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MAJOR ARTICLE

Identification of Risk Factors for Daptomycin-Associated Creatine Phosphokinase Elevation and Development of a Risk Prediction Model for Incidence Probability

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Background. In this study, we investigated the risk factors for daptomycin-associated creatine phosphokinase (CPK) elevation and established a risk score for CPK elevation.

Methods. Patients who received daptomycin at our hospital were classified into the non-elevated or elevated CPK group based on their peak CPK levels during daptomycin therapy. Univariable and multivariable analyses were performed, and a risk score and prediction model for the incidence probability of CPK elevation were calculated based on logistic regression analysis.

Results. The non-elevated and elevated CPK groups included 181 and 17 patients, respectively. Logistic regression analysis revealed that concomitant statin use (odds ratio [OR], 4.45 [95% confidence interval {CI}, 1.40–14.47]; risk score 4), concomitant antihistamine use (OR, 5.66 [95% CI, 1.58–20.75]; risk score 4), and trough concentration (C_{min}) between 20 and <30 μg/mL (OR, 14.48 [95% CI, 2.90–87.13]; risk score 5) and ≥30.0 μg/mL (OR, 24.64 [95% CI, 3.21–204.53]; risk score 5) were risk factors for daptomycin-associated CPK elevation. The predicted incidence probabilities of CPK elevation were <10% (low risk), 10%–<25% (moderate risk), and ≥25% (high risk) with total risk scores of ≤4, 5–6, and ≥8, respectively. The risk prediction model exhibited a good fit (area under the receiver operating characteristic curve, 0.85 [95% CI, .74–.95]).

Conclusions. These results suggested that concomitant use of statins with antihistamines and C_{min} ≥20 μg/mL were risk factors for daptomycin-associated CPK elevation. Our prediction model might aid in reducing the incidence of daptomycin-associated CPK elevation.

Keywords. creatine phosphokinase; daptomycin; incidence prediction model; risk factor; risk score; trough concentration.

Daptomycin, a lipopeptide drug targeting methicillin-resistant *Staphylococcus aureus*, is used to treat skin and soft tissue infections, bacteremia, infective endocarditis, and osteomyelitis. The standard doses of daptomycin are 4 and 6 mg/kg every 24 hours, but in recent years, high doses (≥8 mg/kg) have been used in patients with complicated bacteremia, infective endocarditis, and osteomyelitis [1].

A typical adverse reaction of daptomycin is creatine phosphokinase (CPK) elevation, which occurred in 6.7% of patients in a phase 3 study [2]. This adverse reaction is dose-dependent, and Lai et al reported a significantly higher incidence of CPK elevation at doses of ≥8 mg/kg than at <8 mg/kg [3]. Bhavnani et al verified the breakpoint, finding that the trough concentrations of total daptomycin (C_{min}) >24.3 μg/mL were linked to increased CPK elevation risks [4]. Yamada et al examined the breakpoint of CPK elevation in 20 patients and observed that the risk was increased when C_{min} >19.5 μg/mL [5]. In addition to trough concentrations, studies have identified the concomitant presence of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor (statins) use and antihistamine drug use, body mass index (BMI) >30 kg/m^2, African American ethnicity, and history of rhabdomyolysis as risk factors for daptomycin-associated CPK elevation [6–8]. The package insert of daptomycin recommends that patients with asymptomatic musculoskeletal toxicity should be observed if CPK levels increase to 1000–2000 IU/L during treatment and treatment should be discontinued in those with symptomatic musculoskeletal toxicity [9]. Moreover, although it has been reported that CPK levels normalize 1 day after discontinuing daptomycin treatment [10], its discontinuation can also affect the persistence of methicillin-resistant *Staphylococcus aureus* bacteremia, which causes treatment failure. Therefore, it is important to comprehensively evaluate factors that influence the elevation of

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CPK to >1000 IU/L to predict the probability of daptomycin-associated CPK elevation. However, to our knowledge, no reports simultaneously evaluated C_{min} and other risk factors, identified the risk factors for daptomycin-associated CPK elevation, or examined the probability of CPK elevation based on a risk score.

This study aimed to identify the risk factors for daptomycin-associated CPK elevation and develop a risk score and prediction model for its incidence probability.

