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Original Article

Risk evaluation of carbapenem-induced liver injury based on machine learning analysis

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ABSTRACT

Introduction: Information regarding carbapenem-induced liver injury is limited, and the rate of liver injury caused by meropenem (MEPM) and doripenem (DRPM) remains unknown. Decision tree (DT) analysis, a machine learning method, has a flowchart-like model where users can easily predict the risk of liver injury. Thus, we aimed to compare the rate of liver injury between MEPM and DRPM and construct a flowchart that can be used to predict carbapenem-induced liver injury.

Methods: We investigated patients treated with MEPM (n = 310) or DRPM (n = 320) and confirmed liver injury as the primary outcome. We used a chi-square automatic interaction detection algorithm to construct DT models. The dependent variable was set as liver injury from a carbapenem (MEPM or DRPM), and factors including alanine aminotransferase (ALT), albumin-bilirubin (ALBI) score, and concomitant use of acetaminophen were used as explanatory variables.

Results: The rates of liver injury were 22.9% (71/310) and 17.5% (56/320) in the MEPM and DRPM groups, respectively; no significant differences in the rate were observed (95% confidence interval: 0.710–1.017). Although the DT model of MEPM could not be constructed, DT analysis showed that the incidence of introducing DRPM in patients with ALT >22 IU/L and ALBI scores > −1.87 might be high-risk.

Conclusions: The risk of developing liver injury did not differ significantly between the MEPM and DRPM groups. Since ALT and ALBI score are evaluated in clinical settings, this DT model is convenient and potentially useful for medical staff in assessing liver injury before DRPM administration.

1. Introduction

Drug-induced liver injury (DILI) is a severe adverse drug reaction; idiosyncratic DILI accounts for 11% of all DILI cases [1]. Many studies on DILI have reported antibiotics as the most common causative agents [2]. Carbapenems are broad-spectrum antibiotics used to treat sepsis and septic shock caused by antimicrobial-resistant bacteria, such as AmpC β-Lactamase-producing *Enterobacter* spp [3] and expended β-Lactamase-producing bacteria [4]. Data mining analysis has shown that meropenem (MEPM), a carbapenem, is strongly associated with DILI [5,6], suggesting that liver function should be frequently monitored during its administration. Doripenem (DRPM) is a relatively new carbapenem whose antimicrobial spectrum closely resembles that of MEPM [7]. DRPM is active against antimicrobial-resistant bacteria associated with hospital-acquired pneumonia [8] and febrile neutropenia [9]. Recently, a network meta-analysis reported that the pattern of adverse drug reactions might differ between MEPM and DRPM [10], suggesting that the occurrence rate of DILI in MEPM and DRPM may differ. However, there is limited comparative information regarding DILI from these agents because DRPM is not readily used in clinical settings when compared with MEPM.

Patients with severe infections are treated with carbapenems, suggesting that appropriate management of carbapenem-induced liver injury is cardinal in preventing patient mortality. Because DILI tends to be frequently missed and overlooked in clinical settings, its incidence rate is estimated to be low [11]. Thus, to the best of our knowledge, there is currently no evidence on carbapenem-induced liver injury risk factors. In addition, because patients have multiple risk factors, including age, liver function, and underlying diseases in clinical settings, the combination of these factors requires a comprehensive assessment to understand the relationships with DILI.

Decision tree (DT) analysis, a type of machine learning, consists of a flowchart-like model in which users can easily assess the risk of adverse drug reactions by combining multiple risk factors [12–14]. Therefore,

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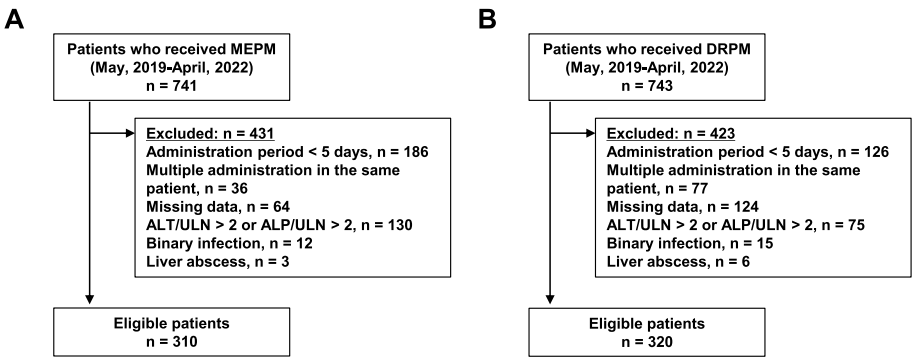

Fig. 1. Flow diagram illustrating the patient selection process.

