Original Article

Risk factors for prolonged intensive care unit and hospital stay among patients with acute drug overdose in Japan

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Aim: Hospital selection for patients with drug overdose (DOD) is a critical issue. In Tokyo, the 50-tablet rule has been widely utilized by paramedics for triaging patients with DOD given that it shortens the triage time. However, studies have not investigated the utility of such a rule in local cities. The present study aimed to identify prognostic pre- and in-hospital factors among patients with DOD and determine whether the 50-tablet rule benefits local cities.

Methods: Clinical records of patients with DOD admitted at the University of Tsukuba Hospital (Tsukuba, Japan) between 2013 and 2017 were retrospectively reviewed.

Results: A total of 93 patients with DOD were enrolled in this study. Multivariate analysis showed that creatine kinase and C-reactive protein values and the total number of ingested pills were in-hospital risk factors that significantly prolonged intensive care unit (ICU) and hospital stay. Moreover, Glasgow Coma Scale score on admission and the total number of ingested pills were identified as significant pre-hospital risk factors for prolonged ICU and hospital stay. Setting the total number of ingested pills to 50 tablets did not significantly influence ICU and hospital stay.

Conclusion: The total number of ingested pills and creatine kinase and C-reactive protein values were identified as predictive factors for prolonged ICU and hospital stay in patients with DOD after admission. Moreover, pre-hospital risk factors included Glasgow Coma Scale score and the total number of ingested pills. However, the 50-tablet rule was determined to be a poor cut-off value for patients with DOD. We presented a subset of our findings at the 46th annual meeting of the Japanese Society for Acute Medicine (Yokohama, Japan) on 20 November 2018.

Key words: 50-tablet rule, drug overdose, risk factor, suicide, triage

INTRODUCTION

DRUG OVERDOSE (DOD) has been one of the major causes of intensive care unit (ICU) admission.[1] Moreover, patients with DOD are occasionally brought to tertiary hospitals by paramedics,[2] although most of the patients admitted to the ICU are overtriaged.[3–6] Unnecessary ICU admission of stable patients with DOD causes patient overflow[1] and generates high medical costs.[7] However, patients with severe DOD require intensive care, including artificial ventilation, hemodynamic stabilization, and specific interventions for toxin elimination to avoid complications and enhance outcomes.[8–11] The time taken to decide which hospital could provide the appropriate treatment for patients with DOD is an important consideration.[2] Accordingly, several scores have been proposed to determine triage level for hospitalization and complications among patients with DOD.

The International Program on Chemical Safety, the Commission of the European Union, and the European Association of Poison Centers and Clinical Toxicologists suggested the utility of the poisoning severity score for telephone inquiries.[12] Moreover, Meulendijks *et al.*[13] reported that the criteria for hospitalization among patients with intentional DOD should include vital signs, serum electrolyte levels, medical history, and electrocardiography. Eizadi Mood *et al.*[14] revealed that the Glasgow Coma Scale (GCS) score, Acute Physiology and Chronic Health Evaluation (APACHE) II, and Modified APACHE II Score obtained 24 h after admission could predict mortality due to mixed-drug poisoning, whereas Liisanantti *et al.*[15] identified respiratory and renal dysfunction and failure as risk factors for poor outcomes among patients with DOD using multivariate

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logistic regression analysis. Furthermore, van den Oever et al.[7] proposed six criteria for predicting the need for medium or intensive care admission among patients with intentional DOD, which included intubation, breathing, oxygenation, cardiac conduction, blood pressure, and consciousness.[7] However, given that the aforementioned studies are not intended for eastern Asian patients, establishing prognostic factors and a standardized triage system for Japanese patients with DOD is of primary importance.

