abandoned. The patient’s family is also faced with having to decide whether to approve certain treatments in an emergency situation, with limited information available, making the mental burden immeasurable, even beyond that faced by the family of young people with head trauma. It is essential for us to present a certain level of outcome prediction information to the patients’ families in order to help reduce the aforementioned burdens, and also to provide information on outcomes if aggressive treatment is employed.

With this in mind, we examined factors that predicted poor outcomes in geriatric TBI patients using univariate and multivariate analyses. We examined the physiological severity, anatomical severity, and injury findings upon hospital arrival from all data of geriatric TBI patients and compared good (good recovery and moderate disability: 215 cases) and poor outcome cases (severely disabled, vegetative state, and death: 1,243 cases). We found that the following factors were significantly associated with poor functional outcomes:

- Age of 75 years and older
- ISS≥25
GCS score ≤ 8

Presence of traumatic subarachnoid hemorrhage

Presence of IVH (extremely strong predictor)

The factors ‘age of 75 years and older’ and ‘initial GCS score ≤ 8’ were also included in previous reports as prognostic determinants for geriatric TBI patients,\(^1\) consistently with the results of the current study.

While the decision of employing an aggressive treatment strategy should not be determined by a single factor associated with poor outcomes, it is unlikely that the combination of many factors will result in a good outcome. Providing treatment at an early stage after the patient has sustained the injury is the most important factor for achieving the maximum therapeutic effect with aggressive treatment for head trauma in elderly patients,\(^{18}\) and rapid decision making is more important for the elderly compared to that required for young patients. We hope this data may be of use in future studies.

In this study, there are several limitations. First, this was a retrospective cohort study of JNTDB, thus the indication of treatment might have varied among institutes, even though all institutes now recognize and use the Brain Trauma Foundation and Japanese treatment guidelines for TBI\(^ {17,19}\). Second, this study used data that were prospectively collected over
20 years. We cannot exclude that the general medical standard might have improved over this longer study duration.

Conclusions

In this study, we found that aggressive treatment improved the life prognosis for geriatric TBI patients. It should be noted that life prognosis improved for some patients even with less invasive forms of aggressive treatment, and despite the increasing age of the affected patients. In the future, subsequent to saving the patient’s life, treatment strategies that improve functional outcomes should be investigated. In addition, it is important to be able to make rapid treatment decisions for patients for whom aggressive treatment strategies are not an option and, thus, often fall into the “absolute poor outcome” group.

Conflict of Interest statement

The authors declare that they have no conflicts of interest.

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1,879 cases were extracted from the dataset of four JNTDB project databases, which was collected over recent 20 years. The 6-month outcome data was missed in 421 cases, and 1,458 cases were applied logistic regression analysis for detecting prognostic factors in elderly TBIs.

Abbreviations: GOS, Glasgow Outcome Scale; GR, good recovery; MD, moderate disability; SD, severely disabled; VS, vegetative state; D, dead.

The patients in project 1998 were registered from 6 years of age; therefore, the youngest age category was 6-9 years. Over the age of 60, the number of patients abruptly increased.

In geriatric traumatic brain injury (TBI) populations, the number of elderly-elder geriatric patients (over 75 years of age) has been increasing. Currently in Japan, half of all TBIs are
observed in patients over the age of 65 years.
Figure 1

Project 1998
(n=1,002)

Elderly patients (≥65)
(n=298)

Project 2004
(n=1,101)

Elderly patients (≥65)
(n=381)

Project 2009
(n=1,091)

Elderly patients (≥65)
(n=479)

Project 2015
(n=1,345)

Elderly patients (≥65)
(n=721)

Elderly patients (≥65)
(n=1,879)

Missing the 6-month outcome
(n=421)

Elderly patients identified 6-month Outcome
(n=1,458)

6-month good outcome
(GOS: GR, MD)
(n=215)

6-month poor outcome
(GOS: SD, VS, D)
(n=1,243)
Figure 2

Age distribution 1998-2015

No of patients

Age

0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-100

P1998 P2004 P2009 P2015
Figure 3
### Table 1. General clinical features of geriatric traumatic brain injury patients in four projects.

