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Title	Factors affecting creatine phosphokinase elevation during daptomycin therapy using a combination of machine learning and conventional methods
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Citation	British Journal of Clinical Pharmacology, 88(3), 1211-1222 https://doi.org/10.1111/bcp.15063
Issue Date	2022-03-01
Doc URL	http://hdl.handle.net/2115/88238
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File Information	Br J Clin Pharmacol bcp.15063.pdf



1	Factors affecting creatine phosphokinase elevation during daptomycin therapy
2	using combination of machine learning and conventional methods
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- 29 **Running title**: Factors of myotoxicity by daptomycin

- 31 PI Statement: The authors confirm that the PI for this paper is Shungo Imai, who had
- 32 direct clinical responsibility for patients.
- 33 Acknowledgements: The authors thank the Health, Clinic, and Education Information
- 34 Evaluation Institute, for database development for the study.
- 35 **Data availability statement**: The data that support the findings of this study are available
- 36 from the corresponding author upon reasonable request.

37	Funding information:	This	research	was	funded	by	JSPS	KAKENHI	(grant	number
38	JP19K23791).									

39	Conflicts of Interest: All authors declared no competing interests for this work.
40	Word, Table, and Figure Count: Abstract: 240; Main Body: 3720; Tables: 5; Figure: 1
41	Author's contributions: SI conceived and designed the study YT, HK, YS, TM, and MS
42	assisted with the research design. SI, YT, and MS obtained the epidemiological data. SI
43	performed statistical analyses. YT, HK, YS, TM, and MS performed the statistical
44	analyses. SI wrote the manuscript. YT, HK, YS, TM, and MS contributed equally to this
45	study. All authors have read and approved the final version of the manuscript.
46	Ethical approval: This study was conducted in accordance with the guidelines for the
47	care of human studies. The institutional review board of the Faculty of Pharmaceutical
48	Sciences of Hokkaido University approved the study protocol (no. 2020-006).
49	
50	Keywords: daptomycin, creatine phosphokinase, statin, drug-drug interaction, electronic
51	medical record database.

94	what is already known about this subject:
55	• Several factors such as obesity and the African American ethnicity associate
56	with daptomycin (DAP)-induced creatine phosphokinase (CPK) elevation.
57	• The interaction between statins and DAP has been not well established.
58	
59	What this study adds:
60	• Hydrophobic statin use was a risk factor of DAP-induced CPK elevation, but
61	hydrophilic statin was not.
62	• Combination of hydrophobic statin use and high baseline CPK value were the
63	highest risk factor.
64	

54 What is already known about this subject:

65 Abstract

66 Aims

Musculoskeletal toxicity is a typical side effect of daptomycin (DAP). However, the risk
factors have not been well established. Here, we aimed to identify independent factors
affecting DAP-induced musculoskeletal toxicity using a combination of machine learning
and conventional statistical methods.

71 Methods

A population-based, retrospective, observational cohort study was conducted using the 72Japanese electronic medical record database. Patients who received DAP between 73October 2011 and December 2020 were enrolled. Two definitions of musculoskeletal 74toxicity were employed: (1) elevation of creatine phosphokinase (CPK) value more than 75twice from baseline and > 200 IU/L, and (2) > 1,000 IU/L. First, multiple logistic 76 regression analyses (a conventional statistical method) were performed to identify 77independent factors affecting CPK elevation. Then, decision tree (DT) analyses, a 78machine learning method, were performed to detect combinations of factors that change 79 CPK elevation risk. 80

81 Results

82 Of the 2,970 patients who received DAP, 706 were included. Elevation of CPK values >

83	200 IU/L and > 1,000 IU/L occurred in 83 (11.8%) and 17 (2.41%) patients, respectively.
84	In multiple logistic regression analysis, baseline CPK value and concomitant use of
85	hydrophobic statins were commonly extracted as independent factors affecting each CPK
86	elevation, but concomitant use of hydrophilic statins was not. In DT analysis, patients
87	who received hydrophobic statins and had high baseline CPK values were classified into
88	the high-risk group.
89	Conclusions
90	Our novel approach revealed new risk factors for CPK elevation. Our findings suggest
91	that high-risk patients require frequent CPK monitoring.

93 1 INTRODUCTION

Daptomycin (DAP) is a lipopeptide antibiotic used in patients with Gram-positive 94 Staphylococcus bacterial infections, such methicillin-resistant aureus.¹ 95as Musculoskeletal toxicity, including rhabdomyolysis and myopathy, is a typical side effect 96 of DAP and can cause life-threatening conditions.² Previous studies reported that 97 myopathy occurs in 2-14% of patients receiving DAP therapy.³⁻¹⁴ In addition, 98rhabdomyolysis occurs in approximately 5% of cases.^{15–17} Therefore, monitoring the 99 patients' creatine phosphokinase (CPK) values weekly during DAP therapy is 100 recommended.¹⁸⁻²¹ Several factors have been reported to be associated with DAP-induced 101 myopathy, such as obesity and the African American ethnicity.^{4,5,9–11,13,14,22,23} In particular, 102the interaction between statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) 103reductase inhibitors] and DAP has been examined in several studies, although some of 104 these studies could not show significant association.^{4,5,10,13,14,22,23} Furthermore, a recent 105106 review describes "published cohort studies do not demonstrate a statistically significant difference in the rate of CPK elevations or musculoskeletal toxicities".²⁴ Therefore, 107108further studies are required to elucidate this issue. In addition, previous studies were mainly conducted in the United States or European countries, but not in Asia.^{4,5,9-} 109^{11,13,14,22,23} Moreover, the difference in the risk of musculoskeletal toxicities between each 110

