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

Shungo Imai[1]*, Hitoshi Kashiwagi[1], Yuki Sato[1], Takayuki Miyai[2], Mitsuru Sugawara[1,3,4], Yoh Takekuma[3]*

[1] *Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12-jo Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan:*

[2] *Graduate School of Life Science, Hokkaido University, Kita 10-jo Nishi 8-chome, Kita-ku, Sapporo 060-0810, Japan:*

[3] *Department of Pharmacy, Hokkaido University Hospital, Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan: and*

[4] *Global Station for Biosurfaces and Drug Discovery, Hokkaido University, Kita 12-jo Nishi 6-chome, Kita-ku, Sapporo 060-0812, Japan.*

*Corresponding authors:

Shungo Imai

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12-jo Nishi 6-chome,

Kita-ku, Sapporo 060-0812, Japan.

Phone: +81-11-706-3978, Fax: +81-11-706-4984,

E-mail: s.imai@pharm.hokudai.ac.jp

Yoh Takekuma

Department of Pharmacy, Hokkaido University Hospital, Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo 060-8648, Japan.

Phone: +81-11-706-5754, Fax: +81-11-706-7616,

E-mail: y-kuma@pharm.hokudai.ac.jp

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What is already known about this subject:

- **Several factors such as obesity and the African American ethnicity associate with daptomycin (DAP)-induced creatine phosphokinase (CPK) elevation.**
- **The interaction between statins and DAP has been not well established.**

What this study adds:

- **Hydrophobic statin use was a risk factor of DAP-induced CPK elevation, but hydrophilic statin was not.**
- **Combination of hydrophobic statin use and high baseline CPK value were the highest risk factor.**

Abstract

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.

Methods

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

Results

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

200 IU/L and > 1,000 IU/L occurred in 83 (11.8%) and 17 (2.41%) patients, respectively. In multiple logistic regression analysis, baseline CPK value and concomitant use of hydrophobic statins were commonly extracted as independent factors affecting each CPK elevation, but concomitant use of hydrophilic statins was not. In DT analysis, patients who received hydrophobic statins and had high baseline CPK values were classified into the high-risk group.

Conclusions

Our novel approach revealed new risk factors for CPK elevation. Our findings suggest that high-risk patients require frequent CPK monitoring.

1 INTRODUCTION

Daptomycin (DAP) is a lipopeptide antibiotic used in patients with Gram-positive bacterial infections, such as methicillin-resistant *Staphylococcus aureus*.[1] Musculoskeletal toxicity, including rhabdomyolysis and myopathy, is a typical side effect of DAP and can cause life-threatening conditions.[2] Previous studies reported that myopathy occurs in 2–14% of patients receiving DAP therapy.[3–14] In addition, rhabdomyolysis occurs in approximately 5% of cases.[15–17] Therefore, monitoring the patients' creatine phosphokinase (CPK) values weekly during DAP therapy is recommended.[18–21] Several factors have been reported to be associated with DAP-induced myopathy, such as obesity and the African American ethnicity.[4,5,9–11,13,14,22,23] In particular, the interaction between statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] and DAP has been examined in several studies, although some of these studies could not show significant association.[4,5,10,13,14,22,23] Furthermore, a recent review describes "published cohort studies do not demonstrate a statistically significant difference in the rate of CPK elevations or musculoskeletal toxicities".[24] Therefore, further 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.[4,5,9–11,13,14,22,23] 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

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2 METHODS

2.1 Data sources

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

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

evaluated baseline CPK values on the earliest possible day after the patients started DAP therapy (within 14 days at most).

2.3 Definition of musculoskeletal toxicity and outcomes

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

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

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

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 recommendation[18] 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

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

2.5 Statistical analysis

First, the proportion of CPK elevations between patients receiving each statin (including their classification) and DAP was compared using Pearson's chi-square or Fisher'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 of statins to be applied in the univariate analysis was determined (e.g., ACC/AHA classification). Second, a multiple logistic regression analysis was performed. For this, all the potential risk factors that were extracted from the characteristics were applied based 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 values. Third, DT analysis, a machine learning method, was performed using the chi-squared automatic interaction detection (CHAID) algorithm.[26,27] Users can determine the order of the splitting variables based on the strength of relation to outcome when using the CHAID algorithm. The procedure of this algorithm was as follows: (1) establishment 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.