METHODS

Patients and Study Procedures

This study was a single-center retrospective observational study conducted in a 300-bed secondary-care hospital in Japan. Patients who received daptomycin for >5 days at Yokohama General Hospital between 1 January 2017 and 15 May 2021 and who underwent CPK measurements before and during daptomycin administration were eligible for inclusion. Patients who discontinued treatment owing to daptomycin-associated CPK elevation within 4 days of treatment initiation were also eligible for inclusion. Patients who received daptomycin for <5 days and those whose CPK levels were not measured before or during daptomycin administration were excluded. Patients with serum creatinine levels <0.4 mg/dL were also excluded because of the risk of overestimating creatinine clearance (CrCl) using the Cockcroft-Gault formula. According to the peak CPK levels observed during daptomycin treatment, patients were categorized into the non-elevated (a peak CPK level of ≤1000 IU/L) and elevated (a peak CPK level of >1000 IU/L) CPK groups. CPK elevation was defined based on modifying a previous study [4] that defined an abnormally high CPK level as a peak CPK level of >1000 IU/L during daptomycin therapy. Patients with abnormal CPK levels before daptomycin administration were classified into the elevated CPK group when their CPK levels increased to >1000 IU/L from baseline during daptomycin therapy. Daptomycin-associated CPK elevation was diagnosed as an adverse reaction to the drug by a physician and antimicrobial stewardship team consulted by a physician.

Evaluation of Estimated C_{min}

In this study, estimated C_{min} was compared between the non-elevated and elevated CPK groups. C_{min} was calculated based on the volume of distribution and clearance using Phoenix WinNonlin software as described previously [11, 12] (Supplementary Table 1).

Identification of Risk Factors Associated With CPK Elevation

Age, sex, renal function, BMI, body temperature, laboratory values, current disease, medical history, concomitant medications, causative organisms, daptomycin dose, and estimated C_{min} were compared between the groups to identify risk factors for daptomycin-associated CPK elevation via univariable and multivariable analyses. Renal function was assessed via CrCl determined using the Cockcroft-Gault formula.

Evaluation of the Rate of CPK Elevation According to the Combination of Risk Factors

In multivariable analysis, the rate of daptomycin-associated CPK elevation for each identified risk factor was assessed by C_{min} (using a cutoff of 24.3 μg/mL as a risk factor for CPK >1000 IU/L based on a previous study [4]). In particular, patients were classified based on the presence of relevant risk factors, excluding C_{min}, in multivariable analysis and validated these factors, including the timing of daptomycin-associated CPK elevation, using the Kaplan-Meier method. In addition, C_{min} was evaluated according to each risk factor and the cutoff C_{min} to predict CPK elevation in patients without risk factors was estimated by excluding C_{min} using the receiver operating characteristic (ROC) curve analysis.

Statistical Analysis

Continuous variables were described using mean ± standard deviation, and categorical variables were described as number (percentage). The statistical comparisons of continuous variables between the groups were performed using independent-samples Student *t* test or Tukey multiple comparison test to account for normality. Fisher exact test was used for categorical variables as appropriate. Multivariable analysis was performed using the binomial logistic regression analysis of significant factors with a *P* value of <.10 in univariable analysis. If the independent variables were correlated with an *r* value of >0.60, the risk factors with low *P* values were incorporated to account for multicollinearity. The risk score and prediction model for the probability of daptomycin-associated CPK elevation were created via binomial logistic regression analysis based on the results of multivariable analysis and C_{min} of daptomycin. We assigned C_{min} as <10, 10–<20, 20–<30, and ≥30 μg/mL. Additionally, a risk score was assigned for each risk factor, based on the β coefficients of binomial logistic regression, in accordance with the methods used in previous studies [13–15]: risk score of 1, β = .01–.20; risk score of 2, β = .21–.80; risk score of 3, β = .81–1.20; risk score of 4, β = 1.21–2.20; and risk score of 5, β >2.20. The reference category was assigned a risk score of 0 for each variable. The predicted probability of daptomycin-associated CPK elevation was calculated using logistic regression model (risk prediction model) and categorized by the probability of daptomycin-associated CPK elevation as follows based on previous studies [16, 17]: low-risk (<10%), intermediate-risk (10%–25%), and high-risk (>25%) groups. The risk prediction model for the probability of daptomycin-associated CPK elevation was validated using ROC curve analysis to evaluate areas under the ROC curves (AUCs). The validity of the risk prediction model for the probability of daptomycin-associated CPK

elevation was also evaluated by the Hosmer-Lemeshow test, and the predicted and observed estimates of daptomycin-associated CPK elevation were compared using a calibration plot. The bootstraps of 1000 replicates were set, and calibration curves were calculated via regression analysis. The Kaplan-Meier method and the log-rank test were used to evaluate the time of onset of daptomycin-associated CPK elevation in the presence or absence of the most relevant risk factors. A P value of <.05 denoted statistical significance. Bonferroni correction was used for pairwise comparisons among 3 or more groups. Statistical analysis was performed using the Ekuseru-Toukei 2015 (Social Survey Research Information) and R (version 4.0.2) software packages.