The 50-tablet rule has been widely used in Tokyo, Japan by paramedics for triaging patients with DOD. The rule states that patients with DOD who ingested more than 50 tablets should be transferred to tertiary care hospitals. This rule was based on an observational study carried out in Japan wherein patients with DOD who ingested more than 50 tablets needed intubation or renal replacement therapy (RRT) at relatively higher rates.[16] However, this rule has remained controversial or otherwise been refuted.[2] Several researchers have investigated whether the 50-tablet rule could be useful in deciding hospitalization and predicting prognosis. Accordingly, Sugita *et al.*[17] identified patients' age, total number of ingested tablets (≥50), or severe consciousness disturbance (Japan Coma Scale [JCS] ≥100) as risk factors for hospitalization. Tarui *et al.*[2] reported that the total number of ingested pills, GCS score, and blood lactate levels on admission were predictive factors for complications among patients with DOD who were admitted to the ICU, which included pneumonia, rhabdomyolysis, decubitus ulcer, nerve palsy, prolonged intubation (≥3 days), prolonged hospitalization (≥5 days), or death. However, the aforementioned studies have several limitations. Given that paramedics cannot measure blood lactate levels, clinical factors should be limited to those that paramedics can evaluate at the pre-hospital scene. Moreover, relatively easy and convenient information using laboratory and physiologic parameters based on the Japanese database of patients with DOD would be desirable for emergency room (ER) staff. Furthermore, considering that the 50-tablet rule was designed only for one hospital in Tokyo, applying such a rule throughout all areas of Japan could be impossible.

The present study, therefore, aimed to identify prognostic factors for patients with DOD before/after admission, as well as determine compliance with the 50-tablet rule in a local Japanese city.

METHODS

Patient management

THIS WAS A retrospective, single-facility study undertaken at the University of Tsukuba Hospital (Tsukuba, Japan), an educational university hospital with a semi-closed ICU and emergency department managed by board-certified doctors in emergency and/or intensive care medicine. Moreover, full-time consultation from a board-certified psychiatric doctor is available during and after intensive care for poisoning.

Primary interventions for poisoning, such as gastric lavage (GL), artificial ventilation, and RRT, were undertaken if necessary, based on standard protocol. Our policy states that physiologically unstable patients, such as those suffering from consciousness disturbance, respiratory failure, shock, serious metabolic disorders, and multiple organ failure, have an emergency indication for ICU admission. Based on this policy, patients with DOD who present with abnormal vital signs, typically loss of consciousness and/or shock, were selected for ICU admission. When stabilized, these patients would then be discharged from the ICU or transferred to a general room.

This study was reviewed and approved by the research ethics committee of the University of Tsukuba Hospital (No. H28-172).

Patient selection

Medical records of consecutive patients with DOD hospitalized at the Department of Emergency and Critical Care Medicine between 2013 and 2017 were reviewed. The following key words were used to identify target patients with Diagnosis Procedure Combination: "overdose/poisoning" ("Acute drug poisoning," "Benzodiazepine poisoning," "Antidepressant drug poisoning," "Drug poisoning," "Pharmaceutical poisoning," "Tricyclic antidepressant poisoning," "Tetracyclic antidepressant poisoning," "lithium poisoning," and "Acetaminophen poisoning"). Cases with other potential types of poisoning, such as alcohol, carbon monoxide, methyl alcohol, paraquat, ethylene glycol, aconit (trikabuto), organophosphorus compound, hypochlorous acid, and chronic overdose, were excluded. Patients with multiple admissions were counted more than once.

Data analysis

The following patient data were analyzed from emergency medical records: demographics (age, sex, weight, and height), medical history, drug ingestion details (estimated time interval between ingestion and arrival at the hospital, type of drug, maximum number of ingested pills, and the total number of regularly ingested pills prescribed for 1 day), and clinical status on admission (GCS and JCS scores). Moreover, laboratory data included blood creatine kinase (CK) concentrations, serum lactate levels, C-reactive

protein (CRP) levels, and blood gas analysis. Results of Triage DOA (Alere Medical Co., Tokyo, Japan), a simplified qualitative urine test for metabolites of eight major abused drugs using an immunoassay kit, were reviewed for those who were tested. Additionally, electrocardiogram abnormalities, such as prolongation of corrected QT (QTc) interval, were also reviewed. Interventions and critical management at the ER or ICU, including artificial ventilation, GL with or without charcoal, RRT, and antidote usage, were reviewed. Major outcomes included the length of ICU and hospital stay at our hospital. Sequential Organ Failure Assessment (SOFA)[19] and APACHE II scores[20] for each patient were calculated based on their clinical data. In cases where electrocardiogram and blood gas analysis were lacking, patients were assumed to be normal.

