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Relationship between extravascular leakage and clinical outcome on computed tomography of isolated traumatic brain injury

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Abstract

Aim: This study investigated whether contrast extravasation on computed tomography (CT) angiography in patients with traumatic brain injury (TBI) is associated with death or surgical procedures.

Methods: Patients over 18 years old, directly brought in by ambulance with an isolated head injury and confirmed to have acute intracranial hemorrhage on a CT scan upon admission between 2010 and 2020, were included. The primary outcome was mortality, and the secondary outcome was neurosurgical procedures performed from admission to discharge from the intensive care unit. Multivariable logistic regression analyses were performed to evaluate the association between these outcomes and contrast extravasation.

Results: The analysis included 188 patients with a median age of 65 years, 123 men (65.4%), 34 deaths (18.1%), and 91 surgeries (48.4%). Among the 66 patients with contrast extravasation, 22 (33.3%) died and 47 (71.2%) required surgery. Among the 122 patients with no contrast extravasation, 12 (9.8%) died, and 44 (36.1%) required surgery. The presence or absence of extravascular leakage was associated with death (odds ratio, 3.6 [95% CI: 1.2–12.2]) and surgery (odds ratio, 7.6 [95% CI: 2.5–22.7]).

Conclusion: Contrast extravasation was associated with mortality and performance of surgery in patients with an isolated head injury.

KEYWORDS

contrast extravasation, head injury, mortality, surgery

INTRODUCTION

Contrast-enhanced computed tomography (CT) is widely used as one of the initial screening tests to detect traumatic vascular injuries in patients with traumatic brain injury (TBI).[1] The French Society of Anaesthesia, Critical Care, and Perioperative Medicine guidelines suggest that patients with risk factors such as skull base fractures and focal neurological deficit not explained by brain imaging should undergo intracranial vascular examinations using contrast-enhanced CT head scans.[2] A contrast-enhanced head CT scan may reveal a contrast accumulation within the hematoma that is not contiguous with the blood vessels identified on the plane CT scan (Figure 1). This finding has been reported to be associated with hematoma expansion, neurological prognosis, and death in patients who were followed up without emergency surgery.[3–6] Previous reports have suggested that this condition is due to progressive hemorrhage at the time of evaluation by contrast-enhanced head CT scan, leading to hematoma expansion and decreased survival.[3] Detecting contrast extravasation is crucial because it identifies patients at high risk for hematoma expansion and death.[3] However,

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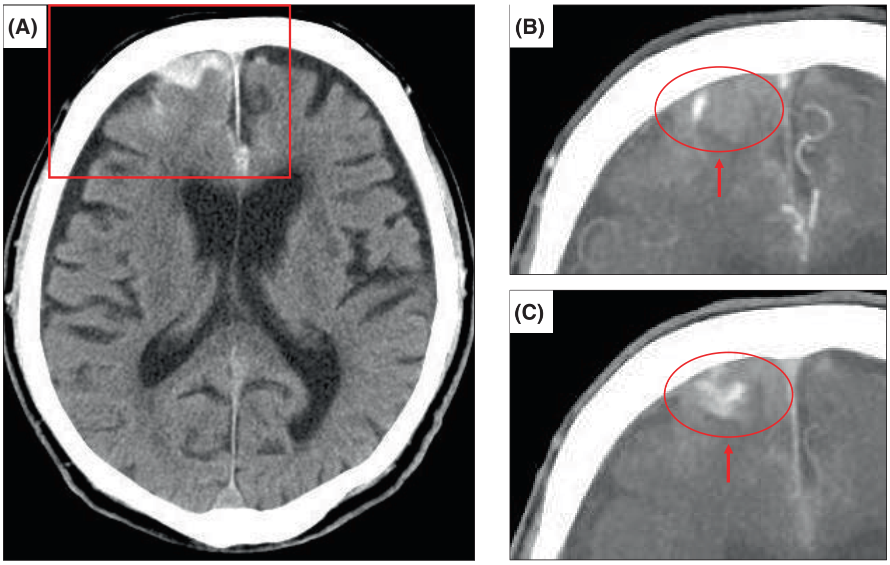