111	statin and DAP is unclear. For example, the strength of the effect of statins, such as low-
112	to high-intensity effects, may be relevant to this drug-drug interaction. ²⁵
113	Previously, we showed the usefulness of decision tree (DT) analysis, a typical machine
114	learning method, in identifying risk factors for adverse drug events. ²⁶ By employing DT
115	analysis, a flow chart-like risk prediction model can be constructed. In other words, users
116	can estimate combinations of factors that can increase or decrease the risk of events. ²⁷
117	Therefore, combining DT analysis with a conventional statistical method (i.e., logistic
118	regression analysis) can provide more useful information for predicting DAP-induced
119	musculoskeletal toxicity.
120	Accordingly, we performed a population-based, retrospective, observational cohort
121	study using a large Japanese electronic medical record (EMR) database for the following
122	three aims: (1) identifying independent factors affecting DAP-induced musculoskeletal
123	toxicity by using logistic regression analysis, (2) estimating the combinations of factors
124	that change the risk of events by using DT analysis, and (3) evaluating the difference in
125	risk of musculoskeletal toxicities between each combination of statins (including their

126 classification) and DAP.

129 2 METHODS

130 2.1 Data sources

We employed a Japanese large EMR database named the RWD database, which is 131maintained by the Health, Clinic, and Education Information Evaluation Institute (HCEI; 132Kyoto, Japan).^{28,29} This database consists of approximately 20 million individuals from 133approximately 160 medical institutions across Japan since 2000. The RWD database 134includes information about patient demographics, diagnoses, drug prescriptions, 135136 procedures, and laboratory results from outpatient and inpatient services. The data were 137automatically extracted from the EMRs at each medical institution. In addition, data were anonymised, and individual patient numbers were added to each patient. 138

139

140 2.2 Subjects

Among patients who were registered in the RWD database, we identified subjects who received DAP intravenously from October 2011 to December 2020. DAP was identified using the Anatomical Therapeutic Chemical system (ATC) code J01XX09. The exclusion criteria were: (1) duration of DAP therapy < 3 days, (2) baseline CPK values not measured, (3) baseline CPK value > 200 IU/L, (4) CPK values not measured during DAP therapy, (5) operation during DAP therapy, (6) age < 18 years, and (7) other missing values. We 147 evaluated baseline CPK values on the earliest possible day after the patients started DAP148 therapy (within 14 days at most).

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- 150

0 2.3 Definition of musculoskeletal toxicity and outcomes

Musculoskeletal toxicity was detected based on elevation of CPK value, as the 151presence or absence of symptoms could not be collected from the database. Thus, the 152following two definitions of CPK elevations were employed with some modifications 153from previous reports^{4,5,13,22}: (1) elevation of CPK values more than twice from baseline 154and > 200 IU/L (> 1 time the upper limit of normal [ULN]) at any point during DAP 155therapy, (2) elevation of CPK values more than twice from baseline and > 1,000 IU/L (> 1565 times the ULN) at any point during DAP therapy. In this study, we defined a new 157criterion of CPK elevation, that is, "elevation of CPK values more than twice from 158baseline." This is to prevent patients with high baseline CPK values from easily meeting 159160 the definition of CPK elevation. To evaluate CPK elevation > 1,000 IU/L, we only included patients with normal baseline CPK values (i.e., < 200 IU/L) based on our 161 inclusion criteria.^{13,22} This is because when patients with high baseline CPK values (i.e., 162163200-1,000 IU/L) are included, fluctuation of CPK values cannot be ignored as this may be caused by factors that cause increased baseline CPK values. 164

The following outcomes were evaluated: (1) factors affecting each CPK elevation 165during DAP therapy, (2) the combination of risk factors that changes the risk of each CPK 166 elevation by DT analysis, and (3) risk of CPK elevation between the combination of each 167168statin and DAP. Statins were classified based on their intensity according to the American College of Cardiology/American Heart Association (ACC/AHA) classification 169 170(low to high intensity) and Japanese traditional classification (strong statins: atorvastatin, rosuvastatin, and pitavastatin; standard statins: pravastatin, simvastatin, and fluvastatin), 171as well as based on their water affinity (hydrophobic statins: atorvastatin, pitavastatin, 172simvastatin, and fluvastatin; hydrophilic statins: rosuvastatin and pravastatin).^{25,30–32} We 173defined statins with octanol water partition coefficients < 1 as hydrophilic statins, and 174those with octanol water partition coefficients ≥ 1 as hydrophobic statins.³² Several 175176international treatment guidelines for the prevention of cardiovascular disease, including the ACC/AHA classification, classify statins based on their intensity rather than their 177water affinity.^{25,33–35} 178

