Value of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in predicting the hospital mortality for postoperative brain tumor patients admitted to the intensive care units in Japan: A Retrospective Case-Control Study.

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Research Article

Keywords:

Posted Date: December 14th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3703173/v1
Abstract

Objective

No prognostic predictors for brain tumors based on ICU admission data have been reported. APACHE II is a score based on the data of patients admitted to the ICU and is often correlated with the severity of the disease and prognosis. However, no studies have reported an association between APACHE II and the prognosis of brain tumor patients. Since 2014, the Japanese Intensive care Patients Database (JIPAD) was established by the Japanese Society of Intensive Care Medicine (JSICM) to construct a high-quality ICU database as a national registry with the goal of improving the quality of care and pursuing the development of intensive care medicine in Japan. We used JIPAD to examine the factors associated with in-hospital mortality based on the background of postoperative patients with brain tumors admitted to the ICU and the data from the ICU.

Methods

Patients aged ≥16 years enrolled in JIPAD between April 2015 and March 2018 after surgery for brain tumors underwent craniotomy or biopsy. We examined factors related to outcomes at discharge from data such as blood tests and medical procedures during ICU admission, tumor type, and APACHE II score.

Results

Of the 1,454 cases (male:female ratio: 1:1.1, mean age: 62 years) included in the study, 32 cases (2.2%) died in hospital. In multivariate analysis, male (OR 2.70 [95%CI 1.21–6.03]), malignant tumor (OR 2.94 [95%CI 1.31–6.59]), ventilator use (OR 2.67 [95%CI 1.19–5.98]), APACH II score ≥ 15 (OR 5.46 [95%CI 2.49–11.9]) were significantly associated with in-hospital mortality.

Conclusion

Factors related to in-hospital mortality in postoperative brain tumor patients cannot be improved in advance, but by picking up cases with a high risk of in-hospital death at an early stage, it is possible to devise methods of treatment and support for the patient’s family.

Introduction

In patients with hematologic malignancies or solid tumors admitted to the ICU, many prognostic predictions using data during ICU admission have been reported, and the results have led to improvements in ICU management and prognosis.
Compared to patients with hematologic malignancies or solid tumors, the incidence of brain tumors itself is low, and the data available for brain tumor patients admitted to the ICU is limited. It would be useful for perioperative management and prognosis prediction if in-hospital mortality could be predicted from the results of vital signs, blood tests, and treatments upon admission to the ICU.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is widely used in patients admitted to the ICU. Numerous reports have shown that it correlates with disease severity and prognosis with hematologic malignancies or solid tumors. In the field of neurosurgery, the usefulness of this score in evaluating severity and predicting the long-term prognosis of patients with head injuries and those admitted to the Neuro ICU has already been reported, but there are no case reports on the relationship between this score and the prognosis of patients with brain tumors.

Since 2014, the Japanese Society of Intensive Care Medicine has been collecting information on patients’ disease status, test results, treatment during ICU admission, and their outcomes to operate the Japanese Intensive care Patient Database (JIPAD). The purpose of this retrospective study was to analyze data from JIPAD to investigate factors related to in-hospital mortality of postoperative patients with brain tumors admitted to the ICU.

**Materials and Methods**

**Patient selection**

JIPAD was established by the Japanese Society of Intensive Care Medicine (JSICM) to construct a high-quality ICU database as a national registry with the goal of improving the quality of care and pursuing the development of intensive care medicine in Japan. We obtained approval from the Institutional Ethics Committee of Tokushima University (Approval number: 3753-2) and this database project started in 2014\(^1\). In this study, the data from April 2015 to March 2018 were used. Of 85,558 ICU admitted patients, postoperative patients aged 16 years and older with brain tumor were included. Patients with missing data or those who did not undergo craniotomy or biopsy were excluded in this study. The final sample consisted of 1415 patients (Fig. 1).

**Study design**

This study was designed as a retrospective case-control study.