Table 1
Baseline of characteristics treated with MEPM or DRPM.

Factors	MEPM	DRPM	*p* value
	n = 310	n = 320	
Sex (Male/Female)	192/137	231/111	0.014[a]
Age (years)	78 (67, 85)[f]	77 (69, 84)[f]	0.674[c]
BMI (kg/m^2)	20.97 (18.42, 23.60)[f]	21.17 (18.89, 23.75)[f]	0.271[c]
eGFR (mL/min)	54.88 (35.61, 76.67)[f]	53.47 (33.05, 72.90)[f]	0.383[c]
BUN (mg/dL)	19.10 (13.33, 31.40)[f]	17.20 (12.88, 28.45)[f]	0.242[c]
ALT (IU/L)	18 (12, 28)[f]	17 (12, 27)[f]	0.944[c]
AST (IU/L)	25 (17, 34)[f]	22 (18, 31)[f]	0.245[c]
ALP (IU/L)	240 (178, 304)[f]	240 (193, 321)[f]	0.180[c]
ALBI score	−1.58 ± 0.66[e]	−1.65 ± 0.59[e]	0.160[d]
CRP (mg/dL)	10.78 (5.00, 18.41)[f]	11.40 (5.69, 18.72)[f]	0.440[c]
WBC (× 10^2/μL)	106.8 (80.8, 151.6)[f]	112.5 (71.8, 151.6)[f]	0.861[c]
Concomitant drugs			
Acetaminophen, n (%)	10 (3.2)	14 (4.4)	0.451[a]
Acyclovir, n (%)	2 (0.6)	0 (0.0)	0.242[b]
Daptomycin, n (%)	1 (0.3)	0 (0.0)	0.492[b]
Fluconazole, n (%)	2 (0.6)	0 (0.0)	0.242[b]
Pazufloxacin, n (%)	0 (0.0)	1 (0.3)	1.000[b]
Vancomycin, n (%)	3 (1.0)	2 (0.6)	0.682[b]
Teicoplanin, n (%)	0 (0.0)	1 (0.3)	1.000[b]
Site of infection, n (%)			
Blood stream	24 (7.7)	25 (7.8)	–
Pulmonary	72 (23.2)	105 (32.8)	–
Urinary	33 (10.6)	82 (25.6)	–
Cerebrospinal fluid	18 (5.8)	1 (0.3)	–
Unknown	82 (26.5)	63 (19.7)	–
Others	81 (26.1)	44 (13.8)	–

ALBI: albumin-bilirubin. ALP: alkaline phosphatase. ALT: alanine aminotransferase. AST: aspartate aminotransferase. BMI: body mass index. BUN: blood urea nitrogen. CRP: C-reactive protein. eGFR: estimated glomerular filtration rate. WBC: white blood cell.

[a] Chi-square test.
[b] Fisher's exact test.
[c] Mann-Whitney *U* test.
[d] Student's t-test.
[e] Each value represents the mean ± standard deviation.
[f] Each value represents the median (25%, 75% percentile).

DT analysis may be a valuable assessment tool for DILI in carbapenems administered by medical staff; however, this remains to be explored.

In this study, we aimed to compare the DILI rate between MEPM and DRPM and construct a simple flowchart that can be used to predict liver injury before initiating carbapenem therapy.