179

180 2.4 Data collection

Patient demographics (age, sex, and body weight [BW]), comorbidities, type of
infection, baseline laboratory data (serum creatinine, creatinine clearance [CrCl], blood

urea nitrogen, total protein [TP], total bilirubin [T-bil], haemoglobin [Hb], albumin [Alb], 183aspartate aminotransferase, alanine aminotransferase, and C-reactive protein), baseline 184 concomitant medications including statins, and daptomycin data (dosing and duration) 185186 were evaluated. CPK values at the baseline and during DAP therapy were also extracted. The details of comorbidities, type of infections, and concomitant medications are shown 187 in Tables S1-S3. Age was calculated on the day of DAP therapy initiation. Baseline 188 laboratory data were extracted on the day of starting DAP therapy (within 14 days). CrCl 189was calculated using the Cockcroft-Gault equation.³⁶ CrCl was also classified as ≥ 30 or 190 < 30 mL/min.^{5,14,23} Although obesity, defined as body mass index (BMI) > 30, was 191reported as a risk factor for DAP-induced musculoskeletal toxicity^{5,22}, we could not assess 192193BMI because information on body height was not obtained in the RWD database. Thus, as an alternative index, "estimated over BW" was created in this study (male: 84.4 kg, 194female: 71.4 kg). This criterion was defined as a weight over a BMI of 30 at the average 195height of Japanese adults (male: 1.677 m, female: 1.543 m).³⁷ A DAP dose exceeding the 196 Japanese package insert recommendation¹⁸ was considered as "overdose." As we could 197not obtain data on current tobacco use, "brinkman index \geq 400" (cut-off value of 198199increasing risk of chronic obstructive pulmonary disease) at the timing of hospitalisation was used as an alternative index.³⁸ Alcohol dependence as a comorbidity was defined 200

according to its International Classification of Diseases, 10th Revision classification.
Further details are shown in Table S1.

203

204 2.5 Statistical analysis

First, the proportion of CPK elevations between patients receiving each statin 205206(including their classification) and DAP was compared using Pearson's chi-square or 207Fisher's exact test. Fisher's exact test was used if more than 20% of the cells had expected frequencies of less than 5 in a contingency table. Based on these results, the classification 208of statins to be applied in the univariate analysis was determined (e.g., ACC/AHA 209classification). Second, a multiple logistic regression analysis was performed. For this, 210all the potential risk factors that were extracted from the characteristics were applied 211212based on univariate analysis with a P value < 0.1. In the logistic regression analysis and DT analysis, the dependent variable was the presence or absence of elevation in CPK 213values. Third, DT analysis, a machine learning method, was performed using the chi-214squared automatic interaction detection (CHAID) algorithm.^{26,27} Users can determine the 215order of the splitting variables based on the strength of relation to outcome when using 216217the CHAID algorithm. The procedure of this algorithm was as follows: (1) establishment of multiple 2×2 contingency tables between dependent variables and each independent 218

219	variable, (2) selection of the most significant independent variable in a chi-squared test,
220	(3) branching of the tree, (4) repeat of steps 1 to 3, and finally (5) termination of branching
221	when the stop criteria are achieved. The stop criteria of the branches were as follows: (1)
222	once three levels of depth were achieved, (2) parent nodes ≤ 20 subjects and/or child
223	nodes ≤ 10 subjects, (3) or no significant differences among the independent variables.
224	Because the CHAID algorithm cannot adjust for confounding factors, the independent
225	variable was extracted from the risk factors identified in the multiple logistic regression
226	analysis.
227	DT analysis was conducted using the SPSS Decision Trees Version 24 (IBM, Tokyo,
228	Japan). The JMP 14 software (SAS Institute, Inc., Cary, NC, USA) was used for other
229	statistical analyses. P value < 0.05 was considered to indicate significant difference in all
230	statistical analyses.
231	
232	
233	3 RESULTS
234	3.1 Patients
235	Out of the 2,970 patients who received DAP therapy between October 2011 and
236	December 2020, 706 patients were included in this study (Figure). Elevation of CPK

values more than twice from baseline and > 200 IU/L as well as > 1,000 IU/L occurred in
83 (11.8%) and 17 (2.41%) patients, respectively. The median (interquartile range; IQR)
durations of CPK elevation after the initiation of DAP therapy were 4 (2-10) and 5 (2.515) days, respectively. The patient's ethnicity could not be identified, but it was
considered that almost all of them were Japanese.

242

243 3.2 Risk of CPK elevation during concomitant use of each statin

Atorvastatin, rosuvastatin, and pitavastatin were commonly used concomitantly during 244DAP therapy (Table 1). There were no patients treated with fluvastatin and high-intensity 245statins. The details of the ACC/AHA classification are shown in Table S4. The proportion 246of CPK elevation was significantly higher in patients treated with hydrophobic statins 247(atorvastatin, pitavastatin, and simvastatin) than in those treated with hydrophilic statins 248(rosuvastatin and pravastatin). No significant differences were observed in other 249contingency tables. Based on these results, we classified statins as hydrophobic and 250hydrophilic statins and applied them to the univariate analysis. 251Additionally, the number of patients among those who were excluded (n=2,264), with 252253statin, hydrophobic statin, and hydrophilic statin use were 440 (19.4%), 262 (11.6%) and 178 (7.86%), respectively. Similar proportions were observed among eligible patients. 254

256 3.3 Univariate analysis

Table 2 shows the demographics and comorbidities of patients. BW and "estimated over BW" were observed (P < 0.1) in the CPK elevation > 200 IU/L group. To avoid correlation between variables, estimated over BW was selected to a factor applying multivariate analysis because it is an alternative index for obese patients. Type 1 DM was observed (P < 0.1) in the CPK elevation > 1,000 IU/L group.

Although sepsis was most commonly observed, the type of infection could not be 262identified in many patients from this database (Table 3). Regarding baseline laboratory 263data, baseline CPK values tended to be higher in patients with CPK elevation than those 264without CPK elevation, in the CPK elevation > 200 IU/L, and CPK elevation > 1,000 265266IU/L groups (Table 3). Pneumonia, baseline CPK value, TP value, Hb value, and Alb value were extracted as factors using multivariate analysis (P < 0.1) in the CPK elevation 267> 200 IU/L group. Baseline CPK value, T-bil value, and Hb value were also selected in 268the CPK elevation > 1,000 IU/L group. 269Concomitant use of hydrophobic statins was extracted as a factor in the multivariate 270

- analysis (P < 0.1) in both groups, but concomitant use of hydrophilic statins was not
- 272 (Table 4). Durations of DAP were selected in the CPK elevation > 200 IU/L group.