| Project | 1998 | 2004 | 2009 | 2015 | p-value |
|---------|------|------|------|------|---------|
| N (>65 y.o) | 298  | 381  | 479  | 721  |         |
| Gender  |      |      |      |      |<0.0001 |
| Male    | 189  | 229  | 283  | 376  |         |
| Female  | 103  | 152  | 196  | 345  |         |
| Unknown | 5    | 0    | 0    | 0    |         |
| Age     | 75.3 ± 7.4 | 75.4 ± 6.9 | 77.1 ± 7.5 | 77.5 ± 7.6 | <0.0001 |
| Physical severity | | | | | |
| GCS score | 5.0 (4.0-8.0) | 6.0 (4.0-9.2) | 6.0 (4.0-9.0) | 6.0 (4.0-9.0) | 0.0125 |
| Median (IQR) | | | | | |
| Systolic blood pressure(mmHg) | 140.2 ± 53.9 | 150.3 ± 49.4 | 147.0 ± 47.9 | 150.0 ± 45.3 | 0.0204 |
| Heart rate (/min) | 86.6 ± 31.6 | 87.4±26.2 | 86.5±27.0 | 87.6 ± 26.1 | 0.8873 |
| Respiratory rate | 19.4 ± 9.0 | 20.5 ± 8.0 | 20.3 ± 9.9 | 19.6 ± 7.4 | 0.3019 |
|                         |                         |                         |                         |                         |                         |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                         | /min                    |                         |                         |                         |                         |
| **Body temperature**    |                         |                         |                         |                         |                         |
|                         |                          | 36.1 ± 1.1              | 36.0 ± 1.2              | 36.1 ± 1.2              | 36.2 ± 1.3              | 0.1495                  |
|                         | (°C)                    |                          |                          |                          |                          |                         |
|                         |                          | 36.0 ± 1.2              | 36.0 ± 1.2              | 36.0 ± 1.2              | 36.0 ± 1.2              |                         |
| **PaO2 (mmHg)**         | 177.8 ± 142.2           | 217.9 ± 141.7           | 219.9 ± 144.1           |                          | 192.3 ±                  | 0.0003                  |
| **PaCO2 (mmHg)**        | 39.8 ± 20.4             | 40.2 ± 14.3             | 39.0 ± 10.6             | 42.1 ± 15.6             |                          | 0.0098                  |
| **pH**                  | 7.38 ± 0.13             | 7.38 ± 0.12             | 7.38 ± 0.11             | 7.37 ± 0.12             |                          | 0.4631                  |
| **Pupil abnormality**   |                         |                          |                          |                          |                          |                         |
|                         |                         | 122 (40.9)              | 166 (43.6)              | 207 (43.2)              | 248 (34.4)              | 0.0036                  |
|                         | N, (%)                  |                          |                          |                          |                          |                         |
| **Anatomical severity** |                         |                          |                          |                          |                          |                         |
| **ISS**                 | 25.0                    | 25.0                    | 25.0                    | 25.0 (17.0-)            |                          | 0.0353                  |
| **Median (IQR)**        | (25.0-27.0)             | (17.0-29.0)             | (16.0-27.0)             | 27.0                    |                          |                         |
| **Vault fracture**      | 144 (48.3)              | 179 (47.0)              | 185 (38.6)              | 304 (42.2)              |                          | <0.0001                 |
|                         | (N, %)                  |                          |                          |                          |                          |                         |
| **Basal skull**         | 25 (8.4)                | 48 (12.6)               | 94 (19.6)               | 151 (20.9)              |                          | <0.0001                 |
|                         | N   | %   |
|-------------------------|-----|-----|
| **Fracture (N, %)**     |     |     |
| Intracranial air        |     |     |
| (N, %)                  |     |     |
|                         | 10  | 3.3 |
|                         | 40  | 10.5|
|                         | 66  | 13.8|
|                         | 108 | 15.0|
|                         | <0.0001 |     |
| Traumatic               |     |     |
| subarachnoid hemorrhage |     |     |
| IVH                     |     |     |
|                         | 47  | 15.8|
|                         | 43  | 11.3|
|                         | 65  | 13.6|
|                         | 127 | 17.6|
|                         | <0.0001 |     |
| Focal injury            |     |     |
| (N, %)                  |     |     |
|                         | 256 | 44.1|
|                         | 298 | 78.2|
|                         | 358 | 74.7|
|                         | 539 | 74.8|
|                         | 0.0007 |     |
| Diffuse injury          |     |     |
| (N, %)                  |     |     |
|                         | 42  | 55.9|
|                         | 83  | 21.8|
|                         | 121 | 25.3|
|                         | 182 | 25.2|
|                         | 0.0007 |     |

Abbreviations: ISS, Injury Severity Score; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage. IQR: interquartile range
Table 2. Transition of treatment in geriatric traumatic brain injury patients.

