

The independent risk factors for abnormal head computed tomography in patients with hepatic encephalopathy

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Abstract

It's known that head computed tomography (CT) is used excessively to exclude intracranial hemorrhage in patients with hepatic encephalopathy (HE) in the emergency department. However, the independent risk factors for abnormal head CT in patients with HE have not been studied extensively to date. In this retrospective study, patients with an ammonia level of >90 U/L who were clinically considered HE and had head CT were included. The characteristics of patients with abnormal head CT and independent risk factors for abnormal CT were investigated. Three hundred seventy-eight patients were included in the study. CT findings of 18 (4.8%) of the patients were abnormal: 12 had intracranial hemorrhage, 1 had an ischemic stroke, and 5 had an intracranial mass. Intracranial hemorrhage (odds ratio [OR] 12.5), history of recent trauma (OR 23.4), history of active malignancy (OR 10.3), thrombocyte count <100.000/µL (OR 4.3), and international normalized ratio ≥1.5 (OR 3.2) were found to be independent risk factors for abnormal head CT. Head CT scan may be considered in patients with HE if any of the following are present: intracranial bleeding history, recent trauma history, active malignancy, platelet count <100,000/µL, and international normalized ratio >1.5.

Abbreviations: CT = computed tomography, ED = emergency department, HE = hepatic encephalopathy, INR = international normalized ratio, OR = odds ratio.

Keywords: computed tomography (CT), hepatic encephalopathy (HE), intracranial hemorrhage, liver failure, multislice CT, risk factors

1. Introduction

Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities such as personality changes, intellectual impairment, and altered mental status in patients with liver failure. HE is one of the common causes of admission to the emergency department (ED) for patients with cirrhosis. In these patients, the tendency to intracranial hemorrhage increases due to acquired thrombocytopenia and decreased production of the coagulation factors.^[1] Therefore, head computed tomography (CT) is frequently requested by physicians for patients with chronic liver failure who present to the ED with altered mental status, even if the initial diagnosis is HE. However, it has been shown that head CT has a low diagnostic yield in patients with a higher pretest probability of HE and it has been concluded that CT is used aggressively in those patients.^[2–5]

Due to the retrospective study design, patients' consent could not be obtained. The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The approval of the Ethics Committee for Clinical Studies of Dokuz Eylul University School of Medicine (Decision No: 2020/12-35, date: 08.06.2020) was obtained for the study.

* Correspondence: Nese Colak, Associate Professor of Emergency Medicine, Dokuz Eylul University, School of Medicine, Department of In the literature, there are several studies investigating the use of head CT in cirrhosis patients who presented to the ED with altered mental status.^[2–5] However, there are no generally accepted protocols determining the CT indications in patients with suspected HE in the practice of emergency medicine.

We investigated the clinical features of patients with abnormal head CT and the independent risk factors associated with abnormal head CT in ED patients with a diagnosis of HE.

2. Methods

2.1. Study design

This is a retrospective cross-sectional study. ED patients with a clinical diagnosis of HE and those who had a head CT between December 2012 and December 2018 were enrolled in the study.

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Key points

- Computed tomography (CT) scanning is still a matter of debate for patients presenting with hepatic encephalopathy.
- It is known that the diagnostic efficiency of routine brain CT scans in these patients is low.
- We aimed to determine which emergency department patients presented with hepatic encephalopathy should undergo CT by investigating the independent risk factors associated with abnormal head CT.
- History of intracranial hemorrhage, history of recent trauma, history of active malignancy, thrombocyte count <100.000/µL, and international normalized ratio >1.5 are independent risk factors for high-risk patients.

2.2. Study setting

The study was carried out in the emergency medicine department of a third-level university hospital, where annual patient admissions are approximately 100,000. The approval of the Ethics Committee for Clinical Studies of Dokuz Eylul University School of Medicine (Decision No: 2020/12-35, date: 08.06.2020) was obtained for the study.

2.3. Population

First, electronic files of patients with serum ammonia levels above the cutoff value (>90 μ g/ dL) were scanned from the hospital information management system to identify patients with suspected HE. In these patients, if there was an altered mental status (Glasgow Coma Score <15), impaired cognition, diminished attention, or flapping tremor a clinical diagnosis of HE was made. Patients who were not clinically considered for HE despite having high serum ammonia levels (who present with symptoms not associated with HE such as trauma, valproic acid use and gastrointestinal bleeding) were excluded from the study. Three authors independently reviewed the clinical chart to determine if an HE diagnosis could be made. Among the HE patients identified in this way, those with head CT were included in the study. Due to the retrospective design of the study, a standardized algorithm could not be applied to which HE patients undergo head CT.