FIGURE 1 Example of contrast extravasation on CT angiography in a patient with traumatic brain injury. (A) Plain CT scan showed an acute subdural hematoma. (B) Imaging findings in the arterial phase of the contrast-enhanced CT scan. The square in A is enlarged. Contrast extravasation was observed in the area of the red oval as indicated by the arrow. (C) Imaging findings in the venous phase of the contrast-enhanced CT scan. Extravascular leakage of contrast agent was also observed in the area of the red oval as indicated by the arrow. CT, computed tomography.

most of these reports have focused on TBI patients with acute intracranial hemorrhage who did not require emergency surgery but were followed up. And, there are no reports evaluating the prognosis of patients who underwent emergency surgery and those who were followed up without emergency surgery. Therefore, using extravascular leakage images in TBI patients requiring emergency surgery was not a common practice. Thus, the relationship between extravascular leakage of contrast media and clinical outcomes, such as death or surgery, in TBI patients with acute intracranial hemorrhage, including those who required emergency surgery, has not been clarified. If these findings can be clarified, the imaging findings of contrast-enhanced CT of the head may assist in treatment strategies for TBI in the initial medical examination and the intensive care unit.

This study investigated whether the presence or absence of contrast extravasation on a head contrast CT scan was associated with mortality and neurosurgical procedures in patients with an isolated head injury who were transported to our hospital.

MATERIALS AND METHODS

Study design and setting

This was a single-center, retrospective, observational study. This study was conducted at Osaka University Medical Hospital, a tertiary emergency medical institution, from January 2010 to December 2020. The center performs contrast-enhanced CT head scans of patients with acute intracranial hemorrhage to evaluate vascular damage at the time of initial treatment. The protocol and parameters used for imaging are shown in the Appendix S1. Note that at our center, treatment was performed by an emergency physician who read the images in the emergency room. TBI treatment was performed per the guidelines for the management of TBI issued by the Japanese Society of Neurotraumatology.[7–9]

Participants

Patients with a single head injury over 18 years old and directly brought in by ambulance were included in this study if they had a plane CT scan at the time of presentation and acute intracranial hemorrhage was confirmed. Patients with an isolated head injury were defined as having an Abbreviated injury scale 98 (AIS) <3 other than the head. Patients with out-of-hospital cardiopulmonary arrest, patients who did not have a CT head contrast scan at the time of initial care, patients who had a CT head contrast scan performed in non-protocol methods, and patients who did not request surgery or intensive care were excluded.

Variables

A health record review was performed, and collected variables were described in the Appendix S1. All neurosurgical procedures, such as endovascular surgery, ventricular drainage, and intracranial pressure (ICP) monitor insertion, were included in this surgery. Poor neurological prognosis was defined as Glasgow Outcome Scale (GOS): 1–3 at discharge. In this study, the definition of emergency surgery was defined as surgery that was judged by the physician in charge to be necessary immediately, rather than by follow-up, based on comprehensive consideration of clinical symptoms and other factors at the time the plane CT scan of the head was completed during the initial examination. Surgeries deemed necessary due to worsening symptoms during under observation were not included as emergency surgeries in this study. The indications for surgery for acute subdural hematoma are (1) hematoma thickness of more than 1 cm, (2) midline shift of more than 5 mm with impaired consciousness, and (3) neurological symptoms due to hematoma or cerebral edema. To determine the need for surgery in cases of acute epidural hematoma, the following factors are considered: (1) hematoma thickness of 1 cm or greater, (2) hematoma volume of 20–30 cc or more, or (3) presence of neurological symptoms due to the hematoma. Indication for surgery for cerebral contusion is neurological symptoms due to hematoma or cerebral edema. ICP sensor was implanted when GCS ≤8 or when there was a decrease of more than 2 points. Extravascular leakage images do not determine the indication of emergency surgery.

This study's definition of contrast extravasation was based on a previous study (Appendix S1),[5] and the four emergency physicians read the images (Appendix S1). The study's primary endpoint was mortality, and the secondary endpoint was a neurosurgical procedure between admission and discharge from the intensive care unit. Surgeries from admission to discharge from the intensive care unit were the sum of emergency surgeries and surgeries performed during observation. In a subgroup analysis, patients under observation without emergency surgery were included, and death and neurosurgical procedures between admission and discharge from the intensive care unit, i.e., surgeries performed under observation, were evaluated similarly.