RESULTS

Patient Characteristics and Evaluation of Estimated C_{min}

In total, 295 patients received daptomycin during the study period, and 198 patients satisfied the inclusion criteria. Of the 198 patients, 181 (91.4%) and 17 (8.6%) were categorized into the non-elevated and elevated CPK groups, respectively (Supplementary Figure 1). The mean patient ages were 76.3 ± 13.2 and 70.1 ± 10.7 years in the non-elevated and elevated CPK groups, respectively (P = .04). The mean CrCl values in the non-elevated and elevated CPK groups were 25.8 ± 22.5 and 43.9 ± 30.0 mL/minute, respectively (P = .005). The mean daptomycin doses and the mean peak CPK levels in the non-elevated and elevated CPK groups were 6.1 ± 2.3 and 6.4 ± 1.9 mg/kg/day, respectively (P = .90), and 73 IU/L (interquartile range [IQR], 39–183 IU/L) and 1775 IU/L (IQR, 1882–3582 IU/L), respectively.

C_{min} was significantly higher in the elevated CPK group than in the non-elevated CPK group (19.7 ± 9.9 μg/mL vs 11.5 ± 7.0 μg/mL, P < .001; Supplementary Figure 2).

Identification of Risk Factors Associated With CPK Elevation

The results of univariable and multivariable analyses in both groups for the evaluation of risk factors of CPK elevation are presented in Table 1. Univariable analysis illustrated that the elevated CPK group included higher proportions of patients with CrCl of <50 mL/minute and surgical site infection than the non-elevated CPK group. The rates of CrCl of <30 mL/minute, acute renal injury, dyslipidemia, hemodialysis (including continuous hemodiafiltration), and concomitant drug use including statins, antihistamine, sedative, catecholamine use, and C_{min} ≥24.3 μg/mL were significantly higher in the elevated CPK group than in the non-elevated CPK group. Multivariable analysis identified concomitant statin use (odds ratio [OR], 4.24 [95% confidence interval {CI}, 1.09–16.52]; P = .04) and concomitant antihistamine use (OR, 5.13 [95% CI, 1.22–21.62]; P = .03) as significant risk factors for CPK elevation and C_{min} ≥24.3 μg/mL (OR, 6.12 [95% CI, .97–38.53]; P = .05) as an affecting factor for CPK elevation, which was not statistically significant.

Evaluation of the Rate of CPK Elevation Based on Combinations of Risk Factors

Supplementary Tables 2 and 3 present the risk of daptomycin-associated CPK elevation according to the concomitant use of statins and antihistamines. Both statin and antihistamine drug use was associated with daptomycin-associated CPK elevation, and patients who used both statins and antihistamine drugs concomitantly with daptomycin tended to have a higher incidence of CPK elevation.

Analysis of the cumulative incidence of daptomycin-associated CPK elevation in the concomitant use of statin plus antihistamine drug group (n = 6), statin group (n = 33), antihistamine drug group (n = 27), and group without risk factors (nonconcomitant use of risk factor drug group, n = 132) revealed that the concomitant statin plus antihistamine drug group had a significantly earlier onset of CPK elevation than the nonconcomitant use of risk factor drug group (P < .001; Figure 1). There was no significant difference in C_{min} among the 4 groups (Supplementary Figure 3). The cutoff of C_{min} for predicting the risk of daptomycin-associated CPK elevation in the nonconcomitant use of risk factor drug group based on ROC curve was 22.4 μg/mL (P < .001; Supplementary Figure 4).

Development of a Predictive Risk Model for the Probability of CPK Elevation and Verification of Its Accuracy

Logistic regression analysis based on the use of statins, antihistamine, and daptomycin, and C_{min} is shown in Table 2. The risk scores were 4, 4, 0, 2, 5, and 5 based on the β coefficient of the statins; antihistamine drugs; and C_{min} of <10, 10–<20, 20–<30, and ≥30 μg/mL, respectively. Based on the multiple logistic regression model, a risk prediction model for daptomycin-associated CPK elevation was constructed as follows:

Logit $(P) = -4.33 + 1.49 \times$ statins $+ 1.73 \times$ antihistamine drugs + β (according to C_{min} category) (1), where statins, yes = 1, no = 0; antihistamine drugs, yes = 1, no = 0.

The probability of developing CPK elevation based on risk scores with the predicted and observed sets is shown in Figure 2. A risk score of 0–4 indicated low risk (incidence of CPK elevation, <10%), a risk score of 5–6 indicated intermediate risk (incidence of CPK elevation, between 10% and <25%), and a risk score of ≥8 indicated high risk (incidence of CPK elevation, ≥25%).