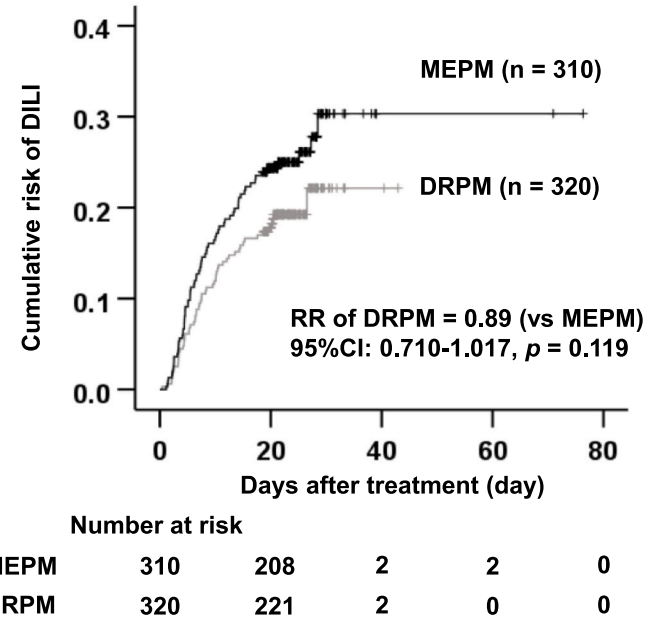

Fig. 2. Comparison of DILI rate between MEPM and DRPM.
Kaplan–Meier curves depicting accumulation rate of MEPM or DRPM-induced liver injury.
95% CI, 95% confidence interval; DILI, drug-induced liver injury; DRPM, doripenem; MEPM, meropenem; RR, relative risk.

2. Materials and methods

2.1. Study design and patient enrollment

This single-center retrospective case-control study was conducted at the National Hospital Organization Mie Chuo Medical Center (Mie, Japan) using electronic medical records. Patients aged ≥18 years treated with MEPM or DRPM between May 1, 2019, and April 30, 2022, were enrolled. The exclusion criteria were: (a) treatment periods of MEPM or DRPM <5 days in compliance with the DDW-J scoring scale [15] and a previous report [16], (b) multiple drug administrations in the same patients, (c) missing data, (d) baseline alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) levels more than twice the upper limit of normal (ULN), and (e) biliary infection and liver abscesses, with biliary infection instead of DILI being reported in error [17]. Exclusion criteria (d) and (e) were established to remove the possibility of non-drug-induced liver injury during MEPM or DRPM administration. The first episode was used to analyze when a single patient had multiple dosing periods. Multiple dosing was defined as re-administration within 14 days from the end of the first dosing period.

Table 2
Comparison of patient's characteristics between those with DILI and non-DILI by MEPM.

Factors	Non-DILI	DILI	*p* value
	n = 239	n = 71	
Sex (Male/Female)	140/99	41/30	0.901[a]
Age (years)	78 (68, 85)[f]	78 (65, 85)[f]	0.820[c]
BMI (kg/m^2)	20.66 (18.14, 23.46)[f]	21.69 (19.44, 23.94)[f]	0.083[c]
eGFR (mL/min)	53.91 (35.47, 74.09)[f]	57.63 (36.15, 83.50)[f]	0.191[c]
Daily dose (mg/day)	1000 (1000, 1500)[f]	1000 (1000, 1500)[f]	0.563[c]
BUN (mg/dL)	19.30 (13.65, 31.40)[f]	17.50 (12.00, 29.40)[f]	0.281[c]
ALT (IU/L)	16 (11, 28)[f]	22 (15, 29)[f]	0.005[c]
AST (IU/L)	25 (17, 34)[f]	26 (20, 36)[f]	0.099[c]
ALP (IU/L)	235 (176, 300)[f]	254 (199, 314)[f]	0.158[c]
ALBI score	−1.59 ± 0.65[e]	−1.53 ± 0.66[e]	0.462[d]
CRP (g/dL)	10.94 (5.62, 17.96)[f]	9.85 (2.96, 22.78)[f]	0.899[c]
WBC (× 10^2/μL)	107.0 (81.5, 153.7)[f]	106.5 (79.2, 147.3)[f]	0.430[c]
Concomitant drugs			
Acetaminophen, n (%)	4 (1.7)	6 (8.5)	0.011[b]
Acyclovir, n (%)	1 (0.4)	1 (1.4)	0.406[b]
Daptomycin, n (%)	0 (0.0)	1 (1.4)	0.229[b]
Fluconazole, n (%)	1 (0.4)	1 (1.4)	0.406[b]
Pazufloxacin, n (%)	0 (0.0)	0 (0.0)	–
Vancomycin, n (%)	3 (1.3)	0 (0.0)	1.000[b]
Teicoplanin, n (%)	0 (0.0)	0 (0.0)	–
Site of infection, n (%)			
Blood stream	21 (8.8)	3 (4.2)	–
Pulmonary	55 (23.0)	17 (23.9)	–
Urinary	27 (11.3)	6 (8.5)	–
Cerebrospinal fluid	6 (2.5)	12 (16.9)	–
Unknown	63 (26.4)	19 (26.8)	–
Others	67 (28.0)	14 (19.7)	–

ALBI: albumin-bilirubin. ALP: alkaline phosphatase. ALT: alanine aminotransferase. AST: aspartate aminotransferase. BMI: body mass index. BUN: blood urea nitrogen. CRP: C-reactive protein. eGFR: estimate glomerular filtration rate. WBC: white blood cell.
[a] Chi-square test.
[b] Fisher's exact test.
[c] Mann-Whitney *U* test.
[d] Student's t-test.
[e] Each value represents the mean ± standard deviation.
[f] Each value represents the median (25%, 75% percentile).