Statistical analysis

Summary data is presented as medians (interquartile range) for continuous variables and numbers (%) for categorical variables. To detect differences between the two groups of patients, the Mann–Whitney U test was used for continuous variable items, and the chi-square test or Fisher's exact test for items using nominal variables. Logistic regression analysis was performed to evaluate the association between the primary endpoint of death and contrast extravasation, and odds ratios and 95% confidence intervals were calculated. For adjustment factors, we selected age, fibrinogen, and the Marshall CT classification, which can be evaluated by plane CT scan, as they are associated with mortality according to previous papers.[10–14] Logistic regression analysis was performed to evaluate the association between surgical procedure and contrast extravasation, a secondary endpoint. In addition to background age and gender, the Glasgow Coma Scale (GCS) at presentation, AIS – head, and fibrinogen was selected as an adjustment factor, which was considered related to the indication for surgery. Next, logistic regression analysis was performed on patients under observation without emergency surgery as a subgroup analysis.

Statistical analysis was performed using commercially available statistical analysis software (JMP pro 16 software, SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant.

RESULTS

Five hundred thirty-six patients aged 18 years or older with an isolated head injury were sent directly to our hospital during the study period. Of these, 278 patients met the inclusion criteria, and after excluding those who met the exclusion criteria, 188 patients were included in the analysis (Figure 2).

The background of the 188 patients included in the analysis is shown in Table 1. The median age was 65 years, and 123 (65.4%) were male. Sixty-six patients had extravascular leakage, and 122 patients had no extravascular leakage. The two groups were compared in terms of background factors. AIS and Injury Severity Score (ISS) were significantly higher in patients with extravascular leakage. There was also a significant difference in hematoma morphology between the

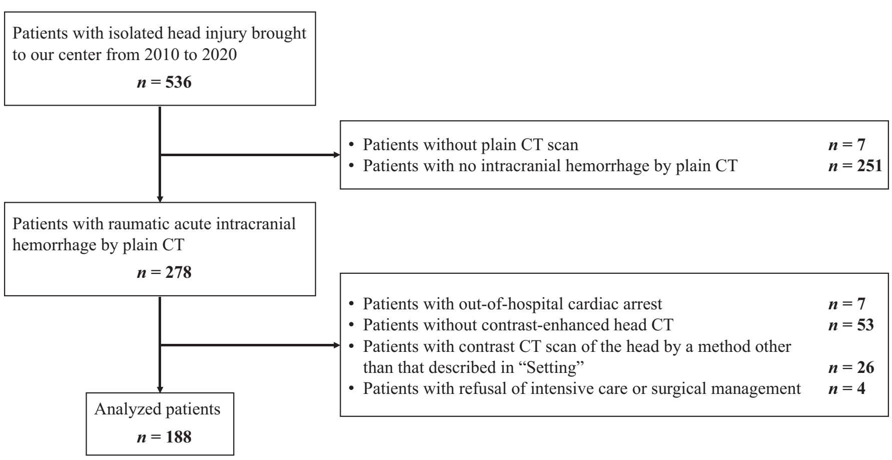

FIGURE 2 Patient flowchart. Among 536 patients with an isolated head injury, 278 patients met the inclusion criteria, and 90 patients met the exclusion criteria. In total, 188 patients were included in the analysis. CT, computed tomography.

TABLE 1 Clinical and radiologic characteristics of patients with and without contrast extravasation.