274 3.4 Multiple logistic regression analysis

As shown in Table 5, baseline CPK value, concomitant use of hydrophobic statins, and duration of DAP therapy were extracted as independent factors affecting CPK elevation > 200 IU/L. Baseline CPK value, T-bil value, and concomitant use of hydrophobic statins were extracted as independent factors affecting CPK elevation > 1,000 IU/L.

279

280 3.5 DT analysis

Based on the results of multiple logistic regression analysis, independent variables affecting CPK elevation were applied to the DT analysis. For continuous variables, a cutoff value that had the strongest relationship to CPK elevation was automatically determined.

In a DT model predicting CPK elevation > 200 IU/L, concomitant use of hydrophobic statins was selected as the first splitting variable. The proportion of CPK elevation was 29.1% (23 out of 79 patients) for patients with concomitant use of hydrophobic statins and 9.57% (60 out of 627 patients) for those without. Among patients with concomitant use of hydrophobic statins, a baseline CPK value > 82 IU/L was extracted as the second splitting variable. In patients with a baseline CPK value > 82 IU/L, proportion of CPK elevation was 62.5% (15 out of 24 patients), and patients with a baseline CPK value ≤ 82 IU/L was 14.5% (8 out of 55 patients).

The same variables were extracted to construct a risk prediction model of CPK elevation > 1,000 IU/L. One difference was that the cut-off value of baseline CPK was 115 IU/L. The proportion of CPK elevation > 1,000 IU/L was 10.1% (8 out of 79 patients)

for patients with concomitant use of hydrophobic statins and 1.44% (9 out of 627 patients)

297 for those without. Among patients with concomitant use of hydrophobic statins, a baseline

298 CPK value > 115 IU/L was extracted as the second splitting variable. In patients with a

baseline CPK value > 115 IU/L, proportion of CPK elevation was 36.4% (4 out of 11

300 patients), and patients with a baseline CPK value ≤ 115 IU/L was 5.88% (4 out of 68 301 patients).

302

303 4 DISCUSSION

Considering that there are racial differences in the occurrence of adverse drug reactions³⁹, reports from diverse regions are important for the safe use of drugs. This is the first large-scale study in Asia to investigate the risk factors for CPK elevation during DAP therapy.

308 Dare *et al.* reported that the proportion of CPK values elevated to > 200 IU/L during

309	DAP therapy was 4.2% in academic medical centre in the U.S. ⁵ Although this value was
310	lower than our result of 11.8%, they postulated that the true incidence may be higher,
311	because the denominator of this proportion, the number of patients who received DAP,
312	may be inaccurate. Indeed, Bland et al. reported that 14 out of 220 (6.36%) patients had
313	CPK elevation > 1,000 IU/L ⁴ ; this value was higher than our result of 2.41%. Moreover,
314	two other studies conducted in the U.S., which also defined CPK elevation as $> 1,000$
315	IU/L, the proportions of events were 3.41% and 3.17%, respectively. ^{13,22} In a study by
316	Bland <i>et al.</i> , the proportions of study participants with BMI > 30 and African Americans,
317	which were extracted as risk factors of CPK elevation, were 57.3% and 27.2%,
318	respectively. ⁴ In this study, which targeted Japanese patients, 6.66% of patients were
319	classified to "estimated over BW (alternative index of BMI of 30)". The percentage of
320	Japanese adults with $BMI > 30$ was only 4.5% according to the official statistics of
321	Japan. ³⁷ In addition, our target patients appeared to have a shorter duration of DAP
322	therapy compared with those in the previous studies. ^{4,13,22} Thus, these factors might have
323	affected the proportions of CPK elevation; we could not simply conclude that the risk of
324	CPK elevation in the Japanese population is relatively lower than that in the U.S.
325	population.

326 Common to the two multivariate logistic regression analyses (i.e., elevations of CPK

327	value > 200 and 1,000 IU/L), concomitant use of hydrophobic statins was extracted as a
328	risk factor for CPK elevation, but that of hydrophilic statin was not. Musculoskeletal
329	toxicity of DAP is caused by a direct effect on the plasma membrane of the sarcolemma. ⁴⁰
330	Because statins interrupt HMG-CoA reductase, they cause intracellular depletion of the
331	intermediate metabolites and end products (i.e., cholesterol, dolichols, and ubiquinone)
332	downstream of the cholesterol synthesis pathway. ⁴¹ In particular, it has been known that
333	cholesterol deficiency of the sarcolemma adversely affects membrane physical properties,
334	integrity, and fluidity. ⁴¹ Thus, statins and DAP commonly affect the "sarcolemma", which
335	may cause a synergistic effect. Among the statins, hydrophobic statins are likely to induce
336	this interaction because they can easily permeate the cell membrane. ³¹ Indeed, Kobayashi
337	et al., using a prototypic embryonal rhabdomyosarcoma cell line, showed that the muscle
338	cytotoxicity of hydrophobic statins was clearly stronger than that of hydrophilic statins. ⁴²
339	Furthermore, they reported that the cholesterol-lowering effect of statins did not correlate
340	with their muscle cytotoxicity. ⁴² Clinically, hydrophobic statins are often used in patients
341	with CPK elevation during DAP therapy. ^{5,22} Considering these facts, it is reasonable to
342	conclude that hydrophobic statins have been identified as a new risk factor for CPK
343	elevation during DAP-therapy. However, although significant differences were not
344	observed, the proportions of CPK elevation tended to be higher with moderate-intensity

statins and strong statins than with other statins. In addition, there are no definite conclusions from clinical data, regarding the high or low myopathy risk between each statin alone, owing to the absence of randomised trials.⁴¹ Therefore, our observation needs to be verified through additional clinical and basic research.