Abbreviations: HITT, hematoma irrigation and trepanation therapy; ICP, intracranial pressure.

| Project                                      | 1998   | 2004   | 2009   | 2015   | p-value |
|----------------------------------------------|--------|--------|--------|--------|---------|
| Surgical procedure                           |        |        |        |        |         |
| Burr hole and irrigation                     | 43 (11.8) | 40 (10.5) | 97 (20.5) | 172 (23.9) | <0.0001 |
| (including HITT) N, (%)                      |        |        |        |        |         |
| Craniotomy N, (%)                            | 102 (34.2) | 152 (39.9) | 184 (38.4) | 236 (32.7) | 0.0313  |
| HITT followed by craniotomy N, (%)           | 6 (2.0)  | 3 (0.8)  | 29 (6.1)  | 12 (1.7)  | 0.0585  |
| Critical care                                |        |        |        |        |         |
| ICP monitoring N, (%)                        | 67 (22.5) | 73 (19.2) | 116 (24.2) | 264 (36.6) | <0.0001 |
| Barbiturate N, (%)                           | 3 (1.0%) | 3 (0.8%) | 15 (3.1%) | 0 (0)    | 0.1339  |
| Intensive temperature treatment              |        |        |        |        |         |
| N, (%)                                       | 20 (6.7) | 101 (26.6) | 144 (30.1) | 163 (22.6) | <0.0001 |
| Hypothermia N, (%)                           | 20 (6.7) | 19 (5.0)  | 29 (6.1)  | 11 (1.5)  |         |
|                              | -  |  83 (21.8)  |  115 (24.0) |  152 (21.1) |
|------------------------------|----|------------|----------|------------|
| Intensive normothermia N, (%)|    |            |          |            |
| Aggressive treatment N, (%)  | 157 (67.0) | 226 (58.7) | 344 (71.4) | 500 (69.3) | <0.0001 |
Table 3. Glasgow outcome scale on discharge

| Project       | 1998     | 2004     | 2009     | 2015     | p-value |
|---------------|----------|----------|----------|----------|---------|
| Total         | 290      | 381      | 479      | 721      |         |
| Length of hospital stay (days) |          |          |          |          |         |
|               | 27.6 ± 42.8 | 34.5 ± 51.8 | 29.0 ± 42.8 | 26.9 ± 34.2 | 0.0357 |
| GOS on discharge |          |          |          |          |         |
| (N,%)         |          |          |          |          |         |
| GR            | 22 (7.4) | 29 (7.6) | 29 (6.1) | 47 (6.5) | 0.0003  |
| MD            | 20 (6.7) | 38 (10.0)| 47 (9.8) | 70 (9.7) |          |
| SD            | 44 (14.8)| 79 (20.7)| 95 (19.8)| 168 (23.3)|         |
| VS            | 24 (8.1) | 50 (13.1)| 58 (12.1)| 111 (15.8)|         |
| D             | 188 (62.8)| 185 (48.6)| 250 (52.2)| 322 (44.7)|         |
| Survival rate (N,%) | 102 (35.1) | 196 (51.4) | 229 (47.8) | 399 (55.3) | <0.0001 |
| Dependent survivors | 68 (23.2) | 129 (33.9) | 153 (31.9) | 279 (39.1) | <0.0001 |

Abbreviations: GR, good recovery; MD, moderate disability; SD, severely disabled; VS, vegetative state; D, death.
Table 4. Transition of mortality and functional outcomes 6 months after injury.

| Project | 1998 | 2004 | 2009 | 2015 | p-value |
|---------|------|------|------|------|---------|
| Total   | 248  | 271  | 389  | 550  |         |