Characteristic	Total ($n=188$)	Contrast extravasation ($n=66$)	No contrast extravasation ($n=122$)	p value
Age, median (IQR), years	65 (43–76)	69 (51.5–77)	61 (40.8–75.3)	0.076
Male sex, n (%)	123 (65.4)	47 (71.2)	76 (62.3)	0.22
Patients taking anticoagulant medicine, n (%)	15 (8.0)	4 (6.1)	11 (9.0)	0.58
Patients taking antiplatelet medicine, n (%)	17 (9.0)	4 (6.1)	13 (10.7)	0.43
Admission GCS, median (IQR)	11 (6–14)	11 (6–14)	12 (6–14)	0.45
Admission systolic blood pressure, median (IQR), mmHg	151 (130–180)	155 (136–188)	149 (129–173.5)	0.17
Admission diastolic blood pressure, median (IQR), mmHg	91 (77–105)	90.5 (79.3–109)	91 (72–103)	0.56
Mechanism of injury, n (%)				0.15
Fall from standing	44 (23.4)	15 (22.7)	29 (23.8)	
Fall from height	34 (18.1)	16 (24.2)	18 (14.8)	
Hit by object	3 (1.6)	0 (0.00)	3 (2.46)	
Bicycle accident	47 (25.0)	18 (27.3)	29 (23.8)	
Struck by pedestrian	21 (11.2)	8 (12.1)	13 (10.7)	
Motorbike	36 (19.1)	7 (10.6)	29 (23.8)	
Automobile	3 (1.6)	2 (3.03)	1 (0.82)	
Traffic accident	107 (56.9)	35 (53.0)	72 (59.0)	0.43
Marshall CT classification, n (%)				0.014
I	0 (0.00)	0 (0.00)	0 (0.00)	
II	122 (64.9)	35 (53.0)	87 (71.3)	
III	0 (0.00)	0 (0.00)	0 (0.00)	
IV	4 (2.1)	2 (3.0)	2 (1.6)	
V	38 (20.2)	14 (21.1)	24 (19.7)	
VI	24 (12.8)	15 (22.7)	9 (7.4)	
Type of traumatic intracranial hemorrhage, n (%)				<0.001
ASDH	80 (42.6)	29 (43.9)	51 (41.8)	
AEDH	14 (7.5)	10 (15.2)	4 (3.3)	
ICH	29 (15.4)	19 (28.8)	10 (8.2)	
tSAH	64 (34.0)	8 (12.1)	56 (45.9)	
IVH	1 (0.53)	0 (0.00)	1 (0.82)	
AIS-head, median (IQR)	5 (4–5)	5 (5–5)	4 (3–5)	<0.001
ISS, median (IQR)	25 (17–26)	25 (25–29)	21 (16–25.3)	<0.001
Fibrinogen[a], median (IQR), mg/dL	242 (185.3–287.3)	203 (168–261)	251 (205–303)	<0.001
Platelet count[a], median (IQR), $\times 10^3/\mu L$	214 (168–250)	198 (152.8–235.3)	222 (175.5–256.5)	0.011
PT-INR[a], median (IQR)	1.1 (1.0–1.1)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.17
aPTT[a], median (IQR), s	27 (25–32)	29 (25–35)	27 (24–30)	0.014
FDP[a], median (IQR), μg/mL	36.5 (17.0–97.4)	92.2 (47.8–256)	24.4 (9.25–52.1)	<0.001
D-dimer[a], median (IQR), μg/mL	13.2 (5.52–28.8)	24.1 (15.3–69.2)	8.7 (3.4–20.1)	<0.001
Time from onset to arrival, median (IQR), min	36 (29–45)	35 (29–45.3)	36 (28–45)	0.45
Time from onset to CTA, median (IQR), min	66 (56.8–79.3)	65.5 (56–75.3)	66.5 (57.3–87)	0.29
Emergent surgery, n (%)	73 (38.8)	34 (51.5)	39 (32.0)	0.009
Surgery performed under observation, n (%)	18 (9.6)	13 (19.7)	5 (4.1)	0.001
Surgery performed between arrival and discharge from the intensive care unit[b], n (%)	91 (48.4)	47 (71.2)	44 (36.1)	<0.001
GOS at discharge, median (IQR)	3 (2–4)	2 (1–4)	3 (3–4)	<0.001
GOS at discharge (≤3), n (%)	114 (60.6)	49 (74.2)	65 (53.3)	0.005
In-hospital mortality, n (%)	34 (18.1)	22 (33.3)	12 (9.8)	<0.001

Abbreviations: AEDH, acute epidural hematoma; AIS, Abbreviated Injury Scale; aPTT, activated partial thromboplastin time; ASDH, acute subdural hematoma; CTA, computed tomography angiography; FDP, fibrinogen degradation products; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; ISS, Injury Severity Score; IVH, intraventricular hemorrhage; PT-INR, prothrombin time-international normalized ratio; tSAH, traumatic subarachnoid hemorrhage.