Patient's demographic data, high-risk of history characteristics (such as a history of intracranial hemorrhage, recent trauma, history of HE, antiaggregant/anticoagulant use), clinical findings (such as the focal neurological deficit, the grade of HE, Glasgow Coma Score) and laboratory results (platelet count, international normalized ratio [INR] level, electrolytes, and ammonia level on ED admission) were recorded on the data collection form.

2.4. Outcome measures

All CTs with intracranial bleeding, ischemic stroke, and mass lesions were classified as "abnormal CT." Pathological CTs (chronic atrophy, physiological calcification, etc) were not associated with the patient's clinical presentation, and CTs without any lesion were categorized as "normal CT." Official radiology reports were accepted as the gold standard for CT results. Head CT scans were obtained by the 160-slice CT scanner (Toshiba® CT Aquilion, Japan) with a slice thickness of 3 mm.

The primary endpoint of the study is to compare the clinical characteristics of patients with normal and abnormal CT and to investigate independent risk factors that predict abnormal head CT.

2.5. Data analysis

The data was recorded and analyzed with statistical package for social sciences for windows SPSS v22. Kolmogorov–Smirnov test was used for normality analysis. Continuous variables are presented as median with interquartile ranges because of the abnormal distribution. The Mann–Whitney *U* test was used to compare the continuous variables. Categorical variables were expressed as numbers and percentages. Fisher exact test and chi-square test were used to compare the categorical variables. A binary logistic regression analysis was used to determine the threshold of the variables for entry into the multivariate models. The multivariate model constituted the variables with P < .2in binary analysis and some important clinical variables. The goodness of fit of the model was evaluated with the Hosmer– Lemeshow test. *P* value <.05 was accepted as significant.

3. Results

Medical records of 932 patients were screened, and 378 of them were included in the study. The patient flow diagram is shown in Figure 1. The median age was 63 (interquartile range 57–72) years and 70.4% of the patients were male.

CTs of 360 (95.2%) of the patients were categorized as normal. Intracranial hemorrhage in 12 (3.2%) patients, intracranial mass in 5 (1.3%) patients, and ischemic stroke in a patient (0.3%) were detected. The clinical characteristics of the patients with normal and abnormal head CT are shown in Table 1. Four of the intracranial hemorrhage were chronic subdural hematoma, 3 were acute subdural hematoma, 1 was intraparenchymal hemorrhage, 2 were subarachnoid hemorrhage, 1 was acute subdural hematoma + intraparenchymal hemorrhage, and 1 was subarachnoid hemorrhage + intraparenchymal hemorrhage. The clinical characteristics of the patients with abnormal CT findings are shown in Table 2.

Ten variables were included in the univariate analysis. A logistic regression model was constituted with 7 variables with *P* value <.2 in univariate analysis and a variable with clinical significance (history of HE). The goodness of fit of the model was found as *P* = .791. As a result of the multivariate analysis, history of recent trauma (odds ratio [OR] 23.4), history of intracranial hemorrhage (OR 12.5), history of active malignancy (OR 10.3), thrombocyte count <100.000/µL (OR 4.3), and INR ≥1.5 (OR 3.2) were found to be independent risk factors for having abnormal head CT (Table 3).

4. Discussion

We found that a history of intracranial hemorrhage, history of recent trauma, history of active malignancy, thrombocyte count <100,000/µL, and INR ≥1.5 are independent risk factors for abnormal head CT. In the literature, independent clinical risk factors for abnormal head CT have not been previously revealed by using a logistic regression model. While previous studies generally revealed the incidence of intracranial bleeding in patients with HE, in our study we also evaluated intracranial malignant mass and ischemic strokes.

In chronic liver disease, HE is a common and recurrent clinical condition. Many patients may have to need >1 head CT scan during their long-term observation. Unnecessary head CTs extend the length of stay in the ED, increase the cost, and cause unnecessary radiation exposure. In our study, head CT was performed in 75.5% of the patients who were considered to have HE. Therefore, identifying CT indications in patients presenting with HE will make an important contribution to clinical practice.

Cirrhosis patients have an increased tendency to bleeding due to thrombocytopenia and inadequate production of coagulation factors; this condition is called "cirrhotic coagulopathy." In a large population-based case-control study (3.522 cases



Figure 1. Patients flow diagram.

Table 1

Baseline characteristics of patients.