High baseline CPK values were commonly extracted as independent factors affecting 349 CPK elevations in two multivariate logistic regression analyses, and their cut-off values 350were determined by DT analysis (82 and 115 IU/L in the prediction model of CPK 351elevation > 200 IU/L and 1,000 IU/L, respectively) in subgroups with concomitant use of 352hydrophobic statins. Because we excluded patients with baseline CPK > 200 IU/L, 353baseline high CPK value means high value "within the ULN." Dare et al. reported that 354355the risk of rhabdomyolysis decreases with age, and they considered this to be due to younger patients having more muscle mass (they did not evaluate baseline CPK value).⁵ 356 In addition, high CPK values are known to be related to high muscle mass.⁴³ In this study, 357high baseline CPK values within the ULN reflected high muscle mass, which may have 358been associated with CPK elevation. In addition, considering that CPK values fluctuate 359as a result of various factors⁴⁴, these unknown factors may have contributed. Despite this 360 361 limitation, our results showed the usefulness of baseline CPK values as a clinical indicator for predicting CPK elevation during DAP therapy. 362

363	Lehman et al. evaluated the cumulative incidence of CPK elevation during DAP
364	therapy. ²² In their Kaplan-Meier curve, the slope was steep until approximately 20 days
365	after the start of administration. ²² In addition, the median number of days from the
366	initiation of DAP therapy to the occurrence of CPK elevation ranged from 11.5 to 21
367	days. ^{4,5,14} Therefore, our result of "risk of CPK elevation > 200 IU/L increases with a
368	prolonged duration of DAP" is reasonable. In contrast, the median time to CPK elevation
369	in our study was 4-5 days, which is clearly shorter than that in these previous studies,
370	because the median duration of DAP administration (11 to 12 days) is approximately half
371	of that in these studies. ^{4,5,14}
372	By using DT analysis, which is a typical method of machine learning, we found that
373	patients with both concomitant use of hydrophobic statins and high baseline CPK values
374	were at the highest risk of CPK elevation during DAP therapy. The proportions of CPK
375	elevation in these patients were 62.5% and 36.4% in the prediction model of CPK
376	elevation > 200 IU/L and 1,000 IU/L, respectively, which are surprisingly high compared

groups" by evaluating the combination of multiple factors, which one strong point of this
machine learning method.^{26,27} A weak point of the CHAID algorithm, which was used in

377

with those in previous reports.^{3–17} In this way, DT analysis can identify "notable high-risk

380 the DT analysis, is that it cannot adjust for confounding factors. In addition, few patients

381	are eligible for analysis with increasing tree branching, which reduces the reliability of
382	results. As a countermeasure, we attempted a novel approach combining machine learning
383	and conventional statistical methods. That is, the independent variables applied in the DT
384	analysis were based on the factors extracted in the multiple logistic regression analysis.
385	Therefore, our findings are reasonable and suggest that frequent CPK monitoring is
386	required for these high-risk patients during DAP therapy.
387	Our study had several limitations. First, we could not detect symptoms of
388	musculoskeletal toxicity. A prospective, observational study is necessary because a
389	retrospective study may not have detected all symptoms. Second the causal relationship
390	between DAP and CPK elevation could not be assessed because CPK values fluctuate
391	due to many factors. ⁴⁴ However, this is also a common limitation in previous studies. ^{4,5,9–}
392	^{11,13,14,22,23} Third, the type of infection could not be identified in many patients, and
393	information on their pathogens was not evaluated owing to the absence of data. However,
394	in most previous studies, these factors did not seem to have a significant effect on CPK
395	elevation. ^{4,9–11,13,14,22,23} In the only report that showed a relationship between the type of
396	infection and CPK elevation, deep abscess was related to the occurrence of myopathy, but
397	not to rhabdomyolysis. ⁵ Fourth, owing to careful selection of eligible patients, most of
398	the 2,970 patients were excluded. In logistic regression analysis, the required number of

399	patients for an event group was 10-fold higher than the number of factors for the
400	analysis. ⁴⁵ That is, the number of patients was not sufficient in the CPK elevation $> 1,000$
401	IU/L group for multiple logistic regression analysis. However, we believe that there is
402	some validity for baseline CPK and hydrophobic statins, because they are common
403	factors in the CPK elevation > 200 IU/L group. Moreover, as for "T-bil", which was
404	extracted only in the CPK elevation > 1,000 IU/L group, its reliability was not high, and
405	it was unclear why it was extracted as a risk factor. Lastly, few patients used hydrophobic
406	statins concomitantly.

408 **5 CONCLUSION**

Through a combination of DT and logistic regression analyses, we revealed that patients who received concomitant use of hydrophobic statins and had high baseline CPK values were at the highest risk of CPK elevation during DAP therapy. Our findings require further verification but may eventually result in the revision of product information and clinical guidelines for infectious disease therapy.

