# The Characteristics of Withdrawal or Withholding of Life-Sustaining Treatment in Severe Traumatic Brain Injury: A Single Japanese Institutional Study

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■ OBJECTIVES: **There is little evidence on the factors influencing the decision to withdraw or continue life-sustaining treatment in the setting of severe traumatic brain injury in Japanese institutions. We investigated the factors associated with the withdrawal or withholding of life-sustaining treatment (WLST) for severe traumatic brain injury at a single Japanese institution.**

■ METHODS: **A total of 161 patients with severe traumatic brain injury were retrospectively reviewed. Patient characteristics and injury types were compared between patients with and without the WLST.**

■ RESULTS: **Of the 161 patients, 87 (54%) died and 52 (32%) decided to undergo WLST. In 98% of the WLST cases, the decision was made within 24 h of admission. The mean duration between WLST and death was 2 days. The predicted probabilities for mortality and unfavorable outcomes were highest in patients with WLST within 24 h. Patients with WLST were older and had a higher frequency of falls on the ground, ischemic heart disease, and acute subdural hemorrhage than those without WLST.**

■ CONCLUSIONS: **The decisions of almost all WLST cases were made within 24 h of admission for severe traumatic brain injury in a Japanese institution because of Japanese patients' religious and cultural backgrounds.**

## INTRODUCTION

Severe traumatic brain injury (TBI) is a potentially fatal condition affecting patients of all ages.[1] TBI has an extremely huge impact on survivors' quality of life, with one-third of patients suffering from neurological sequelae.[2] In the setting of severe TBI, decisions about which life-sustaining treatments (LSTs) are appropriate or when to forego these interventions are extremely difficult for health care providers, patients, and their family members.[3] Withdrawal or withholding of life-sustaining treatments (WLST) is recommended when the patient's prognosis is considered very poor and there is little chance of recovery to an acceptable quality of life. Withdrawal implies discontinuing medical interventions that have already begun. Withholding implies the decision not to perform invasive interventions.

Older age was shown to be an independent factor related to the choice of WLST in American, Canadian, French, and Dutch studies on severe TBI.[4-8] Previous reports have found that patients with WLST have a higher frequency of acute subdural hematoma (ASDH) than those without WLST in severe TBI settings.[6] However, there is little evidence on the factors influencing the decision to withdraw or continue LSTs in the setting of severe TBI in Japanese institutions. The factors associated with WLST for severe TBI were examined in a retrospective study of severe TBI at a single Japanese institution.

## MATERIALS AND METHODS

The institutional review board of our institution approved this retrospective study, and the need for patient consent was waived because of the retrospective study design. We reviewed a consecutive series of 264 patients with severe TBI who were

**Key words**
- Confucianism
- Severe traumatic brain injury
- Withdrawal or withholding of life-sustaining treatment

**Abbreviations and Acronyms**
**AIS**: Abbreviated Injury Scale
**ASDH**: Acute subdural hemorrhage
**GCS**: Glasgow Coma Scale
**IMPACT**: International Mission for Prognosis and Analysis of Clinical Trials in TBI
**LST**: Life-sustaining treatment
**TBI**: Traumatic brain injury
**WLST**: Withdrawal or withholding of life-sustaining treatments

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admitted to our institution between January 1, 2012, and December 31, 2021.

Patient data were obtained from hospital records. Patients with any type of trauma admitted to our institution were included in this study. Severe TBI was defined by an Abbreviated Injury Scale (AIS)—Head score of 3–5 and a Glasgow Coma Scale (GCS) score of 3–8 on arrival. After excluding 40 patients under the age of 18 years and 63 patients with cardiopulmonary arrest on arrival, 161 eligible patients were evaluated retrospectively. Patient data included age, sex, systolic blood pressure and heart rate on arrival, GCS score on arrival, pupil reactivity on arrival, injury severity score, probability of survival, mortality, cause of death, length of hospital stay, mechanism of injury, past medical history, intracranial injury, and concomitant extracranial injury.