Statistical analysis

Results were expressed as median and interquartile ranges unless otherwise stated. To examine the 50-tablet rule according to reports thereof,[16] a receiver operating characteristic (ROC) curve was initially prepared with artificial ventilation or RRT as the state variable and total number of ingested pills as the probability test variable. The cut-off value for this parameter was determined using this ROC curve. In choosing the number of variables, statistical validity was supported in published reports.[21] To investigate pre-hospital prognostic factors, multiple regression analysis of variables, such as sex, age, weight, time interval between ingestion and hospital arrival, 50 tablets as the maximum of number of pills ingested, and total number of regularly ingested pills prescribed for 1 day, was carried out. "The total number of regularly ingested pills prescribed for 1 day" means the number of tablets that the patient has been prescribed on a daily basis of a drug that a patient overdosed. For example, in the patients with lithium overdose, if the daily lithium regular prescription of the patient's is two tablets, count it as two tablets. To investigate in-hospital prognostic factors, variables, such as total number of ingested pills, GCS score on admission, CK and CRP concentrations, total number of regularly ingested pills prescribed for 1 day, and prolonged QTc interval, that had a P-value of <0.05 during univariate analysis were used for multiple regression analysis. Multiple regression analysis used the forced injection method with ICU and hospital stay as explanatory variables. All analyses were undertaken using SPSS version 24 software (IBM, SPSS, Chicago, IL, USA). Differences were considered significant at $P < 0.05$.

RESULTS

Patient characteristics

A TOTAL OF 121 patients with DOD were identified, among whom 93 remained for analysis after excluding

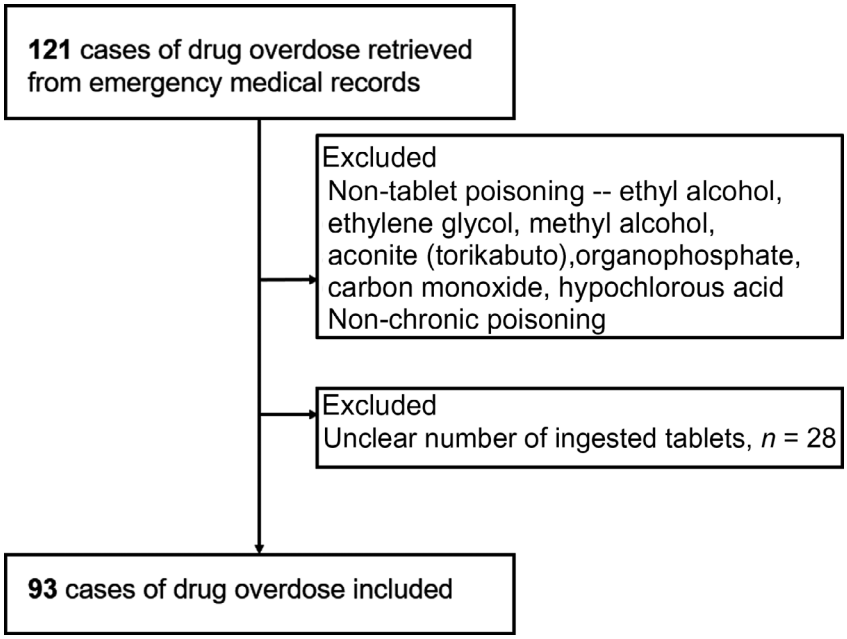

Fig. 1. Flowchart of patient inclusion. Patients with acute drug overdose were identified from the medical records using the key words "overdose/poisoning" during the observation period.

those who met the exclusion criteria (Fig. 1). There were no non-tablet cases among the original 121 cases. As shown in Table 1, the median maximum number of pills ingested was 69 (30–120). On admission, the median APACHE II, SOFA, and GCS scores were 9 (4–12), 1 (0–3), and 12 (6–14), respectively, whereas CRP and CK concentrations were 0.05 (0.00–0.19) mg/dL and 77 (56–131) IU/L, respectively. Common drugs ingested included benzodiazepines, antipsychotics, antidepressants, and analgesics (Table 2). Artificial ventilation was induced in 7 (7.5%) patients, whereas RRT was provided to 2 (2.1%) patients. None of the patients died during hospital stay. The median length of ICU and hospital stay was 28 (18.3–44.3) h and 2 (2–3) days, respectively (Table 2).