2.2. Evaluation of DILI

The primary outcome was liver injury after treatment with a carbapenem. DILI was defined as ALT and/or ALP levels greater than twice the upper limits of normal (ULN) for males or females [16]. The ULN was selected as follows: male (ALT, 42 IU/L; ALP, 322 IU/L) and female (ALT, 23 IU/L; ALP, 322 IU/L) [16]. According to a previous study [16], ALT and ALP were monitored during carbapenem administration and until 14 days after treatment. When ALT/ALP at baseline was above the ULN before carbapenem administration, DILI was defined as a 2-fold increase from baseline owing to carbapenem administration. The pattern of DILI was defined by the ratio of ALT/ULN to ALP/ULN as follows: ALT/ALP <2 indicated cholestatic-type injury, ALT/ALP >5 indicated hepatocellular injury, and 2< ALT/ALP <5 indicated mixed cholestatic-hepatocellular injury [16]. The albumin-bilirubin (ALBI) score, a hepatic functional reserve, was calculated using the following formula: [log10 T-bil (μmol/L) × 0.66] + [Alb (g/L) × −0.085] [18]. Concomitant drugs were defined as those that were administered during the same period as MEPM or DRPM, while that of acetaminophen was defined as 1500 mg/day used for 3 consecutive days as previously reported [16].

Table 3
Comparison of patient's characteristics between those with DILI and non-DILI by DRPM.

Factors	Non-DILI	DILI	*p* value
	n = 264	n = 56	
Sex (Male/Female)	182/82	35/21	0.349[a]
Age (years)	78 (70, 84)[f]	77 (68, 85)[f]	0.680[c]
BMI (kg/m^2)	21.14 (18.87, 23.54)[f]	21.44 (19.26, 25.64)[f]	0.487[c]
eGFR (mL/min)	51.63 (31.93, 71.70)[f]	58.35 (44.25, 74.37)[f]	0.170[c]
Daily dose (mg/day)	750 (500, 750)[f]	750 (500, 750)[f]	0.178[c]
BUN (mg/dL)	17.30 (13.08, 28.90)[f]	16.65 (12.53, 28.00)[f]	0.839[c]
ALT (IU/L)	16 (11, 25)[f]	23 (17, 32)[f]	<0.001[c]
AST (IU/L)	21 (17, 29)[f]	31 (22, 37)[f]	<0.001[c]
ALP (IU/L)	239 (191, 321)[f]	246 (195, 314)[f]	0.517[c]
ALBI score	−1.68 ± 0.58[e]	−1.51 ± 0.62[e]	0.046[d]
CRP (g/dL)	11.13 (5.58, 18.66)[f]	14.19 (7.72, 19.56)[f]	0.121[c]
WBC (× 10^2/μL)	115.4 (74.4, 153.6)[f]	106.4 (60.9, 136.3)[f]	0.204[c]
Concomitant drugs			
Acetaminophen, n (%)	10 (3.8)	4 (7.1)	0.279[b]
Acyclovir, n (%)	0 (0.0)	0 (0.0)	–
Daptomycin, n (%)	0 (0.0)	0 (0.0)	–
Fluconazole, n (%)	0 (0.0)	0 (0.0)	–
Pazufloxacin, n (%)	0 (0.0)	1 (1.8)	0.175[b]
Vancomycin, n (%)	2 (0.8)	0 (0.0)	1.000[b]
Teicoplanin, n (%)	1 (0.4)	0 (0.0)	1.000[b]
Site of infection, n (%)			
Blood stream	20 (7.6)	5 (8.9)	–
Pulmonary	89 (33.7)	16 (28.6)	–
Urinary	70 (26.5)	12 (21.4)	–
Cerebrospinal fluid	0 (0.0)	1 (1.8)	–
Unknown	49 (18.6)	14 (25.0)	–
Others	36 (13.6)	8 (14.3)	–

ALBI: albumin-bilirubin. ALP: alkaline phosphatase. ALT: alanine aminotransferase. AST: aspartate aminotransferase. BMI: body mass index. BUN: blood urea nitrogen. CRP: C-reactive protein. eGFR: estimate glomerular filtration rate. WBC: white blood cell.
[a] Chi-square test.
[b] Fisher's exact test.
[c] Mann-Whitney *U* test.
[d] Student's t-test.
[e] Each value represents the mean ± standard deviation.
[f] Each value represents the median (25%, 75% percentile).