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.

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 cut-off 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

291 elevation was 62.5% (15 out of 24 patients), and patients with a baseline CPK value ≤ 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 ≤ 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 reactions[39], 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/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 *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

value > 200 and 1,000 IU/L), concomitant use of hydrophobic statins was extracted as a risk factor for CPK elevation, but that of hydrophilic statin was not. Musculoskeletal toxicity of DAP is caused by a direct effect on the plasma membrane of the sarcolemma.[40] Because statins interrupt HMG-CoA reductase, they cause intracellular depletion of the intermediate metabolites and end products (i.e., cholesterol, dolichols, and ubiquinone) downstream of the cholesterol synthesis pathway.[41] In particular, it has been known that cholesterol deficiency of the sarcolemma adversely affects membrane physical properties, integrity, and fluidity.[41] Thus, statins and DAP commonly affect the "sarcolemma", which may cause a synergistic effect. Among the statins, hydrophobic statins are likely to induce this interaction because they can easily permeate the cell membrane.[31] Indeed, Kobayashi *et al*., using a prototypic embryonal rhabdomyosarcoma cell line, showed that the muscle cytotoxicity of hydrophobic statins was clearly stronger than that of hydrophilic statins.[42] Furthermore, they reported that the cholesterol-lowering effect of statins did not correlate with their muscle cytotoxicity.[42] Clinically, hydrophobic statins are often used in patients with CPK elevation during DAP therapy.[5,22] Considering these facts, it is reasonable to conclude that hydrophobic statins have been identified as a new risk factor for CPK elevation during DAP-therapy. However, although significant differences were not 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 factors[44], 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

are eligible for analysis with increasing tree branching, which reduces the reliability of results. As a countermeasure, we attempted a novel approach combining machine learning and conventional statistical methods. That is, the independent variables applied in the DT analysis were based on the factors extracted in the multiple logistic regression analysis. Therefore, our findings are reasonable and suggest that frequent CPK monitoring is required for these high-risk patients during DAP therapy.

Our study had several limitations. First, we could not detect symptoms of musculoskeletal toxicity. A prospective, observational study is necessary because a retrospective study may not have detected all symptoms. Second the causal relationship between DAP and CPK elevation could not be assessed because CPK values fluctuate due to many factors.[44] However, this is also a common limitation in previous studies.[4,5,9–11,13,14,22,23] Third, the type of infection could not be identified in many patients, and information on their pathogens was not evaluated owing to the absence of data. However, in most previous studies, these factors did not seem to have a significant effect on CPK elevation.[4,9–11,13,14,22,23] In the only report that showed a relationship between the type of infection and CPK elevation, deep abscess was related to the occurrence of myopathy, but not to rhabdomyolysis.[5] Fourth, owing to careful selection of eligible patients, most of the 2,970 patients were excluded. In logistic regression analysis, the required number of

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

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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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 (%)	*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)	

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	*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 (53.1–66.4)	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 ≥ 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	*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

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	*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 (5.19–7.00)	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