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416 **References**

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579 Figure legends

- 580 Figure. Flowchart of patients included in this study
- 581 DAP, daptomycin; CPK, creatine phosphokinase; EMR, electronic medical record.

Tables

Description	n	CPK elevation > 200 U/L, n (%)	P value	CPK elevation > 1,000 U/L, n (%)	P value
Statins					
Atorvastatin	38	11 (28.9)	$0.093^{a)}$	3 (7.89)	0.059 ^{a)}
Rosuvastatin	38	4 (10.5)		0 (0)	
Pitavastatin	38	11 (28.9)		4 (10.5)	
Pravastatin	14	1 (7.14)		0 (0)	
Simvastatin	3	1 (33.3)		1 (33.3)	
Fluvastatin	0	N/A		N/A	
Japanese traditional classification					
Strong statin	114	26 (22.8)	0.300 ^{b)}	7 (6.14)	1.000 ^{a)}
Standard statin	17	2 (11.8)		1 (5.88)	
ACC/AHA classification					
Moderate intensity	78	21 (26.9)	0.060 ^{b)}	6 (7.69)	0.473 ^{a)}
Low intensity	53	7 (13.2)		2 (3.77)	
High intensity	0	N/A		N/A	
Hydrophobic and hydrophilic					
Hydrophobic statin	79	23 (29.1)	0.008* ^{b)}	8 (10.1)	0.022*a)
Hydrophilic statin	52	5 (9.62)		0 (0)	

Table 1. Proportions of CPK elevation during DAP therapy in patients with concomitant use of each statin

CPK, creatine phosphokinase; DAP, daptomycin; ACC/AHA, American College of Cardiology/American Heart Association. ^{a)}Fisher's exact test; ^{b)} Chi-square test; * P < 0.05, was considered significant. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000 IU/L, CPK

elevation more than twice from baseline, and > 1,000 IU/L.

		CPK elevation >	200 IU/L		CPK elevation > 1,000 IU/L				
Description	All patients $(n=706)$	Yes (n= 83)	No (n= 623)	OR	P value	Yes (n= 17)	No (n= 689)	OR	P value
Demographics									
Age (years), median (IQR)	74 (63–82)	72 (62–79)	74 (63–82)	0.992	0.270	74 (58–84)	74 (63–81.5)	0.999	0.943
Sex (male), n (%)	436 (61.8)	50 (60.2)	386 (62.0)	0.930	0.762	10 (58.8)	426 (61.8)	0.882	0.801
Sex (female), n (%)	270 (38.2)	33 (39.8)	237 (38.0)			7 (41.2)	263 (38.2)		
BW (kg), median (IQR)	56.4 (47.6–65.7)	59.5 (53.1-	56.0 (47.3-	1.017	0.031†	58.4 (53.9-	56.3 (47.5-	1.008	0.611
		66.4)	65.6)			63.7)	65.8)		
Estimated over BW, n (%)	47 (6.66)	10 (12.0)	37 (5.94)	2.170	0.040^{+}	1 (5.88)	46 (6.68)	0.874	0.897
Comorbidities									
CHF, n (%)	284 (40.2)	35 (42.2)	249 (40.0)	1.095	0.701	6 (35.3)	278 (40.3)	0.806	0.675
Cirrhosis, n (%)	26 (3.68)	3 (3.61)	23 (3.69)	0.978	0.972	0 (0)	26 (3.77)	0.000	0.990
CKD, n (%)	143 (20.3)	16 (19.3)	127 (20.4)	0.933	0.814	3 (17.6)	140 (20.3)	0.840	0.787
Dialysis, n (%)	74 (10.5)	7 (8.43)	67 (10.8)	0.764	0.518	1 (5.88)	73 (10.6)	0.527	0.538
COPD, n (%)	26 (3.68)	3 (3.61)	23 (3.69)	0.978	0.972	0 (0)	26 (3.77)	0.000	0.990
Type 1 DM, n (%)	6 (0.85)	2 (2.41)	4 (0.64)	3.821	0.125	1 (5.88)	5 (0.73)	8.550	0.056†
Type 2 DM, n (%)	222 (31.4)	30 (36.1)	192 (30.8)	1.271	0.327	5 (29.4)	217 (31.5)	0.906	0.855
HIV infection, n (%)	0 (0)	0 (0)	0 (0)	N/A	N/A	0 (0)	0 (0)	N/A	N/A
Cancer, n (%)	244 (34.6)	30 (36.1)	214 (34.3)	1.082	0.747	4 (23.5)	240 (34.8)	0.576	0.339
BMT, n (%)	0 (0)	0 (0)	0 (0)	N/A	N/A	0 (0)	0 (0)	N/A	N/A

Table 2. Univariate analysis affecting CPK elevation during DAP therapy according to demographics and comorbidities

Thyroid disease, n (%)	109 (15.4)	12 (14.5)	97 (15.6)	0.917	0.792	1 (5.88)	108 (15.7)	0.336	0.293
Paraplegia, n (%)	1 (0.14)	0 (0)	1 (0.16)	0.000	0.988	0 (0)	1 (0.15)	0.000	0.990
Brinkman index \geq 400, n (%)	147 (20.8)	13 (15.7)	134 (21.5)	0.678	0.220	1 (5.88)	146 (21.2)	0.232	0.159
Alcohol dependence, n (%)	1 (0.14)	0 (0)	1 (0.16)	0.000	0.988	0 (0)	1 (0.15)	0.000	0.990

CPK, creatine phosphokinase; DAP, daptomycin; IQR, interquartile range; OR, odds ratio; BW, body weight; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; BMT, bone marrow transplants. Brinkman index was determined using diagnosis procedure combination data at the time of hospitalisation and is an estimation of the lifetime tobacco consumption of each smoker. †P < 0.1, included in multiple logistic regression analysis. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000 IU/L.

