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1 **Factors affecting creatine phosphokinase elevation during daptomycin therapy**
2 **using combination of machine learning and conventional methods**

3

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30

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45 study. All authors have read and approved the final version of the manuscript.

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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.

52

53

54 **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

65 **Abstract**

66 **Aims**

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

71 **Methods**

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

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.

92

93 **1 INTRODUCTION**

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

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.

127

128

129 **2 METHODS**

130 ***2.1 Data sources***

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

139

140 ***2.2 Subjects***

141 Among patients who were registered in the RWD database, we identified subjects who
142 received DAP intravenously from October 2011 to December 2020. DAP was identified
143 using the Anatomical Therapeutic Chemical system (ATC) code J01XX09. The exclusion
144 criteria were: (1) duration of DAP therapy < 3 days, (2) baseline CPK values not measured,
145 (3) baseline CPK value > 200 IU/L, (4) CPK values not measured during DAP therapy,
146 (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 DAP
148 therapy (within 14 days at most).

149

150 ***2.3 Definition of musculoskeletal toxicity and outcomes***

151 Musculoskeletal toxicity was detected based on elevation of CPK value, as the
152 presence or absence of symptoms could not be collected from the database. Thus, the
153 following two definitions of CPK elevations were employed with some modifications
154 from previous reports^{4,5,13,22}: (1) elevation of CPK values more than twice from baseline
155 and > 200 IU/L (> 1 time the upper limit of normal [ULN]) at any point during DAP
156 therapy, (2) elevation of CPK values more than twice from baseline and > 1,000 IU/L (>
157 5 times the ULN) at any point during DAP therapy. In this study, we defined a new
158 criterion of CPK elevation, that is, “elevation of CPK values more than twice from
159 baseline.” This is to prevent patients with high baseline CPK values from easily meeting
160 the definition of CPK elevation. To evaluate CPK elevation > 1,000 IU/L, we only
161 included patients with normal baseline CPK values (i.e., < 200 IU/L) based on our
162 inclusion criteria.^{13,22} This is because when patients with high baseline CPK values (i.e.,
163 200–1,000 IU/L) are included, fluctuation of CPK values cannot be ignored as this may
164 be caused by factors that cause increased baseline CPK values.

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

179

180 **2.4 Data collection**

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

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

201 according to its International Classification of Diseases, 10th Revision classification.

202 Further details are shown in Table S1.

203

204 ***2.5 Statistical analysis***

205 First, the proportion of CPK elevations between patients receiving each statin

206 (including their classification) and DAP was compared using Pearson's chi-square or

207 Fisher's exact test. Fisher's exact test was used if more than 20% of the cells had expected

208 frequencies of less than 5 in a contingency table. Based on these results, the classification

209 of statins to be applied in the univariate analysis was determined (e.g., ACC/AHA

210 classification). Second, a multiple logistic regression analysis was performed. For this,

211 all the potential risk factors that were extracted from the characteristics were applied

212 based on univariate analysis with a P value < 0.1 . In the logistic regression analysis and

213 DT analysis, the dependent variable was the presence or absence of elevation in CPK

214 values. Third, DT analysis, a machine learning method, was performed using the chi-

215 squared automatic interaction detection (CHAID) algorithm.^{26,27} Users can determine the

216 order of the splitting variables based on the strength of relation to outcome when using

217 the CHAID algorithm. The procedure of this algorithm was as follows: (1) establishment

218 of multiple 2×2 contingency tables between dependent variables and each independent

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

237 values more than twice from baseline and > 200 IU/L as well as > 1,000 IU/L occurred in
238 83 (11.8%) and 17 (2.41%) patients, respectively. The median (interquartile range; IQR)
239 durations of CPK elevation after the initiation of DAP therapy were 4 (2-10) and 5 (2.5-
240 15) days, respectively. The patient's ethnicity could not be identified, but it was
241 considered that almost all of them were Japanese.

242

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

244 Atorvastatin, rosuvastatin, and pitavastatin were commonly used concomitantly during
245 DAP therapy (Table 1). There were no patients treated with fluvastatin and high-intensity
246 statins. The details of the ACC/AHA classification are shown in Table S4. The proportion
247 of CPK elevation was significantly higher in patients treated with hydrophobic statins
248 (atorvastatin, pitavastatin, and simvastatin) than in those treated with hydrophilic statins
249 (rosuvastatin and pravastatin). No significant differences were observed in other
250 contingency tables. Based on these results, we classified statins as hydrophobic and
251 hydrophilic statins and applied them to the univariate analysis.

252 Additionally, the number of patients among those who were excluded (n= 2,264), with
253 statin, hydrophobic statin, and hydrophilic statin use were 440 (19.4%), 262 (11.6%) and
254 178 (7.86%), respectively. Similar proportions were observed among eligible patients.