Clinical characteristics		All patients n = 378	Patients with normal CT $n = 360$	Patients with abnormal CT $n = 18$	P value
Male sex [n, (%)]		266 (70.3)	255 (70.8)	11 (61.1)	.378
Age* (yr)		63 (57-71)	63 (57–72)	64.5 (53.8 - 70.3)	.489
Thrombocyte count* (µL)		106.000 (68.750-177.250)	107.000 (69.000-176.750)	91.000 (58.000-185.750)	.505
Patients with thrombocyte count <100.000 μL [(n, %)]	/	174 (46)	163 (45.3)	11 (61.1)	.188
INR*		1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.6 (1.5–1.9)	.012
Patients with INR ≥ 1.5 [n, (%)]		129 (34.1)	119 (33.1)	10 (55.6)	.049
Hepatic encephalopathy stages [n, (%)]	1	120 (31.7)	113 (31.4)	7 (38.9)	.112
	2	119 (31.5)	115 (31.9)	4 (22.2)	
	3	93 (24.6)	91 (25.3)	2 (11.1)	
	4	46 (12.2)	41 (11.4)	5 (27.8)	
Glasgow Coma Score*		14 (12–15)	14 (12–15)	14 (9–15)	.381
Albumin level* (g/dL)		2.8 (2.4–3.2)	2.8 (2.5-3.2)	2.5 (2.2–3)	.291
Total bilirubin level* (mg/dL)		3.0 (1.6-4.9)	2.9 (1.6-4.8)	4.3 (1.6–7.2)	.273
Ammonia level* (µg/dL)		202.5 (154–288)	205 (154–289)	179 (112–238)	1.00
Alanine aminotransferase level* (U/L)		30.5 (20–57)	30 (20–57)	34 (23–78)	.518
Aspartate aminotransferase level* (U/L)		55 (35–111)	54 (35–109)	79 (49–221)	.105
Potassium level* (mmol/L)		4.3 (3.9–4.8)	4.3 (3.9–4.8)	4.4 (3.8–5.1)	.901
Creatinine level* (mg/dL)		1.1 (0.7–1.8)	1.1 (0.7–1.8)	1 (0.7–2.3)	.746
History of intracranial hemorrhage [n, (%)]		24 (6.3)	19 (5.3)	5 (27.8)	<.001
History of recent trauma [n, (%)]		15 (4)	10 (2.8)	5 (27.8)	<.001
History of active malignancy [n, (%)]		88 (23.3)	80 (22.2)	8 (44.4)	.029
Focal neurological deficits [n, (%)]		17 (4.5)	12 (3.3)	5 (27.8)	<.001
History of chronic renal failure [n, (%)]		51 (13.5)	49 (13.6)	2 (11.1)	1.000
Patients on hemodialysis [n, (%)]		8 (2.1)	8 (2.2)	0	1.000
Patients on antiplatelet therapy [n, (%)]		15 (4)	15 (4.2)	0	1.000
Patients on anticoagulant therapy [n, (%)]		30 (7.9)	28 (7.8)	2 (11.1)	.645
History of hepatic encephalopathy [n, (%)]		223 (59)	215 (59.7)	8 (44.4)	.198

 $\mbox{CT}=\mbox{computed tomography}, \mbox{INR}=\mbox{international normalized ratio}.$

* Continuous variables are expressed as median and interguartile ranges (IQR).

rmal head computed tomography.	al History gical Antiplatelet Anticoagulant of recent its Hemodialysis therapy therapy trauma	1	
of patients with ab	History of F intracranial neur hemorrhage de	I	-
cal characteristics	Abnormal CT findings	SDH (chronic)	CDU /ohronio/
Clinic	No.	-	c

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2	SDH (chronic)	+	I	I	I	I	I	I	4	6	58	1.8	117
с	SDH (chronic)	+	I	Ι	I	I	+	Ι	2	15	184	1.7	191
4	SDH (chronic)	+	I	I	Ι	I	I	I	4	6	84	1.5	384
5	SDH (acute)	I	+	I	I	I	I	+	4	8	35	1.2	109
9	SDH (acute)	I	I	I	I	I	+	I	က	9	197	1.5	430
7	SDH (acute)	I	I	I	I	+	I	I		15	245	2.3	177
œ	SDH (acute) + IPH	I	+	I	I	+	+	+	c	11	289	2.8	66
6	Hd	I	+	I	I	I	I	+		15	48	1.3	112
10	IPH + SAH	I	I	Ι	I	I	I	I	2	15	61	1.5	232
÷	SAH	I	I	I	I	I	+	I	4	11	94	2.1	180
12	SAH	+	I	Ι	I	I	I	I	2	13	191	1.6	149
13	Ischemic stroke	+	+	I	Ι	I	+	+		15	76	1.8	159
14	Mass (metastatic)	I	I	Ι	I	I	I	+		14	98	1.6	91
15	Mass (metastatic)	I	+	I	Ι	I	I	+		14	58	1.3	255
16	Mass (metastatic)	I	I	I	Ι	Ι	I	+		15	45	1.5	305
17	Mass (metastatic)	I	I	I	Ι	Ι	I	+	2	14	88	1.4	189
18	Mass (metastatic)	I	I	I	I	I	I	+		15	120	1.7	222
CT = 0	computed tomography, INR -	= , IPH = intraparench	imal hemorrhage, SAH	= subarachnoid hemorrh	nage, SDH = subdura	l hemorrhage.							