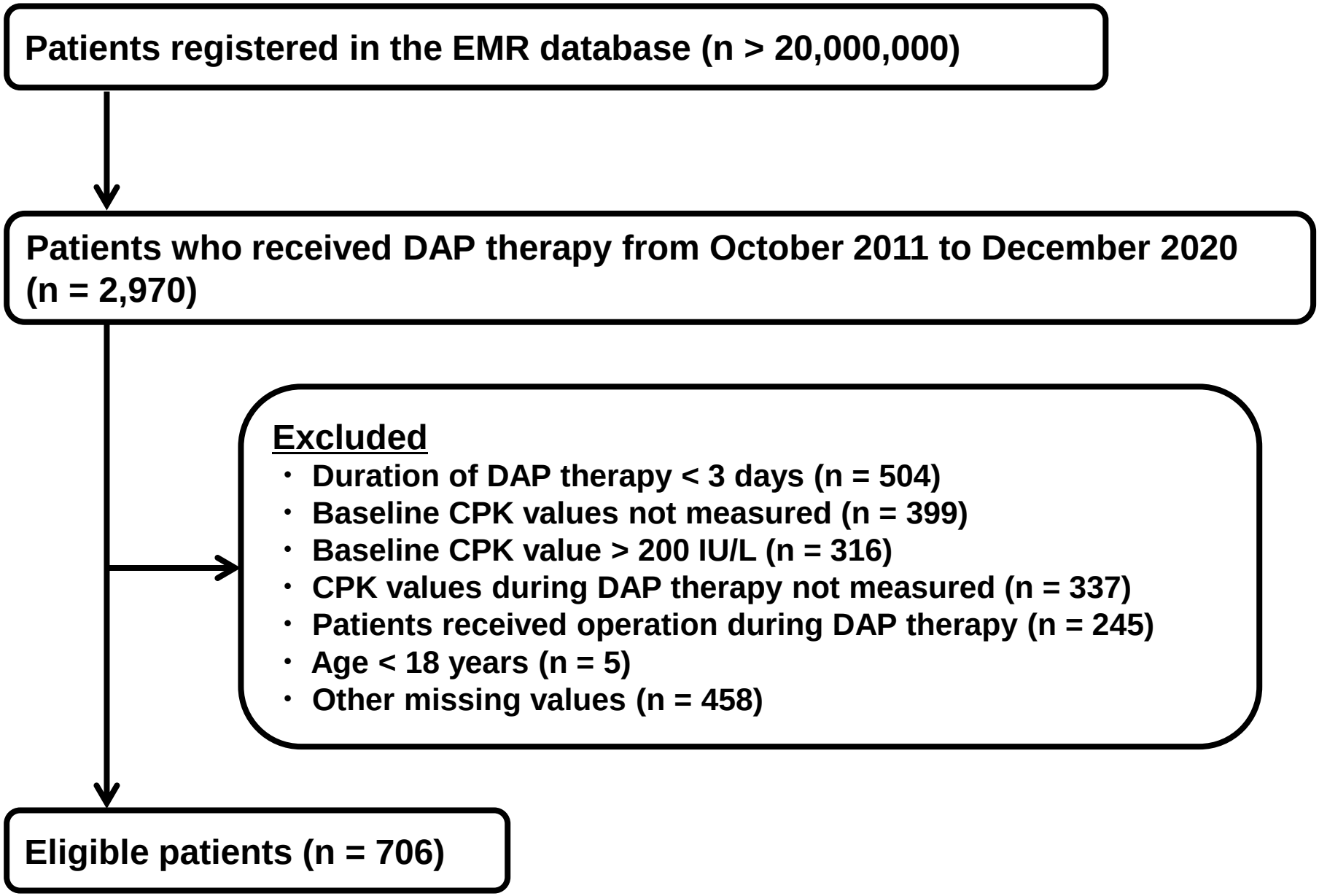
CPK, creatine phosphokinase; DAP, daptomycin; IQR, interquartile range; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor. †$P < 0.1$, included in multiple logistic regression analysis. CPK elevation > 200 IU/L, CPK elevation more than twice from baseline and > 200 IU/L, CPK elevation > 1,000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

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


Patients registered in the EMR database (n > 20,000,000)
Patients who received DAP therapy from October 2011 to December 2020 (n = 2,970)
Excluded
・ Duration of DAP therapy < 3 days (n = 504)
・ Baseline CPK values not measured (n = 399)
・ Baseline CPK value > 200 IU/L (n = 316)
・ CPK values during DAP therapy not measured (n = 337)
・ Patients received operation during DAP therapy (n = 245)
・ Age < 18 years (n = 5)
・ Other missing values (n = 458)
Eligible patients (n = 706)