Table 1. Characteristics of patients with acute drug overdose in Japan

Variable	Median	(Interquartile range)
Age, years	34	(24–43)
Female, *n* (%)	74 (79.6)	
Height, cm	160	(157–165)
Weight, kg	57.1	(48.9–69.3)
GCS score	12	(6–14)
JCS score	20	(3–100)
SOFA score	1	(0–3)
APACHE II score	9	(4–12)
Extension of QTc, *n* (%)	33 (35.5)	
Drug detection, *n* (%)		
Benzodiazepines	25 (26.9)	
Barbiturate	6 (6.5)	
Opioid	6 (6.5)	
CRP, mg/dL	0.05	(0.00–0.185)
CK, IU/L	77	(56–131)
Lac, mmol/L	0.93	(1.68–2.60)
Time interval between ingestion and arrival at hospital, h	3.5	(2.0–5.4)
Maximum number of ingested pills (tablets)	69	(30–120)
Total number of regularly ingested pills prescribed for 1 day (tablets)	4	(1–8)

APACHE II, Acute Physiology and Chronic Health Evaluation II; CK, creatine kinase; CRP, C-reactive protein; GCS, Glasgow Coma Scale; JCS, Japan Coma Scale; Lac, lactic acid; QTc, corrected QT; SOFA, Sequential Organ Failure Assessment.

Table 2. Psychiatric diseases, ingested substances, and outcomes among Japanese patients with acute drug overdose

Variable	*n* (%)
Psychiatric diseases, *n* (%)	
Yes	69 (74.2)
Depression	28 (30.1)
Bipolar disorder	15 (16.1)
Personality disorder	8 (8.6)
Schizophrenia	6 (6.5)
Adjustment disorder	4 (4.3)
Eating disorder	4 (4.3)
Ingested substances, *n* (%)	
Benzodiazepines	57 (61.3)
Antipsychotics	44 (47.3)
Antidepressants	
SSRIs	13 (14.0)
TCAs	7 (7.5)
Analgesics	
Paracetamol	10 (10.8)
NSAIDs	7 (7.5)
Treatments, *n* (%)	
Diuretic	1 (1.1)
Artificial ventilation	7 (7.5)
GL	13 (14.0)
RRT	2 (2.1)
Length of hospital stay (days), median (IQR)	2 (2–3)
Length of ICU stay (h), median (IQR)	28 (18.3–44.3)

GL, gastric lavage; ICU, intensive care unit; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; RRT, renal replacement therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Overall risk factors for prolonged ICU and hospital stay

Table 3 shows the results of univariate regression analysis for factors associated with length of ICU and hospital stay. Accordingly, age, sex, weight, QTc prolongation, GCS score on admission, CRP, Lac and CK concentrations, the maximum number of ingested pills, and the total number of regularly ingested pills prescribed for 1 day significantly prolonged both ICU and hospital stay in univariate analysis (Table 3).