[a]Blood test results at the time of arrival at hospital.

[b]Total number of emergency surgeries and those performed under observation.

two groups. Blood test results at admission showed lower fibrinogen and platelet count in patients with extravascular leakage.

Activated partial thromboplastin time (aPTT), Fibrinogen degradation products (FDP), and D-dimer were significantly higher in patients with extravascular leakage. Regarding clinical course, emergency surgery was performed more frequently in patients with extravascular leakage than those without extravascular leakage. The proportion of all surgeries performed between admission and discharge from the intensive care unit, i.e., emergency surgery and follow-up surgery combined, was also higher. The number and distribution of patients who required emergency surgery, those who deteriorated during follow-up and required surgery, and those who did not require surgery after follow-up are shown in Figure 3. Patients with extravascular leakage had a lower discharge GOS and a higher proportion of patients with poor neurological prognosis at discharge (discharge GOS ≤3). Mortality of patients with extravascular leakage was also high. The neurological prognosis at discharge is shown in Figure S1.

The results of logistic regression analysis are shown in Table 2. Contrast extravasation was associated with death regardless of age, fibrinogen, and Marshall CT classification (adjusted odds ratio 3.6 [95% CI: 1.2–12.2, $p = 0.02$]). Similarly, as shown in Table 3, contrast extravasation was associated with neurosurgical intervention regardless of age, gender, GCS at presentation, AIS-head, and fibrinogen (adjusted odds ratio 7.6 [95% CI: 2.5–22.7, $p = 0.0001$]).

Next, a subgroup analysis was performed on patients who were followed up without emergency surgery. The background of the patients included in the subgroup analysis is shown in Table S1, and the neurological prognosis at discharge is shown in Figure S2. Logistic regression analysis showed that extravascular leakage image of contrast agent was associated with death (crude odds ratio 5.8 [95% CI: 1.0–33.3, $p = 0.049$]) (Table S2) and with surgery, regardless of age (adjusted odds ratio 10.3 [95% CI: 3.3–32.8, $p < 0.001$]) (Table S3).

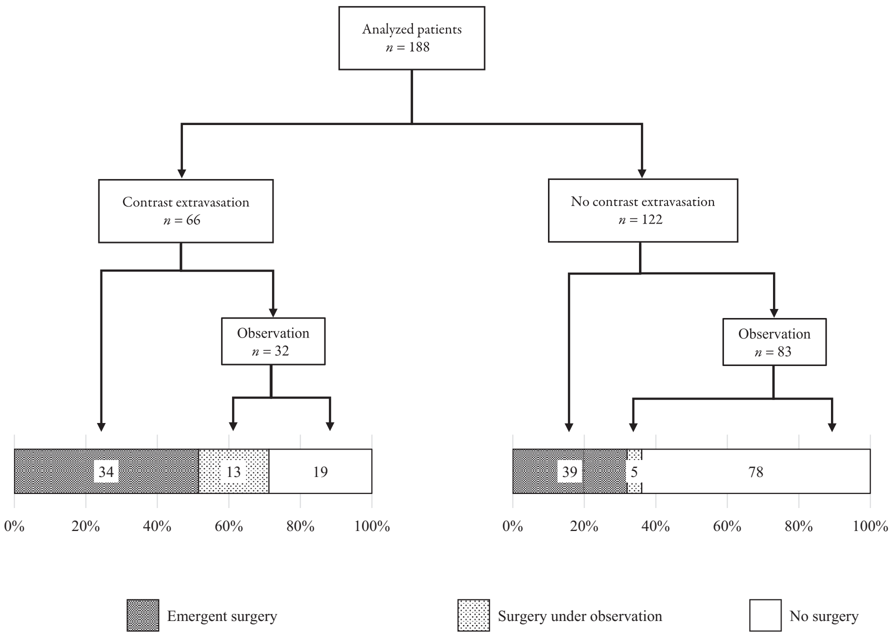

FIGURE 3 Surgical flow of patients with and without contrast extravasation. The CT images showed 66 patients with contrast extravasation and 122 patients with no contrast extravasation. Among them, 34 and 39 required emergency surgery, 32 and 83 patients underwent observation only, and 13 and 5 patients required surgery while under observation, respectively. CT, computed tomography.