The verification of the accuracy of the probability risk prediction model for daptomycin-associated CPK elevation using ROC curves and calibration plots are shown in Figure 3 and Supplementary Figure 5. The AUCs were 0.85 (95% CI, .74–.95; P < .001), revealing that the probability risk model exhibited

Table 1. Univariate and Multivariate Analysis of Risk Factors for Creatine Phosphokinase Elevation

	Univariate Analysis			Multivawriate Analysis	
Characteristic	Elevated CPK Group (n = 17)	Non-elevated CPK Group (n = 181)	*P* Value	Adjusted OR (95% CI)	*P* Value
Patient characteristics					
Age, y, mean ± SD	70.1 ± 10.7	76.3 ± 13.2	.04	…	
Age ≥75 y	7 (41.2)	114 (63.0)	.12	…	
Sex, male	12 (70.6)	107 (59.1)	.44	…	
BMI ≤18.5 kg/m^2	5 (29.4)	53 (29.3)	1.00	…	
BMI ≥25.0 kg/m^2	5 (29.4)	38 (21.0)	.54	…	
BMI ≤30.0 kg/m^2	1 (5.9)	10 (5.5)	1.00	…	
CrCl, mL/min, mean ± SD	25.8 ± 22.5	43.9 ± 30.0	.01	…	
CrCl <50 mL/min	15 (88.2)	117 (64.6)	.06	2.97 (.43–20.35)	.27
CrCl <30 mL/min	11 (64.7)	69 (38.1)	.04	0.44 (.05–3.96)	.46
Body temperature, mean ± SD	37.5 ± 1.0	37.2 ± 0.8	.29	…	
Body temperature ≥37.5°C	8 (47.1)	63 (34.8)	.43	…	
Serum albumin ≤2.5 g/dL	11 (58.8)	103 (56.9)	.61	…	
BUN ≥25 mg/dL	10 (64.7)	76 (42.0)	.21	…	
Acute renal injury	7 (41.2)	27 (14.9)	.01	1.40 (.25–7.86)	.70
Current disease					
Catheter-related bloodstream infection	1 (5.9)	53 (29.3)	.05	0.27 (.02–3.27)	.30
Diabetic foot infection	6 (35.3)	47 (26.0)	.40	…	
Osteomyelitis	0 (0.0)	9 (5.0)	1.00	…	
Surgical site infection	4 (23.5)	15 (8.3)	.06	2.17 (.32–14.93)	.43
Infective endocarditis	1 (5.9)	3 (1.7)	.30	…	
Soft tissue infections of the skin	3 (17.6)	25 (13.8)	.71	…	
Febrile neutropenia	0 (0.0)	4 (2.2)	1.00	…	
Urinary tract infections	1 (5.9)	10 (5.5)	1.00	…	
Medical history					
Hypertension	9 (52.9)	87 (48.1)	.80	…	
Diabetes mellitus	9 (52.9)	74 (40.9)	.44	…	
Dyslipidemia	7 (41.2)	58 (32.0)	.43	…	
Hyperuricemia	0 (0.0)	14 (7.7)	.62	…	
Heart failure	3 (17.6)	29 (16.0)	.74	…	
Liver disease	0 (0.0)	7 (3.9)	1.00	…	
Chronic kidney disease	12 (70.6)	114 (63.0)	.61	…	
Dialysis (including continuous hemodiafiltration)	9 (52.9)	29 (16.0)	.001	2.93 (.41–20.72)	.28
Malignancy	0 (0.0)	17 (9.4)	.37	…	
Concomitant use					
Statins	8 (47.1)	31 (17.1)	.007	4.24 (1.09–16.52)	.04
Proton pump inhibitors	8 (47.1)	88 (48.6)	1.00	…	
Antiplatelet agents	8 (47.1)	51 (28.2)	.16	…	
Antihistamine agents	6 (35.3)	27 (14.9)	.04	5.13 (1.22–21.62)	.03
Biguanide agents	1 (5.9)	7 (3.9)	.52	…	
Pregabalin/mirogabalin	1 (5.9)	13 (7.2)	1.00	…	
Tramadol	1 (5.9)	15 (8.3)	1.00	…	
SSRI/SNRI	0 (0.0)	11 (6.1)	.60	…	
Antipsychotic drug	1 (5.9)	8 (4.4)	.56	…	
Benzodiazepines	2 (11.8)	26 (14.4)	1.00	…	
Opioid analgesics	2 (11.8)	3 (1.7)	.06	9.69 (.78–120.66)	.08
Beta blockers	4 (23.5)	21 (11.6)	.24	…	
Diuretics	4 (23.5)	34 (18.8)	.75	…	
Tolvaptan	2 (11.8)	15 (8.3)	.64	…	
Nalfurafine	1 (5.9)	7 (3.9)	.52	…	
Aldosterone blockers	2 (11.8)	15 (8.3)	.64	…	
Thrombomodulin	0 (0.0)	6 (3.3)	1.00	…	
Sedative agents	3 (17.6)	1 (0.6)	.002	6.67 (.14–325.85)	.34
Catecholamines	5 (29.4)	19 (10.5)	.04	1.28 (.15–10.70)	.82