2.3. DT analysis

A flowchart was constructed based on the chi-squared automatic interaction detection (CHAID) algorithm. CHAID is a multi-branch DT method that repeats the process of conducting a chi-squared test to determine the association between two variables. One dependent variable and one independent variable are set, and the results are divided by the variable combination with the highest chi-square value. This procedure is repeated, and the tree branching stops when the stopping criteria are satisfied. Herein, the stop criteria of the branches were as follows: (i) parent nodes ≤20 individuals or child nodes ≤10 subjects and (ii) no significant differences among the independent variables. The dependent variable was set as MEPM or DRPM-induced liver injury, and the factors with $p < 0.05$ in the Cox proportional hazard analysis were selected as explanatory variables [19]. DT analysis was conducted using SPSS Decision Trees Version 27 (IBM Japan, Tokyo, Japan).

2.4. Model validation

The DT validation criteria constructed in this study were based on a previous study by Miyai et al. [13]. To evaluate the misclassification rate of the flowchart constructed using the CHAID algorithm, 10-fold cross-validation was performed. The population data was divided into 10 subsamples of equal size; nine were analyzed for training purposes,

Table 4
Adjusted hazard ratio of MEPM or DRPM-induced liver injury from COX proportional hazard analysis.

Factors	Adjusted hazard ratio	95% CI	*p* value
MEPM			
Sex (male)	0.90	0.556–1.448	0.656
Age (≥85 years)	1.37	0.795–2.368	0.256
Daily dose of MRPM (≥1500 mg/day)	1.01	0.621–1.640	0.971
Concomitant use of acetaminophen	3.41	1.448–8.028	0.005
ALT (>18 IU/L)	2.14	1.211–3.770	0.009
AST (>18 IU/L)	1.26	0.610–2.597	0.533
ALBI score (>−1.10)	1.08	0.623–1.867	0.787
DRPM			
Sex (male)	0.67	0.383–1.171	0.160
Age (≥85 years)	1.05	0.563–1.950	0.884
Daily dose of DRPM (≥750 mg/day)	1.50	0.813–2.770	0.194
Concomitant use of acetaminophen	2.92	1.021–8.328	0.046
ALT (>18 IU/L)	2.90	1.438–5.841	0.003
AST (>23 IU/L)	1.70	0.850–3.410	0.133
ALBI score (>−1.35)	1.88	1.087–3.251	0.024

ALBI: albumin-bilirubin. ALT: alanine aminotransferase. AST: aspartate aminotransferase. 95% CI, 95% coefficient interval.

and the remaining data were evaluated based on the analysis results. This process was repeated for every subsample, and the mean of 10 iterations was estimated as the misclassification risk value.

2.5. Statistical analysis

Continuous variables were analyzed using Student's *t*-test or Mann–Whitney *U* test. When continuous variables followed a non-normal distribution, the Mann–Whitney *U* test was performed for comparison. Conversely, the Student's *t*-test was used for data with normal distributions. Categorical variables were compared using the chi-square test. Fisher's exact test was used to include one cell with an expected value of <5 in a 2 × 2 contingency table.

To compare the DILI rates between MEPM and DRPM, a sample size of 54 patients in each group was needed to consider a detection power of 80%, a ratio of 1.0, an equivalence margin of 20%, a two-sided 95% confidence interval (CI), and a level of significance of 5%. If the lower and upper limits of the 95% CI were included in the equivalence margin of ±20%, the DILI rate of DRPM was comparable to that of MEPM. The cumulative risk of DILI was determined using a Kaplan–Meier curve and compared using the log-rank test. Significant differences were evaluated by relative risk with 95% CI 14 days after the end of MEPM or DRPM treatment.

The cutoff value was evaluated based on the sensitivity, specificity, and area under the curve (AUC) using receiver operating characteristic analysis. In addition, the cut off dose of MEPM and DRPM was based on the mean of the DILI group. In Cox proportional hazard analysis, DILI was used as an independent variable. Explanatory factors were selected using univariate analysis with $p < 0.05$ because factors influencing carbapenem-induced liver injury have not been clarified in previous studies. Moreover, our previous study revealed that the ALBI score might contribute to micafungin-induced liver injury [20]; thus, the ALBI score was chosen as an explanatory factor. All statistical analyses were performed using SPSS version 27 (IBM Japan, Tokyo, Japan), and the statistical significance was set at $p < 0.05$.