Pre-hospital clinical risk factors for prolonged ICU and hospital stay

Multiple regression analysis of pre-hospital prognostic factors included GCS score on admission, sex, weight,

Table 3. Univariate regression analysis of factors associated with the length of intensive care unit (ICU) and hospital stay among patients with acute overdose

Variables	Hospital stay			ICU stay		
	B′	(95% CI)	*P*′-value	B″	(95% CI)	*P*″-value
Age	0.006	(−0.023 to +0.011)	0.495	−0.294	(−0.723 to +0.135)	0.176
Female sex	0.057	(−0.609 to +0.723)	0.865	−5.943	(−22.84 to +10.95)	0.486
Weight	0.018	(−0.002 to +0.038)	0.080	0.357	(−0.135 to +0.849)	0.153
GCS score*	−0.133	(−0.195 to −0.071)	<0.01	−3.455	(−4.986 to −1.924)	<0.01
QTc prolongation	0.572	(+0.041 to +1.102)	0.035	11.080	(−2.508 to +24.668)	0.109
CRP*	1.340	(+0.776 to +1.903)	<0.01	21.188	(+8.474 to +33.902)	<0.01
CK*	0.000	(+0.000 to +0.000)	<0.01	0.003	(+0.001 to +0.005)	<0.01
Lac	0.023	(−0.185 to +0.231)	0.823	1.112	(−3.887 to +6.110)	0.656
Time interval between ingestion and hospital arrival	0.041	(−0.030 to +0.113)	0.100	1.414	(−0.358 to +3.186)	0.116
Maximum number of ingested pills*	0.009	(+0.006 to +0.012)	<0.01	0.180	(+0.120 to +0.241)	<0.01
Total number of regularly ingested pills prescribed for 1 day*	0.108	(+0.026 to +0.190)	0.011	2.544	(+0.430 to +4.658)	0.019

B′, B″, partial regression coefficient; CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; GCS, Glasgow Coma Scale; Lac, lactic acid; QTc, corrected QT.
*$P < 0.05$.

maximum number of ingested pills, age, and the total number of regularly ingested pills prescribed for 1 day as dependent variables and length of ICU and hospital stay as explanatory variables (Table 4). Accordingly, GCS score on admission ($P = 0.021$; $P < 0.01$) and the maximum number of pills ($P < 0.01$; $P = 0.01$) were significantly associated with prolonged hospital and ICU stay.

Emergency room risk factors for prolonged ICU and hospital stay

Multiple regression analysis for ER prognostic factors included GCS score on admission, the maximum number of pills, the total number of regularly ingested pills prescribed for 1 day, CK and CRP concentrations, and prolonged QTc interval as dependent variables and length of ICU and hospital stay as explanatory variables (Table 5). Accordingly, CK and CRP concentrations and the maximum number of pills were significantly associated with prolonged hospital and ICU stay.

Fifty-tablet rule as a pre-hospital predictor for prolonged ICU and hospital stay

Figure 2 shows the ROC curve prepared with artificial ventilation or RRT as the state variable and maximum number of pills as the probability test variable. Based on the maximum Youden index of this ROC curve, 71 tablets were suggested to be the best cut-off value.

To determine whether the 50-tablet rule can be useful for paramedics before admission, multiple regression analysis was carried out with sex, age, weight, time interval between ingestion and arrival at hospital, 50 tablets as the maximum number of pills ingested, and total number of regularly ingested pills prescribed for 1 day as dependent variables and length of ICU and hospital stay as explanatory variables (Table 6). Accordingly, only GCS score on admission was associated with prolonged outcomes ($P = 0.023$; $P = 0.016$), whereas no such association was found for ingesting a maximum of 50 tablets. Furthermore, ingesting a maximum of 250 tablets was significantly associated with prolonged outcomes with the multiple coefficient of determination (R^2) showing a maximum value.

DISCUSSION

THE PRESENT STUDY identified prognostic factors for patients with DOD considering situations before/after admission. Moreover, this is the first study to thoroughly examine risk factors for prolonged ICU and hospital stay within Japan using laboratory and physiologic parameters. Our study also suggests that in-hospital risk factors for

Table 4. Pre-hospital clinical risk factors for prolonged intensive care unit (ICU) and hospital stay among patients with acute overdose

Independent factor	Hospital stay		ICU stay	
	Partial regression coefficient	*P*-value	Partial regression coefficient	*P*-value
Constant term	3.065	0.022	53.062	0.188
GCS score*	−0.109	0.021	−3.865	<0.01
Maximum number of ingested pills*	0.009	<0.01	0.125	0.010
Female sex	−0.247	0.644	−22.845	0.187
Time interval between ingestion and hospital arrival	−0.019	0.629	−0.020	0.986
Age	−0.007	0.589	−0.048	0.895
Total number of regularly ingested pills prescribed for 1 day	0.007	0.866	0.402	0.751
Weight	0.002	0.853	0.299	0.447

$R^2 > 0.5$ $R^2 < 0.5$.
GCS, Glasgow Coma Scale.
*$P < 0.05$.