Table 1. Continued

Characteristic	Univariate Analysis			Multivawriate Analysis	
	Elevated CPK Group (n = 17)	Non-elevated CPK Group (n = 181)	*P* Value	Adjusted OR (95% CI)	*P* Value
Pathogenic microorganism					
MRSA	8 (47.1)	57 (31.5)	.28	…	
MSSA	2 (11.8)	14 (7.7)	.63	…	
MRCNS	0 (0.0)	26 (14.4)	.14	…	
Streptococcus spp	1 (5.9)	14 (7.7)	1.00	…	
Enterococcus spp	3 (17.6)	16 (8.8)	.21	…	
Corynebacterium spp	0 (0.0)	20 (11.0)	.23	…	
Escherichia coli	2 (11.8)	13 (7.2)	.62	…	
Klebsiella spp	0 (0.0)	8 (4.4)	1.00	…	
Enterobacter spp	1 (5.9)	2 (1.1)	.24	…	
Citrobacter spp	0 (0.0)	3 (1.7)	1.00	…	
Pseudomonas aeruginosa	1 (5.9)	5 (2.8)	.42	…	
Candida spp	0 (0.0)	5 (2.8)	1.00	…	
Dose of administration/concentration					
Dose, mg/kg/day, mean ± SD	6.1 ± 2.3	6.4 ± 1.9	.90	…	
Dose >6 mg/kg	14 (82.4)	154 (85.1)	.73	…	
Dose >6 mg/kg/day	9 (52.9)	126 (69.6)	.18	…	
C_{min}, μg/mL, mean ± SD	19.7 ± 9.9	11.5 ± 7.0	<.001	…	
C_{min} ≥24.3 μg/mL	6 (35.3)	9 (5.0)	<.001	6.12 (.97–38.53)	.05

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; C_{min}, trough concentration of total daptomycin; CPK, creatine phosphokinase; CrCl, creatinine clearance (calculated using the Cockcroft-Gault formula); MRCNS, methicillin-sensitive coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SD, standard deviation; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

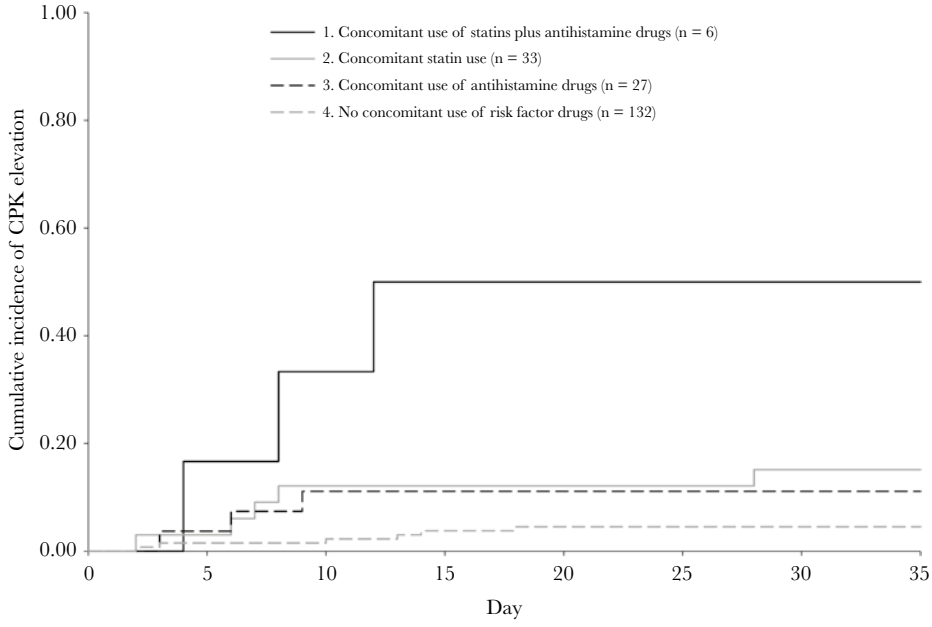

Figure 1. Incidence probability of daptomycin-associated creatine phosphokinase (CPK) elevation with and without concomitant use of risk factor medicines. Kaplan-Meier plots were classified into 4 groups based on concomitant medication as a risk factor for CPK elevation: (1) concomitant use of statins plus antihistamine drugs; (2) concomitant statin use (excluding concomitant of antihistamine drugs); (3) concomitant antihistamine drugs (excluding concomitant statin use); and (4) nonconcomitant use of risk factor group. *P* values using the log-rank test and Bonferroni correction (significant difference at $P < .0083$) are as follows: 1 vs 2, $P = .048$; 1 vs 3, $P = .03$; 1 vs 4, $P < .001$ ($P < .05$); 2 vs 3, $P = .66$; 2 vs 4, $P = .03$; 3 vs 4, $P = .17$.