**Data collection**

Data such as physiological variables, malignancy of tumor, length of stay (LOS), APACHE II score were collected from each patient. Among the brain tumors, those requiring post-treatment (chemotherapy or radiation therapy) were considered malignant (Fig. 2), and those with unknown pathology were excluded. The APACHE II scores were composed by major three items as the physiological score, age points, and chronic physiology score. This score was recorded on the day of admission. The physiological score with 12 items ranged from 0 to 60; from 0 to 6 for age score; and from 0 to 5 for chronic health evaluation.
The 12 items of the physiological score are body temperature, mean arterial pressure, heart rate, respiratory rate, alveolar-arterial oxygen (A-a) gradient; if fractional inspired oxygen concentration was $\geq 0.5$, arterial oxygen tension (PaO2); if fractional inspired oxygen concentration was $< 0.5$, serum bicarbonate (HCO3); if there was no arterial blood gas analysis, arterial pH; serum sodium, serum potassium, creatinine, hematocrit, white blood cell counts, and Glasgow Coma Scale score. Chronic Health Points are added if the patient has a history of severe organ insuiciency or is immune-compromised as defined below, as sign points as follows: 5 points for non-operative or emergency postoperative patients, 2 points for elective postoperative patients.\(^2\) The total score in the APACHE II is 71, which includes the sum of the physiological score, age score, and chronic health evaluation (Table 1).

**Statistical Analysis**

Continuous variables that followed a normal distribution are expressed as mean ± standard deviation (SD) and were analyzed using the t-test, while continuous variables with a non-normal distribution are represented as median (interquartile range) and analyzed using the Wilcoxon rank-sum test. Categorical variables are expressed as absolute and relative frequencies and were analyzed using the $\chi^2$ test or Fisher's exact test. Variables that differ significantly with p values of $<0.05$ were selected as covariates for univariate and multivariate logistic regression analysis. The optimal cut-off values were calculated using receiver operation characteristic (ROC) analysis and the Youden index. Continuous variables were converted into binary variables based on the cut-off values. The stepwise forward selection method was used to select the variables for multivariate analysis. The p-value threshold for entry was set at 0.05. All statistical analyses were performed using JMP®13 (SAS Institute Inc., Cary, NC, USA) and $p < 0.05$ was considered statistically significant.

**Result**

**Tumor type**

Figure 2 shows the pathology of all cases. Among the brain tumors, those requiring post-treatment (chemotherapy or radiation therapy) were considered malignant tumors. Of the 1,454 patients, 953 were categorized as having benign tumors and 501 malignant.

**Characteristics of patients**

A total of 1,454 patients were included. The baseline feature of the patients are shown in table 2. Briefly, the median age of the studied patients was 63 years, and 47.9% of the patients was male. Malignant tumors represented 34.4% of the patients, and of these, 98.6% received craniotomy. Two patients with brain-tumors had a medical history of heart failure, 4 had a history of respiratory failure, 3 had a history of cirrhosis, 15 had a history of lymphoma, 73 were in an immunosuppressive state, and 8 had a history of dialysis. Also, 229 patients received life-supporting interventions during ICU hospitalization. The mean APACHE score was 11.2, and the median LOS of ICU was 1. Overall, 51 patients received emergency
surgery, and 32 patients died in hospital (Table 2). The baseline feature which summarized variables related to APACHE II score is shown in table 3.

**Outcome analysis**

Among the 1,454 patients included, 1,422 (97.8%) were survivors at discharge, and 32 (2.2%) were non-survivors at discharge. By comparison (survivors group vs non-survivors group), male (47.3% vs 71.8%; p = 0.0069), Malignant (33.6% vs 68.7%; p < .0001), mechanical ventilation (13.3% vs 37.5%; p = 0.0007), vasopressors (0.9% vs 6.2%; p = 0.0412), APACHE II score (11.1 ± 4.1 vs 17.8 ± 8.9) and LOS of ICU (median: 1 [IQR, 1] vs 1 [IQR, 1]; p = 0.0004) were significantly different between the two groups (Table 3).