Ethics approval

This study was performed in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by Mie Chuo Medical Center (approval ref. MCERB-202233). Because this study had a retrospective case-control design, consent was obtained from each patient using an opt-out document posted on the website of the respective hospitals.

3. Results

3.1. Comparison of DILI rate between MEPM and DRPM

The number of patients treated with MEPM and DRPM during the drug observation period was 741 and 743, respectively (Fig. 1). Based on the exclusion criteria, 310 patients treated with MEPM (Figs. 1A) and 320 patients treated with DRPM (Fig. 1B) were included in this study, and the target number of patients for each drug was determined. There was a higher percentage of males in the DRPM group than in the MEPM group (Table 1). However, there were no significant differences between the groups in terms of age, body mass index, and laboratory data. The assessment of DILI using MEPM or DRPM is shown in a Kaplan–Meier curve (Fig. 2). The DILI rates were 22.9% (71/310) in the MEPM group and 17.5% (56/320) in the DRPM group. However, there were no significant differences in the DILI rate (95% CI: 0.710–1.017, $p = 0.119$). The expression pattern of MEPM or DRPM-induced liver injury showed that the incidence of hepatocellular-type (MEPM: 75%, 53/71 patients, DRPM: 82%, 46/56 patients) was the highest, followed by that of cholestatic-type injury (MEPM: 14%, 10/71 patients, DRPM: 16%, 9/56 patients) and mixed type (MEPM: 11%, 8/71 patients, DRPM: 2%, 1/56 patients).

3.2. Risk factors for carbapenem-induced liver injury

The MEPM or DRPM-induced liver injury baseline patient data and characteristics are listed in Table 2 and Table 3, respectively. In MEPM, univariate analysis showed that ALT ($p = 0.005$) and concomitant use of acetaminophen ($p = 0.011$) may contribute to the development of DILI. The cutoff values of MEPM-induced liver injury for age, ALT, AST, and ALBI score were 85 years old (sensitivity: 0.324, specificity: 0.724, AUC: 0.491), 18 IU/L (sensitivity: 0.662, specificity: 0.565, AUC: 0.609), 18 IU/L (sensitivity: 0.817, specificity: 0.314, AUC: 0.565), and −1.1 (sensitivity: 0.282, specificity: 0.787, AUC: 0.518), respectively. Table 3 shows that the ALT ($p < 0.001$), AST ($p < 0.001$), and ALBI score ($p = 0.046$) may be associated with the development of DRPM-induced liver injury. Further, in DRPM, the cutoff values of age, ALT, AST, and ALBI score were 85 years old (sensitivity: 0.174, specificity: 0.942, AUC: 0.482), 18 IU/L (sensitivity: 0.436, specificity: 0.686, AUC: 0.666), 23 IU/L (sensitivity: 0.443, specificity: 0.711, AUC: 0.669), and −1.4 (sensitivity: 0.299, specificity: 0.764, AUC: 0.590), respectively. In the COX proportional hazard analysis, the adjusted hazard ratio for MEPM-induced liver injury in patients with concomitant use of acetaminophen was 3.41 (95% CI: 1.448–8.028, $p = 0.005$) and for those with ALT was 2.14 (95% CI: 1.211–3.770, $p = 0.009$) (Table 4). Moreover, the adjusted hazard ratio for DRPM-induced liver injury in patients with concomitant use of acetaminophen was 2.92 (95% CI: 1.021–8.328, $p = 0.046$), ALT was 2.90 (95% CI: 1.438–5.841, $p = 0.003$), and ALBI score was 1.88 (95% CI: 1.087–3.251, $p = 0.024$) (Table 4).