Table 2. Multivariable Analysis of Risk Factors for Daptomycin-Associated Creatine Phosphokinase Elevation

Factors	β	SE	Wald χ^2	*P* Value	OR (95% CI)	Score
Intercept	−4.33	0.72	35.65	<.001	0.013 (.003–.045)	
Statins						
No	…	…	…		1.00 (reference)	0
Yes	1.49	0.59	6.45	.01	4.45 (1.40–14.47)	4
Antihistamine drugs						
No	…	…	…		1.00 (reference)	0
Yes	1.73	0.64	7.23	.01	5.66 (1.58–20.75)	4
C_{min}						
<10 μg/mL	…	…	…		1.00 (reference)	0
10–<20 μg/mL	0.76	0.76	1.01	.31	2.14 (.51–10.95)	2
20–<30 μg/mL	2.67	0.84	10.02	.002	14.48 (2.90–87.13)	5
≥30 μg/mL	3.20	1.03	9.63	.002	24.64 (3.21–204.53)	5

Abbreviations: β, partial regression coefficient; CI, confidence interval; C_{min}, trough concentration; OR, odds ratio; SE, standard error.

a good fit. The results of the Hosmer-Lemeshow test had a χ^2 statistic of 1.1762 ($P = .9969$). The calibration plot revealed that the mean absolute error of the observed and predicted probabilities was 0.033, and the plots of the probability of risk prediction model and the bootstrap method were similar (Supplementary Figure 5).

DISCUSSION

The incidence of daptomycin-associated CPK elevation ranged from 5% to 30% in studies defining CPK elevation as a CPK level >1–3-fold the upper limit of normal (ULN) [2, 3, 5, 18–25] and 3%–10% in studies defining CPK elevation as a CPK level >5-fold ULN or 1000 IU/L [4, 7, 8, 19, 21, 26, 27], in line with the current study. Several trials comprising higher daptomycin doses ≥8 mg or greater proportion of patients with renal impairment reported higher rates of patients with CPK elevation [3, 20, 22, 23]. In our study, the incidence of daptomycin-associated CPK elevation was 8.6%. The mean daptomycin dose of 6.1 mg/kg is the standard dose and the percentage of patients with CrCl <50 mL/minute was approximately 90% in the elevated CPK group, suggesting that daptomycin concentrations were at least 2-fold higher in the elevated CPK group than in those with normal renal function [11]. The Kaplan-Meier analysis revealed that the incidence of CPK elevation was approximately 5–10 days after daptomycin administration. Lehman et al evaluated the incidence of CPK elevation, defined as a CPK level of >1000 IU/L, using the Kaplan-Meier method and reported that approximately 80% of CPK elevations occurred within 1 week [7]. In our study, 70.6% patients in the CPK elevation group developed peak CPK levels within 10 days, suggesting that CPK elevation occurred within 10 days of daptomycin administration.

In our study, concomitant statin use and concomitant antihistamine drug use were identified as risk factors for daptomycin-associated CPK elevation. Moreover, our analyses suggest C_{min} ≥24.3 μg/mL as a potential risk factor, albeit without statistical

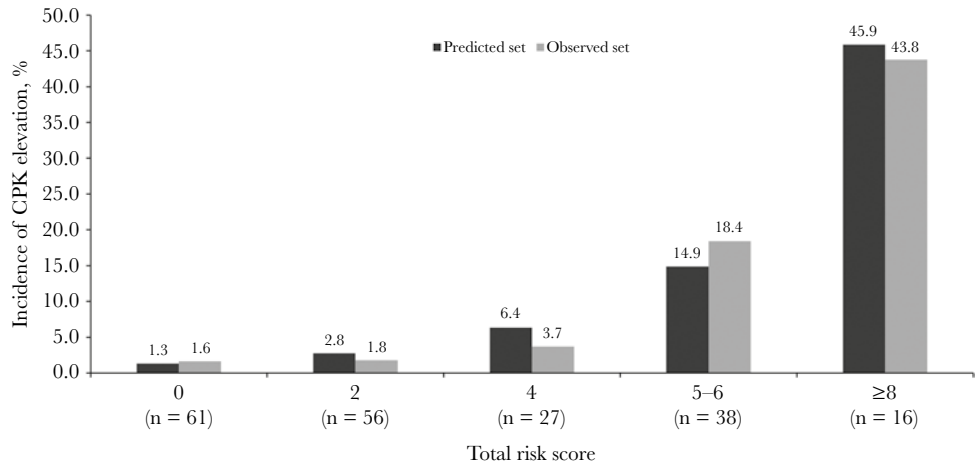

Figure 2. Incidence of daptomycin-associated creatine phosphokinase (CPK) elevation with increasing risk score in the predicted set and the observed set. The individual risk score was calculated using Table 2. The percentages of incidence of daptomycin-associated CPK in the prediction set are shown as the mean of each score.