The medical history collected included ischemic heart disease, cerebral infarction, dementia, diabetes mellitus, end-stage renal disease requiring hemodialysis, and use of anticoagulants and antiplatelet agents. An AIS—Head score of 3–5 was used to define intracranial injuries, including ASDH, brain contusion, acute epidural hemorrhage, intraventricular hemorrhage, diffuse axonal injury, and subarachnoid hemorrhage. Extracranial injury was defined as thoracic, abdominal, or pelvic injury with an AIS score greater than 2.

WLST was the primary end point. Mechanical ventilation, use of vasoactive medications, hemodialysis, or neurosurgical interventions such as craniotomy, craniectomy, or intracranial pressure monitoring were all considered LSTs. The decision to perform WLST was made through discussions between the patient's family and our institution's attending neurosurgeons and emergency/critical care physicians. The characteristics of the WLST and non-WLST groups were then compared.

The probabilities of mortality and unfavorable outcomes were calculated using the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) core model.[9] The probability of mortality and unfavorable outcomes was considered high when the calculated probability was >80%. An unfavorable outcome was defined as the GCS score of less than 4.

The proportion of WLST cases among the deceased cases of 7 individual attending neurosurgeons was analyzed to compare physician factors that influenced the decision to withdraw or continue LST. Categorical variables were reported as percentages and continuous variables as means (interquartile range). Univariate variable analysis was performed using the chi-square test for categorical variables and Mann-Whitney U test for continuous variables. Analysis of the physician's factor was performed using the Kruskal-Wallis test. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

During the 10-year period, there were 87 deaths among 161 patients with severe TBI (54%). The decision to perform the WLST was made in 52 patients (32%). Of the 52 WLST cases, withdrawal was determined in 18 (34%) and the remaining 34 cases took the decision to withhold. Of the 52 patients with WLST, 51 (98.0%) died. A total of 87 patients died, of which 51 (58%) had WLST. TBI was the cause of death in all cases of WLST; however, TBI (41%) and pelvic trauma (41%) were the main causes of death in cases without WLST (Table 1). Patients with WLST were older and had a higher frequency of falls on the ground, ischemic heart disease, and acute subdural hemorrhage than those without WLST (Table 1).

Except for the case where the decision was made after 8 days, all WLST decisions were made within 24 h of admission. The mean time interval between WLST and death was 2 (1–6.5) days. Definitive procedures, such as decompressive craniotomy, were not considered and not performed on patients with WLST.

The probabilities of mortality and unfavorable outcomes were calculated using the IMPACT core model (Table 2). The probability of mortality and unfavorable outcomes was considered high when the calculated probability was >80%. The box plots of the predicted probabilities for the 5 outcome groups are presented in Figures 1 and 2: alive (without WLST), deceased without WLST, deceased after WLST <24 h, deceased after WLST >24 h, and survived after WLST. The predicted probabilities for mortality and unfavorable outcomes were highest in deceased patients with WLST <24 h. Of the 52 patients with WLST, 59% had a high probability of mortality and 86% had a high probability of unfavorable outcomes. Survivors after WLST had a mortality rate of 83% and an unfavorable outcome rate of 91.3%.

The proportion of WLST cases among the deceased cases varied from 44% to 88% among the 7 individual attending neurosurgeons (Figure 3). However, there were no significant differences among the 7 neurosurgeons ($P = 0.423$).