TABLE 2 Results of univariable and multivariable logistic regression analyses for all patients assessing the impact of clinical parameters, including contrast extravasation, on hospital death.

	Univariable analysis			Multivariable analysis		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Contrast extravasation	4.6	2.1–10.1	<0.0001	3.6	1.2–12.2	0.02
Age	1.0	1.0–1.1	0.0008	1.1	1.0–1.1	0.002
Marshall CT classification	2.6	1.9–3.5	<0.0001	2.2	1.5–3.0	<0.001
Fibrinogen[a] <200 mg/dL	5.7	2.5–13.1	<0.0001	3.8	1.2–12.2	0.02

Abbreviations: CI, confidence interval; CT, computed tomography; OR, odds ratio.
[a]Blood test results at the time of arrival at hospital.

TABLE 3 Results of univariable and multivariable logistic regression analyses for all patients assessing the impact of clinical parameters, including contrast extravasation, on surgery.

	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	*p* value	OR	95% CI	*p* value
Contrast extravasation	4.4	2.3–8.4	<0.001	7.6	2.5–22.7	0.0001
Age	1.0	1.0–1.0	0.0007	1.0	1.0–1.1	0.08
Male/Female sex	1.3	0.69–2.3	0.45	0.85	0.30–2.4	0.75
Admission GCS (<9)	17.8	7.7–41.1	<0.001	26.7	8.2–87.5	<0.001
AIS—head	8.2	4.4–15.4	<0.001	5.2	2.4–11.3	<0.001
Fibrinogen[a] <200 mg/dL	2.5	1.3–4.9	0.006	1.8	0.59–5.3	0.31

Abbreviations: AIS, Abbreviated Injury Scale; CI, confidence interval; CT, computed tomography; GCS, Glasgow Coma Scale; OR, odds ratio.

[a]Blood test results at the time of arrival at hospital.

DISCUSSION

In the present study, extravascular leakage was associated with death and neurosurgical procedures from admission to the intensive care unit until discharge from the intensive care unit in patients with an isolated head injury who were transported to our hospital. Patients with extravascular leakage images had higher AIS and more severe TBI than those without extravascular leakage images. Blood tests showed lower fibrinogen and platelet counts and significantly higher levels of aPTT, FDP, and D-dimer, indicating a more traumatic coagulopathy. Since traumatic coagulopathy is associated with increased mortality in TBI patients,[13] the finding of extravascular leakage in patients with an isolated head injury with acute intracranial hemorrhage indicates a more severe TBI. It is associated with surgical procedures and death. In our previous report, we reported on the association between extravascular leakage image and fibrinogen level at admission.[15] The difference is that, while previous reports have focused on differences at admission, this study focuses on final mortality outcomes. Previous reports have discussed the clinical benefit of identifying extravascular leakage images, which may lead to the recognition of low fibrinogen levels and the early administration of fresh frozen plasma. The results of this study suggest that the identification of extravascular leakage may lead to the recognition of mortality outcomes and may serve as an indicator to identify a population at a high risk of mortality. The management of high-risk patients may undergo changes in the future. Previous reports have suggested that the contrast extravasation may indicate bleeding from microvascular damage in the meninges[6] or increased permeability of the blood–brain barrier.[4] Based on the present study, it can be inferred that in severe TBI, the frequency of vascular injury is higher, and the permeability of the blood–brain barrier is increased compared to that in minor TBI. If a contrast CT scan of the head is conducted during the initial examination, it is important to evaluate for vascular damage and extravascular leakage of contrast medium. Recognition of extravascular leakage may lead to recognition of the severity of the injury and mortality outcome. The multivariable logistic regression analysis in this study was adjusted for mortality using the Marshall CT classification as the primary endpoint. The analysis revealed that extravascular leakage has a much higher odds ratio, but it cannot be detected by plane CT scan. This supported the significance of evaluating the presence of extravascular leakage by contrast CT scan. The prevalence of contrast extravasation in our study was 66/188 (35.1%). In previous reports, the prevalence ranged from 17.2% to 40.9%, which is similar to the prevalence of this study.[3–5] In previous studies, the study population was under observation without emergency surgery, and the types of hematomas were acute subdural hematomas and cerebral contusions. This study population included those who underwent emergency surgery and those who were followed up without emergency surgery, and the hematoma morphology was not restricted.