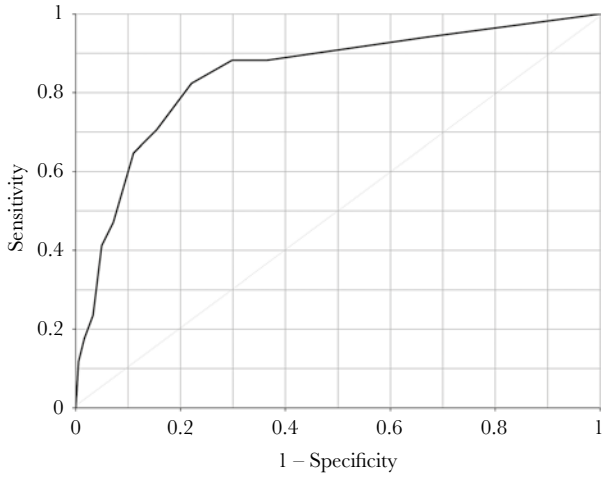

Figure 3. Validation for the discriminatory power of the predictive risk for the incidence of daptomycin-associated creatine phosphokinase elevation using the receiver operating characteristic curve. Area under the curve, 0.85 (95% confidence interval, .74–.95); $P < .001$; sensitivity, 82.4%; specificity, 77.9%.

significance ($P = .05$). Several studies identified high trough concentrations, concomitant statin use, concomitant antihistamine drug use, BMI >30 kg/m^2, African American ethnicity, and history of rhabdomyolysis as risk factors for CPK elevation during daptomycin treatment [6–8]. To our knowledge, no reports have evaluated the risk of daptomycin-associated CPK elevation in relation to the association between C_{min} and other risk factors. The cutoff of C_{min} for predicting the probability of CPK elevation was 22.4 μg/mL in patients with no risk factors related to concomitant drug use, similar to those of 19.5 and 24.3 μg/mL used in previous studies [4, 5]. Conversely, the concomitant use of daptomycin and statins or antihistamines was associated CPK elevation even in patients with C_{min} <24.3 μg/mL. Furthermore, patients who concomitantly used statins and antihistamines had significantly higher rates of daptomycin-associated CPK elevation than those who did not use these drugs and tended to have higher incidence of CPK elevation than those receiving each drug alone. Patients who used daptomycin with statins alone also tended to have higher CPK levels than those who did not use these drugs. These results suggest that the risk of concomitant use of statins alone or together with antihistamine drugs more strongly increases the risk of daptomycin-associated CPK elevation compared with C_{min}. Concomitant statin use was described as a risk factor for daptomycin-associated CPK elevation in the package insert of daptomycin [9]. Case–control studies by Dare et al and Imai et al confirmed the relationship between daptomycin and CPK elevation based on the CPK levels of >ULN and >1000 IU/L or >2000 IU/L, respectively [6, 28]. In several studies, statins were not associated with daptomycin-associated CPK elevation [7, 8, 25, 27, 29]. However, Bland et al [8], McConnell et al [25], and Berg et al [29] reported that the combination of daptomycin and statin treatment tended to increase the incidence of CPK elevation, defined as CPK levels >ULN, >3× ULN, and >1000 IU/L, respectively, by 2- to 5-fold compared with daptomycin alone, although the difference was not significant. These results indicated that combined statin therapy increases the risk of daptomycin-associated CPK elevation. Risk factors for myopathy associated with statins include elderly age, female sex, Asian and African American ethnicity, and cytochrome P450 inhibitor use [30]. In studies examining the risk factors for CPK elevation during combined daptomycin and statin treatment, African American ethnicity was cited as a risk factor, similar to other findings that African Americans have a higher risk of CPK elevation during statin treatment [7, 8]. Similar results were reported by Imai et al, who investigated Japanese patients [28]. In our study, 8 of the 17 patients with CPK elevation received statins concomitantly with daptomycin. Concomitant statin use may increase the risk of daptomycin-associated CPK elevation among Asians.

Antihistamine use was a risk factor for daptomycin-associated CPK elevation [6]. Although antihistamines have been reported to increase the risk of CPK elevation in cases of overdose [31], daptomycin-associated CPK elevation developed at a high incidence in patients who concomitantly used statins and antihistamines in our study. The statins and antihistamines associated with daptomycin-associated CPK elevation when in combination with atorvastatin and rosuvastatin were famotidine, fexofenadine, and hydroxyzine. Of these, atorvastatin and rosuvastatin are the substrates or inhibitors of organic anion transporting polypeptide [30], whereas fexofenadine and hydroxyzine are the substrates or inhibitors of organic anion transporting polypeptide [32, 33], which might affect the concentration of statins or their muscle symptoms.