## DISCUSSION

Previous investigations have identified factors that influence the decision to perform WLST in patients with severe TBI. The current investigation found that patients with WLST were older and had a higher frequency of falls on the ground, ischemic heart disease, and ASDH than those without WLST in the setting of severe TBI at a single Japanese institution. This finding is consistent with previous reports in Europe and America.[2,4-8,10-12]

The present study showed that the decision of WLST was made within 24 h of admission in 98% of WLST cases, and neurosurgical interventions were not used in all WLST cases. Among similar studies, the prevalence and timing of WLST differed not only among nations but also within them.[2,7] Some studies have indicated that this variation is caused by institutional, physician-related, and regional factors. In addition, the definition of WLST varies across previous reports.[2,7] LST was defined as mechanical ventilation, use of vasoactive medications, hemodialysis, or neurosurgical intervention including craniotomy, craniectomy, or intracranial pressure monitoring. Almost all patients in the present study received a WLST decision within 24 h of admission by the attending neurosurgeons and emergency/critical care physicians, contrary to the neurocritical care society's recommendation for the critical care management of devastating brain injury, which recommends making decisions on WLST for patients with devastating brain injuries within 72 h.[13] In addition, no physician factors influenced the decision to withdraw or continue LST in this study. A 72-h observation period is recommended by the neurocritical care society to determine the initial

**Table 1.** Comparison of Patient Characteristics Between with and without WLST

| | With WLST (n = 52) | Without WLST (n = 109) | *P* |
|---|---|---|---|
| Age, years | 77 (67–84) | 65 (43–76) | <0.001* |
| Male sex | 39 (75.0%) | 70 (64.2%) | 0.235 |
| Systolic blood pressure, mmHg | 159 (140–188) | 125 (90–150) | <0.001* |
| Heart rate, bpm | 87 (80–107) | 92 (79–110) | 0.564 |
| Glasgow Coma Scale score | 3 (3–5) | 6 (3–7) | 0.001* |
| Pupil reactivity | | | |
| Both unreactive pupils | 35 (67.3%) | 21 (19.2%) | <0.001 |
| One reactive pupil | 9 (17.3%) | 31 (28.4%) | 0.171 |
| Both reactive pupils | 8 (15.3%) | 57 (52.2%) | <0.001 |
| Injury severity score | 25 (25–35) | 35 (25–45) | 0.003* |
| Probability of survival,% | 27.5 (2.0–42.5) | 21.2 (1.4–63.3) | 0.275 |
| Mortality | 51 (98.0%) | 36 (33.0%) | <0.001* |
| Causes of death | | | |
| Traumatic brain injury | 51 (100%) | 15 (41.6%) | |
| Pelvic trauma | 0 (0%) | 15 (41.6%) | |
| Thoracic hemorrhage | 0 (0%) | 1 (2.7%) | |
| Abdominal hemorrhage | 0 (0%) | 2 (5.5%) | |
| Ischemic heart disease | 0 (0%) | 1 (2.7%) | |
| Pneumonia | 0 (0%) | 2 (5.5%) | |
| Length of hospital stay, days | 2 (1–8) | 25 (5–47) | <0.001* |
| Mechanism of injury | | | |
| Pedestrian | 6 (11.5%) | 40 (36.6%) | 0.001* |
| Fall from the height | 18 (34.6%) | 23 (21.1%) | 0.163 |
| Fall on the ground | 18 (34.6%) | 9 (8.2%) | <0.001* |
| Motorcycle crash | 6 (11.5%) | 16 (14.6%) | 0.766 |
| Motor vehicle accident | 2 (3.8%) | 14 (12.8%) | 0.133 |
| Others | 3 (5.7%) | 7 (6.4%) | 1.000 |
| Past medical history | | | |
| Ischemic heart disease | 7 (13.4%) | 1 (0.9%) | 0.002* |
| Cerebral infarction | 6 (11.5%) | 7 (6.4%) | 0.155 |
| Dementia | 4 (7.6%) | 4 (3.6%) | 0.477 |
| Diabetes mellitus | 4 (7.6%) | 9 (8.2%) | 1.000 |
| End-stage renal failure | 3 (5.7%) | 2 (1.8%) | 0.390 |
| Anticoagulants | 4 (7.6%) | 2 (1.8%) | 0.165 |
| Antiplatelet agents | 9 (17.3%) | 10 (9.1%) | 0.078 |
| Intracranial injury | | | |
| Isolated traumatic brain injury | 36 (69.2%) | 34 (31.1%) | <0.001* |
| Maximum head AIS | 5 (5–5) | 5 (3–5) | <0.001* |
| Skull fracture | 18 (34.6%) | 32 (29.3%) | 0.623 |
| Contusion | 21 (40.3%) | 45 (41.2%) | 1.000 |
| Acute epidural hemorrhage | 5 (9.6%) | 14 (12.8%) | 0.739 |
| Acute subdural hemorrhage | 48 (92.3%) | 59 (54.1%) | <0.001* |
| Intraventricular hemorrhage | 12 (23.0%) | 24 (22.0%) | 1.000 |
| Diffuse axonal injury | 2 (3.8%) | 25 (22.9%) | 0.005* |
| Subarachnoid hemorrhage | 25 (48.0%) | 63 (57.7%) | 0.322 |
| Concomitant extracranial injury | | | |
| Thoracic (AIS > 2) | 13 (25.0%) | 53 (48.6%) | 0.007* |
| Abdominal (AIS > 2) | 2 (3.8%) | 11 (10.0%) | 0.293 |
| Pelvic (AIS > 2) | 1 (1.9%) | 21 (19.2%) | 0.005* |