We then screened out the factors that predicted in-hospital death, according to a logistic regression analysis of variables that differed significantly (p < 0.05). Continuous variables were converted into binary variables based on the cut-off values. To determine the continuous variables threshold for having an outcome, a receiver operating characteristic curve using Youden’s Index was performed (Table 4).

Five factors were screened out, which were male (multivariable analysis OR, 2.70; 95% CI, 1.21–6.03; p = 0.0104), malignant (multivariable analysis OR, 2.94; 95%CI, 1.31–6.59; p = 0.0066), mechanical ventilation (multivariable analysis OR, 2.67; 95%CI, 1.19–5.98; p = 0.0219), and APACHE II score (multivariable analysis OR, 5.46; 95%CI, 2.49–11.9; p < .0001). Vasopressors did not show a significant correlation with clinical outcome (Table 5).

**Discussion**

Though small in number, some patients with brain tumors died in the hospital, so there are reports on the causal relationship between perioperative complications and in-hospital mortality. Other papers have also reported in-ICU and in-hospital mortality for a small number of brain tumor patients admitted to the ICU. However, no large-scale study of prognosis prediction based on ICU admission data has been reported to date. JIPAD collects detailed data on patient disease, severity, treatment contents, outcomes, etc. Since its launch in 2014, data registration has been ongoing, and the number of registered patients continues to grow each year.

The database contains data on approximately 1,400 patients, even when limited to postoperative patients with brain tumors over the past three years. Although there have been several reports on short- and mid-term outcome prediction in patients with brain tumors using ICU data, they have been small in scale. No reports have been made on mid-term outcome prediction using large-scale data sets which were limited to postoperative patients with brain tumors, as in this study.

The results of this study showed that (1) 2.2% of patients admitted to the ICU after brain tumor surgery died in the hospital during that admission, (2) risk factors for in-hospital mortality included being male, having a high tumor grade, use of a ventilator, and the APACHE II score of 15 or higher, (3) as with other
diseases, APACHE II is a useful score in predicting in-hospital mortality of the patients with brain tumors (Table 5).

While the usefulness of the APACHE II score in assessing severity and predicting long-term outcomes in patients with a head injury, GCS is reported to be more useful than the APACHE II score in predicting short-term outcomes. The reason for this is the extent of brain damage, or the GCS score, which is a scale of consciousness disturbance, has a great impact on short-term outcomes in patients with a head injury. In contrast, the APACHE II score has been reported to be useful because of the influence of biological data, rather than GCS, on long-term outcomes.

Meanwhile, others have reported that the APACHE II score is inadequate for predicting in-hospital mortality for patients admitted to the Neuro-ICU. However, this is considered to be true when all cases admitted to the Neuro-ICU are considered, without differentiation by disease. In the present study, it was found that one of the risk factors for in-hospital mortality in postoperative brain tumor patients is the APACHE II score of 15 or higher. In addition to APACHE II, the data analyzed in this study included the APACHE III and simplified acute physiology score (SAPS) II scoring systems. Compared to APACHE III, APACHE II and SAPS II are simpler, and since the ROC curves for each of these three scoring systems yielded the highest AUC for APACHE II (data not presented), we decided to conduct the present study using APACHE II.

The present study also showed that the malignancy of the brain tumor also affects death during continued hospitalization after surgery. However, Miriam et al. reported that tumor grade and in-hospital mortality were not related. They also reported that postoperative complications and in-hospital mortality were associated. Others reported that venous embolism occurs frequently in malignant brain tumors such as metastatic brain tumors, malignant gliomas, and lymphomas. Although not evaluated in this study, events after discharge from the ICU may be a factor in associating malignant brain tumors with in-hospital mortality.