3.3. DT analysis

According to the Cox proportional hazard analysis, ALT, ALBI score, and concomitant use of acetaminophen were selected as independent factors for DT analysis (Table 4). The DT model of MEPM could not be constructed because the stop criteria of the branches were child nodes ≤10 subjects. On the other hand, the tree in DRPM was divided into patients with ALT and ALBI score. As shown in the flowchart (Fig. 3), the tree was divided into two levels, and three groups were extracted. An ALT >22 IU/L was most associated with DILI, followed by a divergence in the ALBI score > −1.87. The development of DILI was lowest (12.6%,

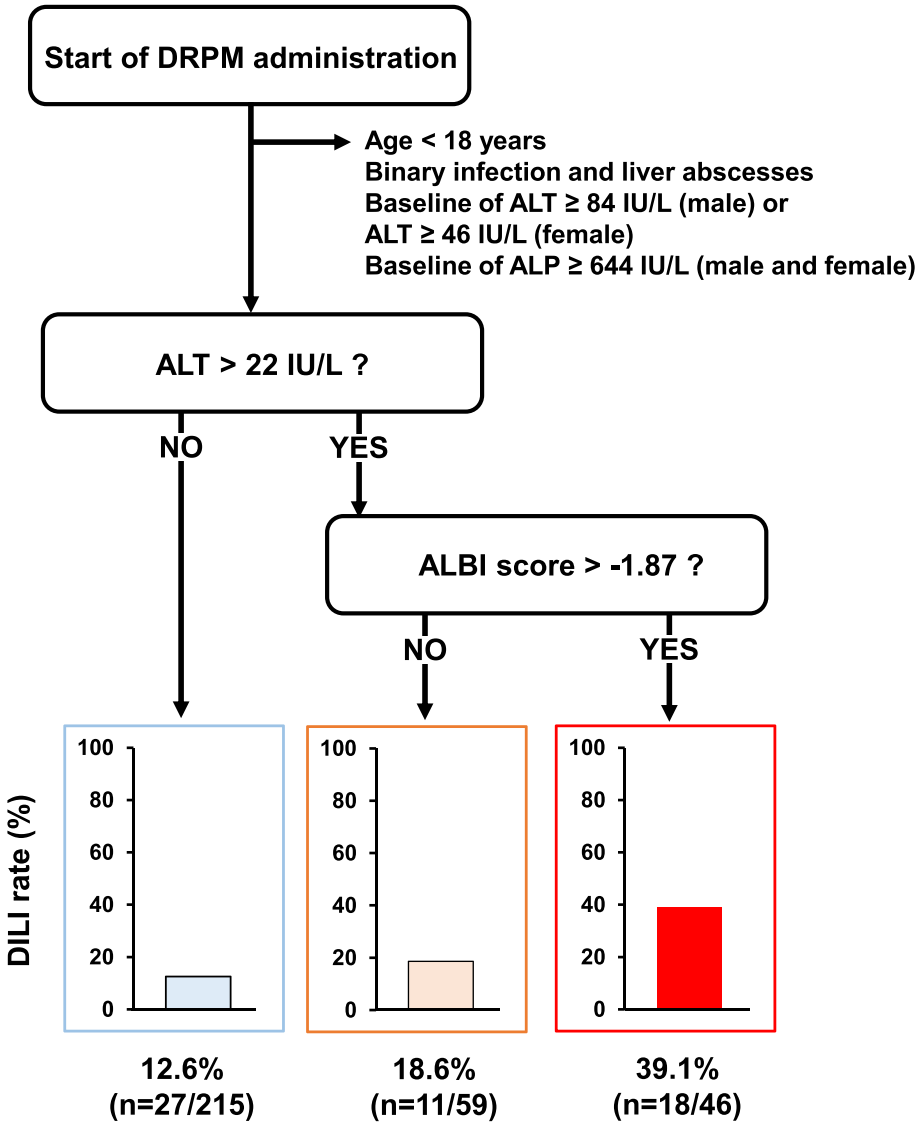

Fig. 3. DT model for predicting DILI in patients treated with DRPM.
ALBI, albumin-bilirubin; ALT, alanine aminotransferase.

27/215) in patients with ALT ≤22 IU/L, whereas that in patients with ALT >22 IU/L and ALBI score > -1.87 was 39.1% (18/46).

3.4. Validation of the DT model

The accuracy rate for the DT analyses in DRPM was 82.5%. The misclassification risk of the flowchart constructed using the CHAID algorithm was estimated to be 17.5 ± 2.1%.

4. Discussion

Currently, the risk factors for carbapenem-induced liver injury remain unclear. However, in quinolone-induced liver injury, a 2.19-fold higher risk has been reported in males [21]. Therefore, herein, we attempted to adjust for sex by propensity score matching; however, the AUC for the propensity score values was 0.523 (data not shown), suggesting a minimal need for matching. Because the expression rate of DILI in DRPM was suggested to be non-inferior to that of MEPM, it was considered necessary to evaluate risk factors for carbapenem-induced liver injury from both MEPM and DRPM.