of intracranial hemorrhage and 35.173 sex- and age-matched population controls) there was a 5-fold increase in intracranial hemorrhage incidence in patients with cirrhotic liver disease.^[1] For the diagnosis of HE, structural brain diseases (such as hemorrhage, infarction, and mass) must first be excluded. Therefore, routine central nervous system imaging is requested by most physicians for fear of underdiagnosing of possible intracranial pathology. In a questionnaire study involving 1.286 physicians, the participants were given different clinical scenarios and asked whether they would order a head CT or not. Physicians of emergency medicine, internal medicine, gastroenterology, and surgery participated in the study. In the first scenario, for a patient with liver cirrhosis who was admitted to the ED with impaired consciousness, but without trauma findings and focal neurological deficits, 79% of physicians of emergency medicine, 60% of surgeons, 52% of physicians of internal medicine, and 32% of gastroenterologists declared that they would order head CT. In the second scenario, if thrombocytopenia and high INR were detected in the same patient, the CT ordering rates were further increased (86%, 64%, 63%, and 41%, respectively). It was found that the frequency of emergency physicians ordering CT in these scenarios was statistically higher than other physicians.^[2] One of the reasons for this result may be that head CT is routinely requested in patients with altered mental status in emergency medicine practice. Also, the lack of a generally accepted algorithm that determines imaging indications in patients with HE increases the frequency of unnecessary imaging.

In the literature, several publications are examining the results of head CT in cirrhosis patients presenting with impaired consciousness (Table 4). However, these studies could not reveal independent risk factors associated with abnormal CT findings. Rahimi RS et al examined 349 patients with chronic liver failure who presented with altered mental status.^[3] CT scan was performed in 223 of the patients and structural lesions were detected in 11.2% of them. Focal neurological deficits were reported in all patients with structural lesions. It has also been reported that there is no difference in mortality between patients with and without CT (34% vs 37%), surprisingly. In the study of Kumar et al, 147 recurrent HE episodes from 67 patients with chronic liver failure were examined.^[4] Those with first HE episodes, stroke history, intracranial space-occupying lesion, and known neurological illness were excluded from the study. Head CT was performed in all HE episodes. Positive CT findings were detected only in 6 episodes. In 5 of these episodes, patients had a history of recent trauma or focal neurological deficits. Intracerebral hemorrhage was detected in a patient who did not have either a history of recent trauma or focal neurological deficits, however, the INR value was 1.5 and the platelet count was 40.000/µL of the patient. There was no difference between INR, platelet count, ammonia, sodium, potassium, bilirubin, and albumin levels between those with and without positive CT findings. This study concluded that the diagnostic yield of head CT in patients presenting with recurrent HE is quite low. In our study, although the frequency of abnormal head CT was lower in patients with a history of HE compared to those who did not (44.4% vs 59.7%), there was no statistical difference between the 2 groups. In addition, in our study, contrary to Kumar's study, patients with abnormal CT had higher INR levels than patients with normal CT. Donovan et al reported the frequency of acute intracranial hemorrhage as 3% in head CT in cirrhosis patients presenting with altered mental status.^[5] History of a fall/trauma, focal neurological deficit, or history of intracranial hemorrhage was present in 13 of the 14 cases with intracranial hemorrhage.

In chronic liver disease, HE is a common and recurrent clinical condition. Therefore, many patients may have to need >1 head CT scan during their long-term observation. Unnecessary head CTs extend the length of stay in the ED, increase the cost, and cause unnecessary radiation exposure. In our study, head CT was performed in 75.5% of the patients who were

Univariate and multivariate analysis.