6-month Glasgow Outcome Scale (N,%)

|        | 1998 | 2004 | 2009 | 2015 |        |
|--------|------|------|------|------|--------|
| GR     | 18 (7.3) | 21 (7.7) | 21 (5.4) | 52 (9.5) | 0.0003 |
| MD     | 13 (5.2)  | 18 (6.6)  | 26 (6.7)  | 46 (8.4)  |        |
| SD     | 22 (8.9)  | 22 (8.1)  | 48 (12.3) | 61 (11.1) |        |
| VS     | 6 (2.4)   | 23 (8.5)  | 27 (6.9)  | 44 (8.0)  |        |
| D      | 189 (76.2)| 187 (69.0)| 267 (68.6)| 347 (63.1)|        |

Dependent survivors (N,% in all)

|        | 1998 | 2004 | 2009 | 2015 | <0.0001 |
|--------|------|------|------|------|---------|
| 28 (11.3) | 45 (16.6) | 75 (19.3) | 105 (19.1) |        |

Abbreviations: GR, good recovery; MD, moderate disability; SD, severely disabled; VS, vegetative state; D, dead.
Table 5. Univariate analysis of good and poor outcomes between 1998-2018

|                      | Good outcome (GR+MD) | Poor outcome (SD+VS+D) | p-value |
|----------------------|----------------------|------------------------|---------|
| **No. of patients**  | 215                  | 1,243                  |         |
| **Age (years)**      | 74.0 ± 6.7           | 77.3 ± 7.5             | <0.0001 |
| **Systolic blood pressure (mmHg)** | 150.4 ± 31.9     | 146.0 ± 54.0           | 0.2401  |
| **Heart rate (/min)**| 86.9 ± 20.6          | 86.5 ± 30.1            | 0.8387  |
| **Respiratory rate (/min)** | 20.7 ± 5.8       | 19.5 ± 8.7             | 0.0785  |
| **Body temperature (°C)** | 36.4 ± 1.0      | 36.0 ± 1.4             | 0.0002  |
| **Blood sugar (mg/dL)** | 155.2 ± 44.7     | 191.0 ± 73.0           | <0.0001 |
| **ISS**              | 23.0                 | 25.0                   | <0.0001 |
| **Median (IQR)**     | (16.0-25.0)          | (18.0-29.0)            |         |
| **GCS score**        | 10.0                 | 6.0                    | <0.0001 |
| **Median (IQR)**     | (6.0-14.0)           | (4.0-8.0)              |         |
| Condition                          | Count (N) | Total (%) | p-value |
|-----------------------------------|-----------|-----------|---------|
| Pupil abnormality                 | 36 (16.7%)| 633 (51.0%)| <0.0001 |
| Vault fracture                    | 83 (38.6%)| 579 (46.5) | 0.0002  |
| Basal skull fracture              | 28 (13.6%)| 240 (17.6%)| 0.0406  |
| Traumatic subarachnoid hemorrhage | 111 (51.6%)| 880 (70.8%)| <0.0001 |
| IVH                               | 8 (3.7%)  | 220 (17.7%)| <0.0001 |
| Focal injury                      | 168 (78.1%)| 968 (77.9%)| 0.2976  |

Abbreviations: ISS, Injury Severity Score; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage. IQR: interquartile range
Table 6. Logistic regression analysis of the probability of an unfavorable 6-month outcome.

|                         | Odds (95% CI)  | p-value  |
|-------------------------|----------------|----------|
| Age $\geq$ 75          | 3.27 (2.34–4.57) | $<0.0001$ |
| GCS score $\leq$ 8     | 2.09 (1.47–2.99) | $<0.0001$ |
| ISS $\geq$ 25          | 2.46 (1.75–3.45) | $<0.0001$ |
| Pupil abnormality: Yes  | 3.11 (2.02–4.79) | $<0.0001$ |
| Vault fracture: Yes     | 1.15 (0.81–1.65) | 0.432    |
| Skull base fracture: Yes| 1.14 (0.69–1.86) | 0.608    |
| Traumatic subarachnoid hemorrhage: Yes | 1.96 (1.38–2.79) | $<0.0001$ |
| IVH: Yes               | 3.79 (1.78–8.06) | $<0.0001$ |

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; IVH, intraventricular hemorrhage.