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Influence of acetaminophen on renal function: a longitudinal descriptive study using a real-world database

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Abstract

Purpose Long-term acetaminophen (APAP) use has poorly defined effects on renal function. We investigated these effects using a real-world database.

Methods We used a database of health data routinely collected from 185 hospitals serving 20 million patients in Japan. Individuals with chronic pain were selected for the study. The primary outcome was the change in renal function, as measured by 1/serum creatinine (SCr) during the postindex period.

Results After excluding individuals who did not meet the inclusion criteria, 241,167 patients were included in the analysis (median age 79.0, range 65–101 years; 111,252 were men). APAP was prescribed significantly more frequently to patients with a low renal function ($P < 0.001$). The annual changes in 1/SCr median and interquartile range (IQR) were − 0.038 (− 0.182 to 0.101) in patients receiving APAP, − 0.040 (− 0.187 to 0.082) in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs), and − 0.025 (− 0.142 to 0.079) in nonmedicated control patients ($P < 0.001$). These changes were not significantly different among patients with a low renal function, with 0.003 (− 0.066 to 0.113) in the APAP group, 0.000 (− 0.089 to 0.090) in the NSAID group, and − 0.009 (− 0.086 to 0.089) in the control group ($P = 0.327$).

Conclusion Physicians tended to select APAP for individuals with a low renal function. The annual changes in 1/SCr were significantly different based on APAP and NSAID use or no analgesia, but the differences were not significant among patients with a low renal function. Overall, long-term use of APAP does not appear to exacerbate the renal function in a clinical setting.

Keywords Acetaminophen · Renal function · Longitudinal study · Real-world database

Abbreviations

AKI	Acute kidney injury
APAP	Acetaminophen
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical record
ICD-10	International Statistical Classification of Disease and Related Health Problems 10th Revision
IQR	Interquartile range
NSAIDs	Non-steroidal anti-inflammatory drugs
RTD	Recommended therapeutic dose
RWD database	Real-World Data database

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SCr Serum creatinine
STROBE Strengthening the Reporting of Observational Studies in Epidemiology

Introduction

Acetaminophen (*N*-acetyl-*p*-aminophenol, APAP) is globally used as an analgesic and antipyretic drug. It is safe at therapeutic levels but can potentially cause hepatic and renal toxicities. In the kidney, APAP can induce interstitial nephritis and acute kidney injury (AKI) [1, 2], which are mentioned as adverse effects in the Pharmaceuticals and Medical Devices Agency reference [3]. Based on this, APAP is contraindicated for individuals with severe renal dysfunction [3]. However, the incidence rate of these adverse effects has not been reported, and APAP is often administered to individuals with renal failure in clinical settings [4].

APAP can also induce renal dysfunction at the recommended therapeutic dose (RTD). An overdose of APAP can reduce tubular epithelial cells in rodents, suggesting a similar possible mechanism in humans [5, 6]. An experimental study indicated that APAP may induce kidney fibroblast proliferation, even at the RTD [7].

In clinical settings, the incidence rate of renal dysfunction due to overdose is estimated at 1–2% [8]. An observational study in patients admitted to the liver intensive therapy unit owing to APAP toxicosis showed that 79% of them had AKI [9]. This suggests that patients with liver dysfunction tend to experience renal dysfunction more frequently [10, 11]. However, research on the RD of APAP is limited compared with studies on its overdose. Clinical cases of healthy young adults with AKI after APAP administration have been reported [12]; nonetheless, an observational study in 1871 individuals indicated no significant association between the therapeutic dose of APAP and AKI [13]. The latter study was conducted using the self-controlled case series method, and the results were obtained after adjustment with a time-varying confounder [status of liver and kidney function, systemic inflammation, and exposure to non-steroidal anti-inflammatory drugs (NSAIDs)]. The findings suggested that APAP can be administered to individuals with kidney failure. Nevertheless, the average duration of APAP use in that study was 16 days, which is insufficient to evaluate long-term influence [13]. Another observational study, which used pharmacy and medical claims, demonstrated that APAP use for longer than 30 days did not increase the risk of renal diseases [14]. One study suggested that heavier APAP use is associated with end-stage renal disease [15]. Although this study focused on lifetime exposure, it only used data obtained from interviewing 1000 individuals, incurring the risk of recall bias. As such, the effect of long-term exposure to APAP on renal function is still unclear. The renal toxicity of long-term NSAID use has been well documented [16, 17], leaving physicians with APAP use as the only remaining option for analgesia and antipyresis in patients with renal failure. Thus, in the present study, we investigated the chronic influence of long-term exposure to APAP on renal function using a real-world database.

Materials and methods

Study design

In this retrospective-cohort study, we used a real-world database of health data routinely collected from 185 hospitals. Individuals with diseases causing chronic pain were included, and the renal function was compared among patients prescribed long-term APAP, those prescribed NSAIDs, and those not prescribed pain medications. We have reported the results according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, with the checklist attached as Supplementary Table 1.