Table 5. In-hospital clinical risk factors for prolonged intensive care unit (ICU) and hospital stay among patients with acute overdose

Independent factor	Hospital stay		ICU stay	
	Partial regression coefficient	*P*-value	Partial regression coefficient	*P*-value
Constant term	1.528	<0.01	40.843	0.013
GCS score	−0.009	0.820	−2.063	0.075
Maximum number of ingested pills*	0.002	0.017	0.086	0.033
Total number of ingested pills regularly prescribed for 1 day	0.007	0.849	0.311	0.747
CRP*	1.203	0.011	28.781	0.038
CK*	0.001	<0.01	0.029	0.031
QTc prolongation	0.233	0.376		

Both $R^2 > 0.5$.
CK, creatine kinase; CRP, C-reactive protein; GCS, Glasgow Coma Scale; QTc, corrected QT prolongation.
*$P < 0.05$.

prolonged stay using laboratory and physiologic parameters can be useful to medical staff given that it allows them to predict the prognosis of patients with DOD.

Remarkably, the present study found that the 50-tablet rule (Table 6), was not appropriate for predicting prolonged ICU and hospital stay for patients with DOD, nor artificial ventilation or RRT (Fig. 2). After examining the validity of the 50-tablet rule by creating sensitivity and specificity curves, Tarui *et al.*[2] reported that a cut-off value of 100 tablets was needed to predict complications among patients with DOD in the ICU. Moreover, following univariate analysis, Sugita *et al.*[17] revealed that patients with DOD who ingested ≥50 tablets were more likely to be hospitalized. The present study is the first to evaluate whether the 50-tablet rule can be useful for predicting prolonged ICU and hospital stay using multivariate analysis, with our results suggesting that 50 tablets might not be the best cut-off value considering other variables available before admission.

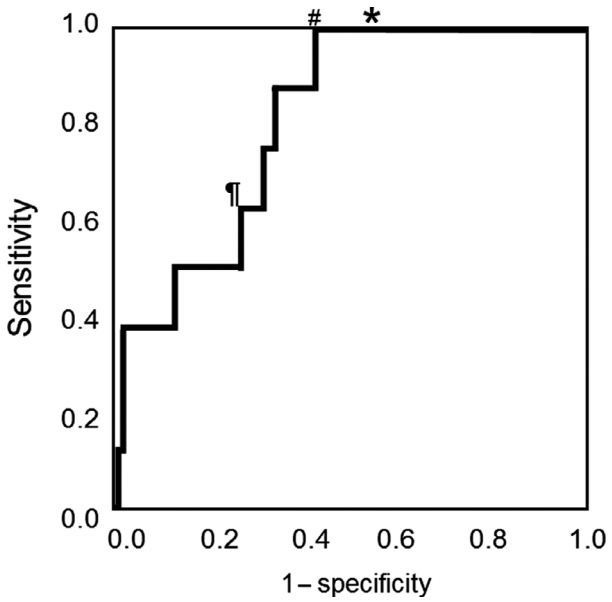

Fig. 2. Receiver operating characteristic curves of the total number of ingested pills to determine the prognostic capabilities of artificial ventilation or renal replacement therapy among 93 patients with acute overdose. Area under the curve is 0.807. Each cut-off point is indicated by *, #, and ¶. *50 tablets, Youden index 0.447; #71 tablets, Youden index 0.576; ¶100 tablets, Youden index 0.3.

Moreover, we showed that both GCS score on admission and the total number of pills can be utilized as prognostic factors before admission (Table 4).