In this study, the risk prediction model for the probability of daptomycin-associated CPK elevation exhibited a good fit based on AUC, sensitivity, and specificity using the ROC curve analysis. The calibration plots illustrated that the mean absolute error for measured and predicted probabilities was as low as 0.033, and the plots of the risk prediction model were similar to those of the bootstrap method. The evaluation of each risk score indicated that the observed incidence of CPK elevation was similar to the predicted incidence of CPK elevation based on the risk prediction model. The results therefore revealed that a risk score of ≤4 was associated with a low risk of CPK elevation and that a risk score of 5–6 was associated with an intermediate risk in patients on concomitant treatment with statins or antihistamines in whom CPK elevation might be avoidable by regular CPK monitoring. By contrast, a risk score of ≥8 indicated an approximately 50% probability of CPK elevation. Therefore, regardless of the daptomycin dose, we recommend that the concomitant use of daptomycin with statins plus antihistamines should be temporarily avoided in patients with a risk score of ≥8. Furthermore, we suggest that the concomitant use

of daptomycin with statins or antihistamines should be temporarily avoided during treatment with high-dose daptomycin in all patients and during treatment with normal-dose daptomycin in those with renal impairment. Although CPK elevation during daptomycin therapy is reversible, a CPK level of >1000 IU/L is a severe adverse reaction classified as grade ≥3 according to the Common Terminology Criteria for Adverse Events and a cause for discontinuing daptomycin treatment regardless of muscle symptoms. In our study, daptomycin was discontinued in 13 of 17 patients with CPK elevation (76.5%); the presence of muscle symptoms in these patients could not be evaluated. Stopping or pausing daptomycin, even for a single dose, or reducing the dose when CPK levels are elevated can affect treatment. It is important to assess the risk factors for daptomycin-associated CPK elevation at an early stage. Therefore, we believe that our risk score and prediction model, which permits the assessment of the risk of daptomycin-associated CPK elevation, is beneficial.

This study has several limitations. First, this study evaluated C_{min} as an estimated value, not as an actual measured value. Moreover, we calculated CrCl based on serum creatinine levels using the enzymatic method, which may have overestimated renal function compared with the Jaffe method. Patients undergoing dialysis may be affected by different dialysis conditions, dialyzers, and dialysis membranes. Additionally, the extracorporeal clearance of patients undergoing continuous hemodiafiltration was established at a rate of 1.2 L/hour in accordance with the Japanese standards, and daptomycin has a high protein-binding rate and is minimally removed by dialysis. However, the estimated C_{min}, which reflects the risk of daptomycin-associated CPK elevation, was similar to that reported in previous studies. Moreover, we evaluated C_{min} in 4 groups after developing the risk score and risk prediction model, which might have reduced its impact. Therefore, we consider the results of this study to be valid. Second, this study only evaluated C_{min} for the total drug concentration. The results of our previous study revealed that the unbound fraction rate was altered by the effects of serum albumin, blood urea nitrogen, and fasting blood glucose; thus, assessment of the total concentration may represent an over- or underestimation of C_{min} values [34]. Meanwhile, because this study evaluated the safety of daptomycin, the over- or underestimation of C_{min} was considered acceptable. Third, this was a retrospective study and could not evaluate the presence of muscle symptoms in patients with CPK elevation. Finally, our risk predictive model has not been validated in clinical practice.

In conclusion, our study suggested that concomitant statin use, concomitant antihistamine use, and C_{min} ≥24.3 μg/mL are relevant risk factors for daptomycin-associated CPK elevation. CPK elevation incidence was higher in patients who used daptomycin together with both statins and antihistamines than in those receiving daptomycin without the concomitant use of risk factor drug. Patients who used statins with antihistamines exhibited significantly earlier daptomycin-associated CPK elevation than those who did not receive concomitant drug therapy, even when C_{min} <24.3 μg/mL. When daptomycin is used in combination with statins and antihistamines, the risk of CPK elevation associated with these drugs must be considered. The risk score and prediction model developed in this study may aid in reducing the incidence of daptomycin-associated CPK elevation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. R. H., N. K., K. Tan., and K. M. organized and coordinated the study. M. S. was the chief investigator and data analyzer. N. H., T. K., K. Tak., F. N., S. K., J. Is., M. U., J. In., Y. E., and K. Tag. developed the study design and performed data analysis. All authors contributed to the writing of the final manuscript, approved its publication, and agreed to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Patient consent. This study was approved by the Ethics Review Committee of Yokohama General Hospital (approval number 202108). We applied the opt-out method to obtain consent on this study.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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