Description	All patients (n=	CPK elevation > 2	00 U/L	CPK elevation > 1,000 U/L					
Description	706)	Yes (n= 83)	No (n= 623)	OR	P value	Yes (n= 17)	No (n= 689)	OR	P value
Type of infections									
BSI, n (%)	63 (8.92)	6 (7.23)	57 (9.15)	0.774	0.565	0 (0)	63 (9.14)	0.000	0.990
Sepsis, n (%)	291 (41.2)	28 (33.7)	263 (42.2)	0.697	0.142	6 (35.3)	285 (41.4)	0.773	0.616
Pneumonia, n (%)	52 (7.37)	2 (2.41)	50 (8.03)	0.283	0.084†	1 (5.88)	51 (7.40)	0.782	0.813
Osteomyelitis, n (%)	36 (5.10)	7 (8.43)	29 (4.65)	1.887	0.148	2 (11.8)	34 (4.93)	2.569	0.222
SSTI, n (%)	154 (21.8)	20 (24.1)	134 (21.5)	1.158	0.592	2 (11.8)	152 (22.1)	0.471	0.321
IE, n (%)	33 (4.67)	3 (3.61)	30 (4.82)	0.741	0.628	1 (5.88)	32 (4.64)	1.283	0.812
UTI or pyelonephritis, n (%)	113 (16.0)	15 (18.1)	98 (15.7)	1.182	0.585	4 (23.5)	109 (15.8)	1.637	0.396
PJI, n (%)	4 (0.57)	0 (0)	4 (0.64)	0.000	0.990	0 (0)	4 (0.58)	0.000	0.991
Peritonitis, n (%)	46 (6.52)	5 (6.02)	41 (6.58)	0.910	0.847	0 (0)	46 (6.68)	0.000	0.987
Spinal cord abscess, n (%)	2 (0.28)	1 (1.20)	1 (0.16)	7.585	0.153	0 (0)	2 (0.29)	0.000	0.990
Unknown, n (%)	237 (33.6)	34 (41.0)	203 (32.6)	1.436	0.130	8 (47.1)	229 (33.2)	1.786	0.239
Baseline laboratory data									
CPK (U/L), median (IQR)	40 (20-69)	58 (30–113)	38 (19–66)	1.010	< 0.001†	101 (40–152.5)	39 (20-68.5)	1.017	< 0.001†
Scr (mg/dL), median (IQR)	0.96 (0.65–2.12)	1.06 (0.68–2.34)	0.94 (0.64– 2.05)	0.999	0.922	0.90 (0.64–2.03)	0.96 (0.65–2.13)	0.963	0.588

Table 3. Univariate analysis affecting CPK elevation during DAP therapy according to types of infection and baseline laboratory data

CrCl (mL/min), median (IQR)	46.8 (21.0-79.8)	49.2 (22.1–75.6)	46.7 (21.0-	0.999	0.544	61.6 (23.9-82.9)	46.7 (20.9–79.8)	0.999	0.830
CrCl < 30 mL/min, n (%)	238 (33.7)	28 (33.7)	80.8) 210 (33.7)	1.001	0.996	6 (35.3)	232 (33.7)	1.074	0.889
BUN (mg/dL), median (IQR)	22.0 (13.8–39.1)	18.7 (13.2–44.0)	22.2 (13.8– 38.5)	0.997	0.632	15.6 (12.5–43.3)	22.0 (13.8–39.1)	0.997	0.800
TP (g/dL), median (IQR)	6.10 (5.40–6.70)	6.20 (5.70–6.90)	6.00 (5.40– 6.70)	1.258	0.062†	6.10 (5.55-6.60)	6.10 (5.40-6.70)	0.976	0.925
T-bil (mg/dL), median (IQR)	0.60 (0.40-1.00)	0.66 (0.42–1.20)	0.60 (0.40– 0.98)	1.057	0.396	0.80 (0.41-1.50)	0.60 (0.40-0.98)	1.181	0.038†
Hb (g/dL), median (IQR)	9.70 (8.40–11.3)	10.0 (8.80–12.0)	9.60 (8.40– 11.1)	1.105	0.063†	11.0 (9.00– 13.05)	9.70 (8.40–11.2)	1.272	0.026†
Alb (g/dL), median (IQR)	2.60 (2.10-3.00)	2.80 (2.20–3.38)	2.50 (2.10– 3.00)	1.669	0.003†	2.70 (2.15-3.21)	2.60 (2.10-3.00)	1.322	0.430
ALT (U/L), median (IQR)	18.0 (11.0–34.0)	18.0 (13.0–33.0)	18.0 (10.0– 34.0)	1.000	0.907	20.0 (14.5-40.5)	18.0 (11.0–33.5)	0.997	0.632

AST (U/L), median (IQR)	23.5 (17.0–38.0)	24.0 (18.0–37.0)	23.0 (17.0– 38.0)	1.000	0.861	26.0 (18.5–60.0)	23.0 (17.0–38.0)	1.000	0.982
CRP (mg/L), median (IQR)	6.51 (2.38-	5.95 (0.82-	6.58 (2.63-	0.983	0.276	11.1 (0.38–17.4)	6.43 (2.40-	1.024	0.388
	13.41)	12.26)	13.58)				13.38)		

CPK, creatine phosphokinase; DAP, daptomycin; IQR, interquartile range; OR, odds ratio; BSI, bloodstream infection; SSTI, skin and soft-tissue infection; IE, infectious endocarditis; UTI, urinary tract infection; PJI, prosthetic joint infection; Scr, serum creatinine; CrCl, creatinine clearance; BUN, blood urea nitrogen; TP, total protein; T-bil, total bilirubin; Hb, haemoglobin; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein. Peritonitis includes an intra-abdominal abscess. †P < 0.1, included in multiple logistic regression analysis. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000 IU/L, CPK elevation more than twice from baseline, and > 1,000 IU/L.