In a similar study of patients who underwent observation without emergency surgery, extravascular leakage was associated with death and surgery during the observation period, similar to the results of existing reports.[3–6] In addition, the patient's background showed that extravascular leakage was associated with death. In terms of patient background, patients with extravascular leakage images had higher head AIS and significant differences in platelet count, aPTT, FDP, and D-dimer compared to patients without extravascular leakage images. Similarly, patients with extravascular leakage tended to have more severe TBI and more severe traumatic coagulopathy in patients who were followed up without emergency surgery. It is important to remember that patients with contrast extravasation may require subsequent surgery, even if emergency surgery is unnecessary.

The study only examined isolated traumatic brain injury and did not consider multiple traumas. It remains uncertain if the results of this study can be applied to cases involving multiple traumas. The focus of future studies is anticipated to be on multiple traumas.

This study only examined the association between extravascular leakage and death or surgery, but not its predictive value. Future prospective studies are needed to determine whether the finding of extravascular leakage is predictive of death or surgery. To determine improved mortality outcomes, it is important to assess if more aggressive multidisciplinary treatment, including surgery and blood transfusion management, is effective in patients with extravascular leakage.

Limitation

The present study was a single-center, retrospective observational study of medical records. About half of the cases were excluded because they did not have intracranial hemorrhage, and 53 patients with intracranial hemorrhage did not undergo contrast-enhanced CT scans at the physician's discretion, which were excluded. They were subject to selection bias. Selection bias may have been present because the definition of emergency surgery was based on the judgment of the physician in charge, not on the time between the CT scan and surgery. In this study, head CT images were read by emergency physicians, not radiologists, indicating possible misclassification, although the kappa coefficient was 0.83, suggesting excellent agreement. Reports vary on the agreement of readings between emergency physicians and radiologists, but a prior article noted that clinically important findings on head CT were rarely missed by emergency physicians.[16,17]

Other factors that may influence death or surgery performed during observation include blood transfusions performed between the time of contrast-enhanced CT scan, the decision to perform surgery during observation, and the nature of postoperative treatment. Our previous manuscript included information on the blood transfusions given within 24 h of the patient's hospital admission. However, it proved challenging to determine the precise quantity of blood and fluid transfusions given during the period between the contrast CT scan and the surgery decision. Identifying all other factors that might influence death or surgery was also difficult. Extracting and evaluating all factors in this study is difficult, and unknown factors may be relevant. And the small sample size limited the number of adjustment factors. The decision of the physician to continue with the surgery could have been affected by selection bias. Despite this, there were no cases where surgery was determined based on extravascular leakage images. GOS at discharge was used to assess neurological prognosis, and it was difficult to assess even long-term prognosis.

CONCLUSIONS

The finding of contrast extravasation on contrast-enhanced CT scans of the head was associated with mortality and surgery in patients with an isolated head injury with acute intracranial hemorrhage. Similar associations were also observed in patients initially admitted without emergency surgery.

CONFLICT OF INTEREST STATEMENT

Dr. Hiroshi Ogura and Dr. Oda Jun are the Editorial Board members of AMS Journal and the co-authors of this article. Dr. Jun Oda is the Editor-in-Chief of the journal. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. Peer review was handled independently by the AMS Journal editorial office and Dr. Yasuyuki Kuwagata as the Editor to minimize bias.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENT

Approval of the research protocol: The study was approved by the Ethics Committee of our hospital (Approval No. 22291) and anonymized by the Act on the Protection of Personal Information.

INFORMED CONSENT

We disclosed information concerning this study on the basis of an opt-out approach.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The study was approved by the Ethics Committee of our hospital (Approval No. 22291) and anonymized by the Act on the Protection of Personal Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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