Data are presented as n (%) and mean (interquartile range).
WLST, Withdrawal or withholding of life-sustaining treatment; AIS, Abbreviated injury Scale.
*$P < 0.05$.

clinical response to injury. This major difference may originate from cultural or racial differences in the practice of WLST between the Western and Japanese people.

Generally, following the assessment of patients' neurological status and prognostication, treatment policies were repeatedly discussed with the patients' families or surrogates regarding whether they should receive aggressive life-sustaining support therapy or whether ongoing life-sustaining therapy should be withheld. Based on the results of in-depth discussions, the final therapeutic policies were determined by multiple physicians, including neurologists.

The question of how much time is required for valid prognostication is important but not easily answered. It could be argued that the answer depends on both the magnitude and direction of pathophysiological changes. Nonetheless, an interval of 72 h is frequently used to determine both the initial effect of an injury and the subsequent trajectory of the response. The implications of withdrawal or withholding of treatment in end-of-life care may be affected by physicians' attitudes toward LST.

The 'Guidelines for Decision-Making Process of End-of-Life Care' issued by the Japanese Ministry of Health, Labor, and Welfare address end-of-life care decision-making by the patient or

**Table 2.** The Predicted Probability of Mortality and Unfavorable Outcome of Patients with and without WLST

| | With WLST (n = 52) | Without WLST (n = 109) | *P* |
|---|---|---|---|
| Predicted mortality | 82.0 (73.5—90.4) | 51.8 (36.3—71.8) | <0.001* |
| Predicted unfavorable outcome | 91.4 (85.6—94.9) | 73.0 (54.2—86.0) | <0.001* |
| High predicted mortality (>80%) | 31 (59.6) | 15 (13.7) | <0.001* |
| High predicted unfavorable outcome (>80%) | 45 (86.5) | 40 (36.6) | <0.001* |

Data are presented as n (%) and mean (interquartile range).
WLST, Withdrawal or withholding of life-sustaining treatment.
*$P < 0.05$.

family health care proxy.[14] The 'Recommendations for End-of-Life Care in Emergency Medicine' issued by the Japanese Association for Acute Medicine defined irreversible brain dysfunction as end of life.[15] However, neither guideline addressed the optimal timing of the WLST decisions.

There was a significant difference in the responses among the different geographical regions in the decision-making process regarding end-of-life care. South African and North American physicians were more likely to encourage patients to write advance directives. Fewer Eastern European and Asian physicians agreed to withdraw LSTs without the consent of patients or their surrogates.[16] Making treatment plans through discussions between physicians and the patient's family is a traditional and common style seen in East Asian countries such as China, South Korea, and Japan.[17-19] This may have been influenced by Confucianism, which has existed in these countries for centuries. However, the degree of Confucianism's influence appears to differ among countries. In Japan, family-centered decision-making at the end of life is preferred as in China and South Korea.[20-22] This is likely because the interdependence and harmony addressed in Confucianism have great significance as social values for the Japanese people.[23,24] This might make it more difficult for Japanese people to accept the concept of living will and advance directives that are generally made by the patient.