Description	All patients	CPK elevation > 200 U/L		CPK elevation > 1,000 U/L					
	(n= /06)	Yes (n= 83)	No (n= 623)	OR	P value	Yes (n= 17)	No (n= 689)	OR	P value
Concomitant medications									
Hydrophobic statin, n (%)	79 (11.2)	23 (27.7)	56 (8.99)	3.881	< 0.001†	8 (47.1)	71 (10.3)	7.737	< 0.001†
Hydrophilic statin, n (%)	52 (7.37)	5 (6.02)	47 (7.54)	0.786	0.619	0 (0)	52 (7.55)	0.000	0.986
SSRI, n (%)	8 (1.13)	2 (2.41)	6 (0.96)	2.539	0.259	0 (0)	8 (1.16)	0.000	0.991
β-Blocker, n (%)	162 (22.9)	23 (27.7)	139 (22.3)	1.335	0.273	4 (23.5)	158 (22.9)	1.034	0.954
Antihistamine, n (%)	52 (7.37)	9 (10.8)	43 (6.90)	1.640	0.201	1 (5.88)	51 (7.40)	0.782	0.813
Antipsychotics, n (%)	66 (9.35)	10 (12.0)	56 (8.99)	1.387	0.370	1 (5.88)	65 (9.43)	0.600	0.623
Fibrate, n (%)	4 (0.57)	1 (1.20)	3 (0.48)	2.520	0.426	0 (0)	4 (0.58)	0.000	0.991
Colchicine, n (%)	0 (0)	0 (0)	0 (0)	N/A	N/A	0 (0)	0 (0)	N/A	N/A
Steroids, n (%)	92 (13.0)	13 (15.7)	79 (12.7)	1.279	0.449	4 (23.5)	88 (12.8)	2.101	0.203
Amiodarone, n (%)	17 (2.41)	3 (3.61)	14 (2.25)	1.631	0.450	0 (0)	17 (2.47)	0.000	0.988
Cyclosporine, n (%)	3 (0.42)	0 (0)	3 (0.48)	0.000	0.991	0 (0)	3 (0.44)	0.000	0.992
Propofol, n (%)	12 (1.70)	0 (0)	12 (1.93)	0.000	0.988	0 (0)	12 (1.74)	0.000	0.990
Daptomycin									
Daily dose (mg/kg), median (IQR)	5.98 (5.19-	5.97 (5.27-	5.98 (5.17-6.97)	0.969	0.392	5.99 (5.39-	5.98 (5.16-	0.961	0.654
	7.00)	7.53)				7.25)	7.00)		
At 24-h intervals, n (%)	488 (69.1)	59 (71.1)	429 (68.9)	1.112	0.681	12 (70.6)	476 (69.1)	1.074	0.895
At 48-h intervals, n (%)	209 (29.6)	24 (28.9)	185 (29.7)	0.963	0.884	5 (29.4)	204 (29.6)	0.991	0.986

Table 4. Univariate analysis affecting CPK elevations during DAP therapy according to concomitant medications and daptomycin data

At 72-h intervals, n (%)	9 (1.27)	0 (0)	9 (1.44)	0.000	0.990	0 (0)	9 (1.31)	0.000	0.991
Overdose, n (%)	344 (48.7)	40 (48.2)	304 (48.8)	0.976	0.918	9 (52.9)	335 (48.6)	1.189	0.725
Durations (days), median (IQR)	11 (7–17)	12 (7–21)	11 (7–16)	1.026	0.004†	13 (8–20.5)	11 (7–16.5)	1.019	0.254

CPK, creatine phosphokinase; DAP, daptomycin; IQR, interquartile range; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor. †P < 0.1, included in multiple logistic regression analysis. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000 IU/L, CPK elevation more than twice from baseline, and > 1,000 IU/L.

Description	CPK elevation	n > 200 U/L	CPK elevation > 1,000 U/L		
	OR	P value	OR	P value	
Estimated over BW	1.875	0.131			
Type 1 DM			6.973	0.104	
Pneumonia	0.349	0.159			
Baseline CPK value	1.010	< 0.001*	1.014	0.004*	
Baseline TP value	1.018	0.912			
Baseline T-bil value			1.199	0.035*	
Baseline Hb value	0.950	0.465	1.096	0.466	
Baseline Alb value	1.312	0.269			
Concomitant use of hydrophobic statin	3.399	< 0.001*	6.624	< 0.001*	
Durations of DAP	1.034	< 0.001*			

Table 5. Multiple logistic regression analysis affecting CPK elevation during DAP therapy

CPK, creatine phosphokinase; DAP, daptomycin; OR, odds ratio; BW, body weight; DM, diabetes mellitus; TP, total protein; T-bil, total bilirubin; Hb, haemoglobin; Alb, albumin. *P < 0.05, considered significant. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000 IU/L, CPK elevation more than twice from baseline, and > 1,000 IU/L.





Eligible patients (n = 706)