Interventions and critical management measures such as GL, RRT, or antidote usage were not used for further analysis. It is true that interventions such as RRT or antidote usage are thought to prolong ICU and hospital stay. However, we focused only on clinical factors that we could obtain quickly at the ER in analyzing risk factors for prolonged ICU and hospital stay. We determined ROC curves, defining intubation or blood purification as the outcome, because we wanted to evaluate the validity of the 50-tablet rule as much as possible, as in the study of Hifumi *et al.*[16]

The present study also found that CK and CRP concentrations and total number of ingested pills were in-hospital prognostic factors (Table 5). We consider that inflammation and organ damage, such as aspiration pneumonia and/or rhabdomyolysis, might have occurred as complications of DOD. Using multivariate logistic regression analysis, Liisanantti *et al.*[15] reported that respiratory and renal dysfunction/failure were risk factors for poor outcomes among patients with acute DOD. In Japan, Tarui *et al.*[2] reported that GCS score on admission, blood lactate levels, and the total number of pills were prognostic factors for patients with DOD. Unlike Tarui *et al.*'s study, however, the present study did not include blood lactate level during multivariate analysis given that univariate analysis did not find it to be significant. Laboratory parameters included herein had been thoroughly considered, and end-points showed this difference. However, there exists a problem in the criteria for rhabdomyolysis (CK >166 IU/L) as a complication in Tarui *et al.*'s report. Considering that no cut-off value has been established, many clinicians have used ranges five times higher than the normal range for

Table 6. Multiple regression analysis of pre-hospital clinical risk factors with 50 tablets as the maximum number of pills ingested for the length of intensive care unit (ICU) and hospital stay among patients with acute overdose

Independent factor	Hospital stay		ICU stay	
	Partial regression coefficient	*P*-value	Partial regression coefficient	*P*-value
Constant term	2.606	0.108	48.013	0.284
GCS score*	−0.133	0.023	−4.022	0.016
50 tablets as the maximum number of pills ingested	0.679	0.150	12.355	0.353
Female	−0.723	0.273	−32.413	0.101
Time interval between ingestion and hospital arrival	0.009	0.843	0.086	0.888
Age	−0.009	0.559	−0.086	0.830
Total number of regularly ingested pills prescribed for 1 day	0.044	0.407	0.797	0.571
Weight	0.019	0.238	0.496	0.256

Both $R^2 < 0.5$.
GCS, Glasgow Coma Scale.
*$P < 0.05$.

rhabdomyolysis.[18] The present study revealed that the median CK concentration of 77 IU/L significantly prolonged ICU and hospital stay among patients with DOD. We speculated that the increase in CK was not necessarily due to rhabdomyolysis but rather the mere lying down of the patient during loss of consciousness.

The present study has some limitations worth noting. First, considering that this was a retrospective, single-facility study undertaken in the southern area of Ibaraki, the results presented herein might not be applicable to other places throughout Japan. However, the prevalent characteristics of our cohort might not be much different from those residing within other areas across Japan.[2,17] Second, we were unable to obtain information regarding outpatients with DOD given the shortcomings in our clinical record system, which made it difficult to acquire information related to the patients' condition and clinical data without admission. Third, the study group was too small to include the type of drug as a variable during multivariate analysis, and the effect of explanatory variables cannot be neglected. Finally, indications for treatment have not been uniform. Further prospective, large-scale multicenter studies are thus necessary to determine the precise cut-off value for the appropriate triage of patients with DOD.

CONCLUSION

THE PRESENT STUDY revealed that the total number of ingested pills and CK and CRP concentrations were in-hospital risk factors for prolonged ICU and hospital stay among patients with DOD. Moreover, the 50-tablet rule was not a predictor of prolonged ICU and hospital stay among patients with DOD as well as artificial ventilation or RRT. The results presented herein can therefore contribute to the assessment of clinical severity before and after admission.

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DISCLOSURE

Approval of the research protocol and informed consent: This study was approved by the research ethics committee of the University of Tsukuba Hospital. The need for informed consent was waived on account of the retrospective study design.
Registry and the registration no. of the study/trial: No. H28-172.
Animal studies: N/A.
Conflict of interest: None.

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