The Japanese Ministry of Health, Labor, and Welfare's Process Guideline stipulates that the healthcare team should make decisions through repeated discussions with patients and their families, with a particular emphasis on respecting the patient's will. It also specifies that if patients cannot express their will, the health-care team should decide the best course of care in light of the family's wishes. The Process Guideline places significant emphasis on consensus building among those involved in the patient's end-of-life care.[13]

Japanese physicians must prioritize family consent over individual autonomy. Although family consent follows similar guidelines to individual consent, it places greater weight on the choices made by families than individuals. This disconnect between the adoption of international principles and actual clinical practice within Japan stems from the Confucian basis of Japanese culture, namely, the cultural norm that authorities (physicians and families) know better than the individual but also that the family is responsible for supporting the patient throughout treatment.[25] This gives a great weight to family members in deciding their fate of a family member with regard to the withdrawal of LST. This is based on Confucianism's religiosity, which is rooted in modern Japan.

Confucianism's religiosity also includes ancestral worship, which preaches that one should not injure the body they received from their parents. Japanese patients or families tend not to request LST, particularly mechanical ventilation or invasive surgery, such as craniotomy, in cases of irreversible brain injury. This may explain why WLST decisions are made within 24 h of admission in Japanese patients with severe TBI.

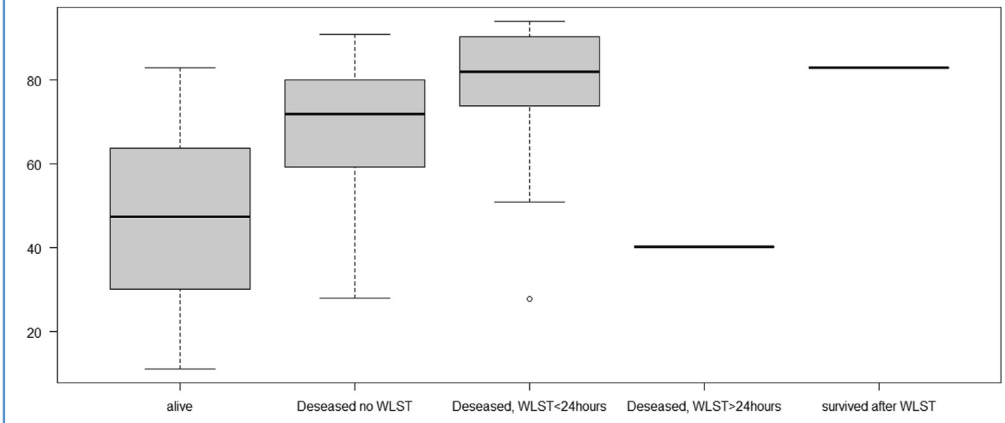


**Figure 1.** The probability of mortality using IMPACT core model for all outcome groups. WLST, withdrawal or withholding of life-sustaining treatment; IMPACT, the International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury.