Past reports have indicated that gender (being male) is one of the factors that can contribute to in-hospital mortality of patients hospitalized for potentially fatal diseases (myocardial infarction, heart failure, pneumonia, gastrointestinal hemorrhage, respiratory obstruction, and stroke), due to differences in preference tendencies such as smoking, daily health-conscious behaviors, and biological differences being noted as reasons.

The present study showed that being male is an independent risk factor for in-hospital mortality of postoperative patients with brain tumors. As noted in previous reports, this may be attributed to differences in preference tendencies such as smoking, daily health-conscious behaviors, and biological differences.

The present study also showed that patients on ventilators in the ICU had a significantly higher rate of in-hospital mortality. Only 4 of the 1,454 patients included in the analysis had originally suffered from
respiratory failure, indicating that pre-existing conditions did not worsen the outcomes of patients on ventilators. Further, some of the patients who required a ventilator were admitted to the ICU while intubated because of the lengthy surgery.

Previously, Patrick et al. reported significantly higher rates of poor functional outcomes and poor OS in patients with glioblastoma and metastatic brain tumors who were on ventilators postoperatively\textsuperscript{10,11}.

It has been pointed out that some patients requiring postoperative management on a ventilator are difficult to extubate due to surgical complications, new neurological symptoms or seizures, and delays in the start of postoperative chemotherapy or radiation therapy in these patients may lead to poor functional outcomes and poor OS\textsuperscript{10,11}. The present study of factors related to in-hospital mortality includes benign tumors, to which the same reasons may apply.

Limitation

The present study was limited to patients admitted to the ICU after surgery. In fact, there are cases where patients are admitted to intensive care wards other than ICU after surgery or return to general wards. Therefore, it is possible that many of the cases examined in this study originally included many cases with high severity. In addition, although the condition after ICU discharge was not examined in this study, there may be factors related to in-hospital death after ICU discharge. Furthermore, since these results were obtained in a Japanese medical environment, similar results may not be obtained outside Japan.

Conclusion

In this study, we examined factors related to in-hospital mortality in postoperative brain tumor patients using a large dataset of approximately 1,400 patients in Japan's intensive care database, JIPAD. Five items found in this study are involved in the survival of patients after brain tumor surgery. Gender and tumor type cannot be changed, but some items included in the APACH score can be improved with postoperative management. ICU management is also important for postoperative brain tumor patients. In the future, it will be possible to examine more detailed predictive factors by using not only ICU data but also tumor location, size, and intraoperative data.

Declarations

The manuscript complies with all instructions to authors.

The authorship requirements have been met, and the final manuscript was approved by all authors.

This manuscript has not been published elsewhere and is not under consideration by another journal.

The authors confirm adherence to ethical guidelines.
Author's contribution: MA and YM conceived the study. NN, MI, and JO collected the data. MA designed the statistical analysis plan and performed the statistical analysis. YM, KN, KH and TF contributed to the interpretation of the results. MA wrote the manuscript. YT supervised the conduct of the study. All authors reviewed the manuscript and revised it critically for intellectual content. All authors approved the final version.

Disclosure of funding received: None.

Conflict of interest: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Previous presentation of material in this manuscript: None.

Acknowledgements: None.

References


Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

Figure 1

85558 ICU admissions

80942 patients aged 16 years and older

11632 patients of neurological disorder

2447 postoperative patients of brain tumor

132 excluded for being incorrect

28 excluded

- Embolization : n = 9
- Hydrocephalus : n = 6
- Cranioplasty : n = 2
- Decompression : n = 1
- Cancel : n = 1
- Not recorded : n = 7

833 excluded for missing data

1454 postoperative patients of brain tumor resection or biopsy
Case-selection flowchart.

**Figure 2**

Distribution of brain tumor types.

Among the brain tumors, those requiring post-treatment (chemotherapy or radiation therapy) were considered malignant.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- checklist.docx
- table.pptx