255

256 **3.3 Univariate analysis**

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

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

270 Concomitant use of hydrophobic statins was extracted as a factor in the multivariate
271 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.

273

274 **3.4 Multiple logistic regression analysis**

275 As shown in Table 5, baseline CPK value, concomitant use of hydrophobic statins, and
276 duration of DAP therapy were extracted as independent factors affecting CPK elevation
277 > 200 IU/L. Baseline CPK value, T-bil value, and concomitant use of hydrophobic statins
278 were extracted as independent factors affecting CPK elevation > 1,000 IU/L.

279

280 **3.5 DT analysis**

281 Based on the results of multiple logistic regression analysis, independent variables
282 affecting CPK elevation were applied to the DT analysis. For continuous variables, a cut-
283 off value that had the strongest relationship to CPK elevation was automatically
284 determined.

285 In a DT model predicting CPK elevation > 200 IU/L, concomitant use of hydrophobic
286 statins was selected as the first splitting variable. The proportion of CPK elevation was
287 29.1% (23 out of 79 patients) for patients with concomitant use of hydrophobic statins
288 and 9.57% (60 out of 627 patients) for those without. Among patients with concomitant
289 use of hydrophobic statins, a baseline CPK value > 82 IU/L was extracted as the second
290 splitting variable. In patients with a baseline CPK value > 82 IU/L, proportion of CPK

291 elevation was 62.5% (15 out of 24 patients), and patients with a baseline CPK value \leq 82
292 IU/L was 14.5% (8 out of 55 patients).

293 The same variables were extracted to construct a risk prediction model of CPK
294 elevation $>$ 1,000 IU/L. One difference was that the cut-off value of baseline CPK was
295 115 IU/L. The proportion of CPK elevation $>$ 1,000 IU/L was 10.1% (8 out of 79 patients)
296 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
299 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 \leq 115 IU/L was 5.88% (4 out of 68
301 patients).

302

303 **4 DISCUSSION**

304 Considering that there are racial differences in the occurrence of adverse drug
305 reactions³⁹, reports from diverse regions are important for the safe use of drugs. This is
306 the first large-scale study in Asia to investigate the risk factors for CPK elevation during
307 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/L⁴; 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 *et al.*, 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

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

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

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
377 with those in previous reports.³⁻¹⁷ In this way, DT analysis can identify “notable high-risk
378 groups” by evaluating the combination of multiple factors, which one strong point of this
379 machine learning method.^{26,27} A weak point of the CHAID algorithm, which was used in
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.<sup>4,5,9–
392 11,13,14,22,23</sup> 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.

407

408 **5 CONCLUSION**

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

414

415

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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.

582

Tables

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

Description	n	CPK elevation > 200 U/L, n (%)	<i>P</i> value	CPK elevation > 1,000 U/L, n (%)	<i>P</i> 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)	

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.

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

Description	All patients (n= 706)	CPK elevation > 200 IU/L		CPK elevation > 1,000 IU/L					
		Yes (n= 83)	No (n= 623)	OR	<i>P</i> value	Yes (n= 17)	No (n= 689)	OR	<i>P</i> 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 (53.1–66.4)	56.0 (47.3–65.6)	1.017	0.031†	58.4 (53.9–63.7)	56.3 (47.5–65.8)	1.008	0.611
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

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

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

Description	All patients (n= 706)	CPK elevation > 200 U/L		CPK elevation > 1,000 U/L					
		Yes (n= 83)	No (n= 623)	OR	<i>P</i> value	Yes (n= 17)	No (n= 689)	OR	<i>P</i> 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

CrCl (mL/min), median (IQR)	46.8 (21.0–79.8)	49.2 (22.1–75.6)	46.7 (21.0–80.8)	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)	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 (2.38–13.41)	5.95 (0.82–12.26)	6.58 (2.63–13.58)	0.983	0.276	11.1 (0.38–17.4)	6.43 (2.40–13.38)	1.024	0.388

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.

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

Description	All patients (n= 706)	CPK elevation > 200 U/L				CPK elevation > 1,000 U/L			
		Yes (n= 83)	No (n= 623)	OR	<i>P</i> value	Yes (n= 17)	No (n= 689)	OR	<i>P</i> 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– 7.00)	5.97 (5.27– 7.53)	5.98 (5.17–6.97)	0.969	0.392	5.99 (5.39– 7.25)	5.98 (5.16– 7.00)	0.961	0.654
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

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.

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

Description	CPK elevation > 200 U/L		CPK elevation > 1,000 U/L	
	OR	<i>P</i> value	OR	<i>P</i> 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*		

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.

Fig.1