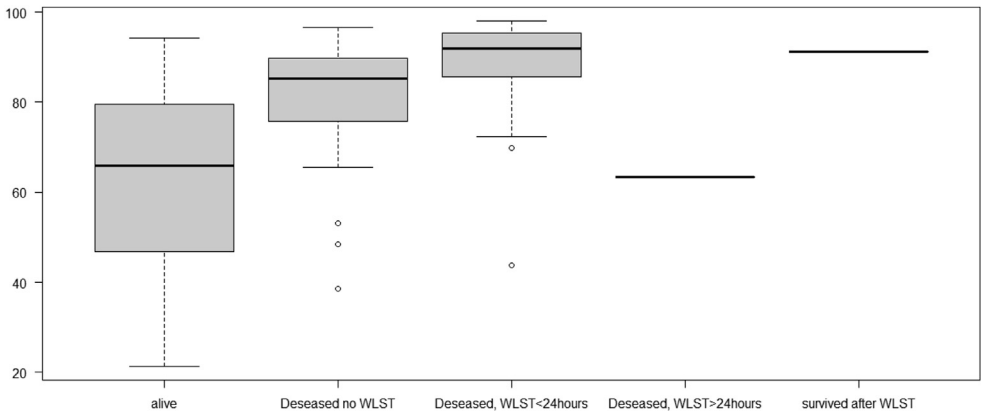


**Figure 2.** The probability of unfavorable outcome using IMPACT core model for all outcome groups, WLST, withdrawal or withholding of life-sustaining treatment; IMPACT, the International Mission for Prognosis and Analysis of Clinical Trials in traumatic brain injury.

In this study, approximately 60% of the patients with WLST had a high probability of mortality. More than 80% of the patients in the WLST group had a high probability of unfavorable outcomes. In addition, a survivor after WLST would not have a reasonable quality of life outcome, even if the LST had been continued, owing to the high probability of mortality and unfavorable outcomes. Thus, the WLST decisions in this study are considered reasonable. However, the ideal timing for decisions on WLST may remain to be clarified, as there was only one deceased case that received a WLST decision in less than 24 h and only one surviving case that received a WLST in this study.

The early decision of WLST can lead to the prevention of unnecessary treatment, although it has the risk of increasing avoidable deaths. The present study found that the mean duration between WLST and death was 2 days, which is similar to the Canadian retrospective analysis in which half of the patients died within the first 3 days.[2] In our institution, the early decision of WLST was not to increase needless deaths, regardless of whether physician bias existed or not, because there was no physician factor influencing the decision to withdraw or continue LST.

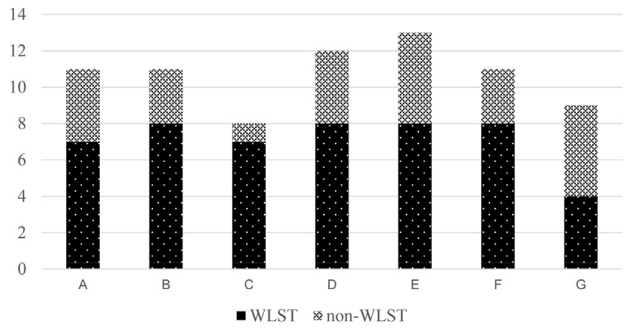


**Figure 3.** The comparison of the WLST cases among the deceased cases between 7 individual attending neurosurgeons. WLST: withdrawal or withholding of life-sustaining treatment.

This study had some limitations. The small sample size, potential bias of a single Japanese institutional study, and uncontrolled bias that is inherent in a retrospective study limited the conclusions reached from these data. This retrospective study attempted to evaluate a complex issue with multiple participants over a 10-year interval. Decisions regarding the withdrawal of life support are invariably complex but typically related to the severity of the brain injury, as defined by a combination of clinical findings, comorbidities, and radiological findings.

## CONCLUSIONS

In conclusion, a single Japanese institutional study found that patients with severe TBI and WLST were older and had a higher frequency of falls on the ground and ASDH than those without WLST. Because of its Japanese religious or cultural background, almost all WLST decisions for severe TBI cases were made within 24 h of admission at the Japanese institution studied here. This was contrary to the recommendation of the Neurocritical Care Society for the management of severe TBI, which recommends making decisions regarding WLST within 72 h. Future research involving WLST with consistent definitions and timings in cases of severe TBI is required.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**Shinsuke Tanizaki:** Conceptualization, Methodology, Formal analysis, Investigation, Writing — original draft, Visualization. **Yasuo Toma:** Conceptualization, Supervision. **Katsuyoshi Miyashita:** Conceptualization, Supervision. **Shigenobu Maeda:** Conceptualization, Supervision.

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