Furthermore, no difference in daily dose was observed between the DILI and non-DILI groups (Table 2, Tables 3 and 4), suggesting that carbapenem-induced liver injury may occur in a dose-independent manner. Immunological pathways, including human leukocyte antigen allele HLA-B*57:01 [22], flucloxacillin-specific T cells [23], and flucloxacillin-specific CD8 + T cells [24], may be potentially relevant to liver injury by flucloxacillin, which has a beta-lactam ring like carbapenem. Moreover, DILI was reported even when ceftriaxone was administered to patients with a history of MEPM-induced liver injury [25]. Accordingly, liver injury from MEPM and DRPM may be influenced by the patient's medical background.

Before DT analysis, Cox proportional hazard analysis revealed three independent predictors of MEPM or DRPM-induced liver injury: ALT, ALBI score, and concomitant use of acetaminophen. The elevation of ALT might be positively associated with DILI, which is consistent with previous studies on anti-tuberculosis DILI [26,27]. Although AST levels were similar to changes in ALT levels, AST was not selected as an independent factor in Cox proportional hazard analysis (Table 4). The expression pattern of AST was not tissue-specific, such as in skeletal muscle, heart muscle, and liver [28], suggesting that ALT may be more specific than AST for predicting carbapenem-induced liver injury. However, the cutoff value of ALT level (>22 IU/L) was within the normal range, as in previous reports [26,27]. In animal experiments, positive correlations existed between ALT levels and hepatocyte necrosis

[29]. Oxidative stress is associated with necrosis, and Kupffer cells eliminate oxidative stress in the liver [30]. Jiang et al. [26] speculated that the function and number of Kupffer cells might be involved in the expression of DILI with ALT levels within the normal range, but the details surrounding this phenomenon are unknown. Therefore, the mechanism of association between carbapenem-induced liver injury and ALT baseline level needs further investigation. The increase in ALBI score is involved in decreased hepatic reserve [18]. Asai et al. reported that ALBI score ≥ -1.29 was a risk factor for micafungin-induced liver injury [20], and this phenomenon was consistent with the present study. Although differences in the mechanisms regarding the association of decreased hepatic reserve with DILI from MEPM and DRPM are unclear, these results suggest that hepatic reserve should be taken into account when assessing the risk of DILI from DRPM.

Because some cases of liver injury caused by MEPM improved following its discontinuation [25,31], the risk assessment of DILI in each individual before the introduction of DRPM is essential for effective and safe use. Herein, we successfully constructed a predictive tool for DRPM-induced liver injury. According to the flowchart (Fig. 3), the incidence of DILI may be relatively high if DRPM is introduced in patients with ALT >22 IU/L and ALBI scores > -1.87. In contrast, patients with lower baseline ALT levels ($\leq$22 IU/L) are likely to be at a lower risk for DILI. The DILI defined in this study was $>2 \times$ the ULN of ALT/ALP, a relatively mild condition. This flowchart does not require avoidance of DRPM administration, despite a classification of high-risk. Therefore, we recommend that the risk of DILI be assessed using this flowchart and that frequent liver function monitoring should be considered to avoid severe DILI. This DT analysis may be valid because its accuracy and misclassification were comparable to those reported in previous studies [12–14, 32].

This study has several limitations. First, because the study had a single-center observational design, the developed flowchart might lack scientific rigor or external validity. Moreover, since the imipenem/cilastatin regimen is not used in our hospital, the risk for DILI caused by this therapy was not elucidated. Second, liver injury may be caused by multiple organ failure because the sequential organ failure assessment score was not evaluated for all patients at Mie Chuo Medical Center. Third, there may have been an inadequate correction of alcohol intake of patients. Considering these limitations, a multicenter trial may be required to develop a more generalized model.

In conclusion, our findings show that the DILI rate might not be significantly different between MEPM and DRPM. We successfully created a prediction flowchart for determining DRPM-induced liver injury. Since ALT and ALBI score are evaluated in clinical settings, the model is straightforward and potentially valuable for medical staff in assessing DILI and the initial administration of DRPM during sepsis.

Authorship

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data: Yuki Asai and Hayahide Ooi.
2. Drafting the article or revising it critically for important intellectual content: Yuki Asai, Hayahide Ooi, Yoshiharu Sato
3. Final approval of the version to be submitted: Yuki Asai, Hayahide Ooi, Yoshiharu Sato

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Declaration of interest

The authors declare no competing interests.

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