	Uni	ivariate analysis		
		95% Cl		
Parameter	OR	Lower	Upper	<i>P</i> value
Sex	1.545	0.583	4.095	.381
Age	0.984	0.943	1.026	.483
History of HE	0.540	0.208	1.400	.205
Focal neurological deficit	11.154	3.424	36.338	<.001
History of ICH	6.903	2.230	21.372	.001
History of recent trauma	13.462	4.023	45.046	<.001
History of active malignancy	2.800	1.070	7.330	.036
Ammonia level	0.996	0.991	1.001	.141
Thrombocyte <100.000/µL	1.899	0.720	5.010	.195
INR ≥1.5	2.532	0.974	6.580	.059
Multivariate analysis				
Ammonia level	0.998	0.993	1.004	.493
History of ICH	12.500	2.292	68.170	.004
Focal neurological deficit	3.284	0.721	14.970	.124
History of recent trauma	23.396	4.515	121.229	.000
History of active malignancy	10.267	2.492	42.308	.001
History of HE	0.497	0.146	1.686	.262
Thrombocyte <100.000/µL	4.263	1.283	14.162	.018
INR ≥1.5	3.183	1.034	9.801	.044

CI = confidence interval, HE = hepatic encephalopathy, ICH = intracerebral hemorrhage, INR = international normalized ratio, OR = odds ratio.

Table 4

The characteristics of studies investigating the effectiveness of computed tomography in cirrhosis patients with altered mental status.

Author, yr	Method, n	Inclusion criteria	Results	Conclusion
Rahimi RS., 2016	Retrospective cohort, 349	Patients with cirrhosis + altered mental status due to hepatic encephalopathy, sepsis, metabolic, toxin, structural,	223 (64%) patients had head CT. 11.2% of patients had structural lesion (5.8% of new infarct or cerebrovascular accident, 4% of ICH, and 1.3% of mass lesion. All of these patients had focal neurological defi- cits. 164 of patients who were classified HE had no acute abnormality	Routine CT imaging is not in- dicated in patients without focal neurologic findings.
Kumar S., 2018	Retrospective cohort, 67	and psychiatric etiologies 67 patients with recurrent HE (147 episodes of HE)	on C1. Most abnormal C1 findings in all patients were cerebral atrophy. All patients underwent CT. Positive CT findings (ICH, epidural hematoma, subdural hematoma, and cerebral edema) observed in 6 episodes. (6/147 = 4%). Except 1 case, 5 patients had a history of recent trauma or focal neurological deficits.	The yield of head CT is extremely low in patients presenting with recurrent HE.
Donovan LM., 2015	Retrospective cohort, 357	357 HE patients with 426 episodes	All episodes evaluated with head CT, 14 (3%) of them revealed acute ICH. In 13 patients with ICH, history of fall/trauma, focal neurological deficit or prior ICH was present. Absence of fall/trauma, focal neurological deficit or prior ICH were significantly associated with the absence of ICH (OR 0.03).	Yield of head CT is low without focal neurologic findings or definite fall history.

CT = computed tomography, HE = hepatic encephalopathy, ICH = intracerebral hemorrhage, OR = odds ratio.

considered to have HE. Therefore, identifying CT indications in patients presenting with HE will make an important contribution to emergency medicine practice.

4.1. Limitations

In our study, patients with ammonia levels >90 μ g/dL were screened and among them, those with a clinical suspicion of HE was included in the study. However, HE patients with low ammonia levels could have also been admitted to our ED during the study period, so we may not have included these patients in the study.

In the study, there were 4 patients with chronic subdural hematoma, however, surgical intervention was not applied to any of them. The clinical picture of these patients may not be associated with chronic subdural hematoma itself. It should be kept in mind that the diagnosis of chronic subdural hematoma in patients with HE may not cause any change in the management of the patient.

Since only patients with brain CT were included in the study, we may have missed some patients (such as early-stage ischemic stroke) who could not be diagnosed with brain CT and could be diagnosed with magnetic resonance imaging. However, we screened the charts of all study patients for 1 week after their ED admission, and there was no patient diagnosed with ischemic stroke during this period.

5. Conclusion

In patients with an initial diagnosis of HE history of intracranial hemorrhage, history of recent trauma, history of active malignancy, thrombocyte count <100.000/ μ L, and INR >1.5 are independent risk factors for having abnormal head CT.

Author contributions

Data curation: Basak Bayram, Ersin Aksay, Sefer Ozgur, Gucluhan Ucar, Nese Colak.

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- Software: Sefer Ozgur, Gucluhan Ucar.
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Writing - review & editing: Basak Bayram, Ersin Aksay, Nese Colak.

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