Data source and study population

We used the commercially available Real-World Data database (RWD database) of the Health, Clinic, and Education Information Evaluation Institute (HCEI; Kyoto, Japan). The RWD database contains electronic medical record (EMR) and claims data from 185 hospitals serving 20 million patients in Japan. We extracted a dataset of patients, including age, sex, diagnosis according to the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10) codes, serum creatinine (SCr; mg/dL), and estimated glomerular filtration rate (eGFR) calculated using an equation established for the Japanese population: eGFR (mL/min/1.73 m^2) = $194 \times SCr^{-1.094} \times age^{-0.287}$ ($\times 0.739$ for women only) [18].

The study overview is presented in Fig. 1. Individuals aged more than 65 years with chronic pain were defined by the ICD-10 codes for diagnoses (Supplementary Table 2) between January 1, 2010, and December 31, 2018. We excluded individuals (i) who underwent dialysis before the study entry date, (ii) who were diagnosed with an uncertain disease, (iii) who were treated for cancer pain, and (iv) whose SCr was assessed only once during the study period.

Drug exposure, study entry date, and follow-up period

We included only individuals who were prescribed oral APAP or NSAIDs, without considering pyrazolone derivatives. Individuals who were not prescribed these

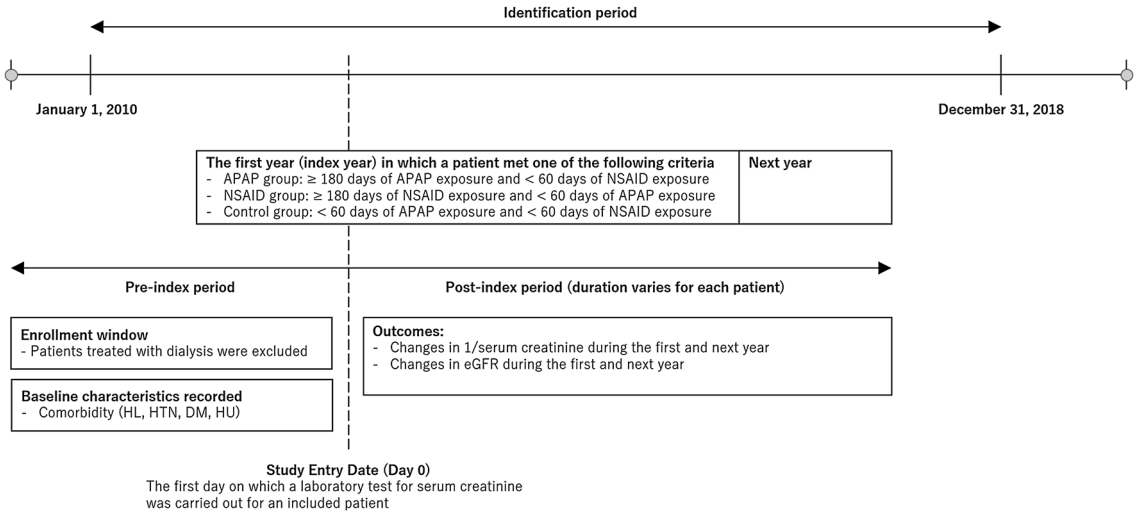

Fig. 1 Study overview

medications were included in the control group. Three groups were established according to the following exposure criteria: ≥ 180 days/year APAP prescription (APAP group); ≥ 180 days/year NSAID prescription (NSAID group); and < 60 days/year APAP and/or NSAID prescription (control group). Individuals prescribed ≥ 180 days/year of NSAIDs with < 60 days/year of APAP were included in the NSAID group. We excluded individuals who did not meet these criteria. The cohort entry date (index date) was defined as the first day of SCr test, and all individuals were subsequently followed up for 2 years.

Primary and secondary outcomes

The primary outcome was a change in renal function as indicated by 1/SCr (dL/mg) during the postindex period. The secondary outcomes were trends in APAP prescription according to group and eGFR category, and a change in renal function and APAP prescription trend in those older than 75 years.

We used the lowest value of SCr when multiple laboratory test results were reported in the EMR on the same day. If the SCr level was measured several times owing to acute illness such as infection and bleeding, we used the lowest value of SCr for the month, as the SCr level can show a transient increase in such cases. To ensure SCr measurement accuracy, values of < 0.2 mg/dL were considered 0.2 mg/dL, and we excluded values ≥ 8.0 mg/dL. The upper limit was determined based on the guidelines for initiating dialysis among Japanese patients [19], as we excluded individuals treated with dialysis before the study entry date.

Statistical analysis

Categorical variables are expressed as number and percentage (%), and continuous variables are expressed as median and range or interquartile range (IQR). We plotted 1/SCr changes using a linear regression line with a 95% confidence interval, and then calculated the changes in 1/SCr as the annual difference [20]. Differences among the groups were compared using a χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables. The slopes of linear regression were compared using the analysis of covariance. The trends in APAP prescription were evaluated using the Cochran–Armitage trend test. Results were regarded as statistically significant at $P < 0.05$. We used R version 3.6.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.

Ethical approval

This study was approved by the Ethics Committee of the Kurashiki Central Hospital (No. 3247) and conducted according to the Declaration of Helsinki. The need for additional informed consent from the study participants was waived according to the guidelines.

Results

A study flow diagram is shown in Fig. 2. The data of 20,113,540 individuals were included in the source database, and 2,473,400 individuals were diagnosed with diseases relevant to this study. Based on the inclusion and exclusion criteria, 121,142 individuals were included in the analysis.

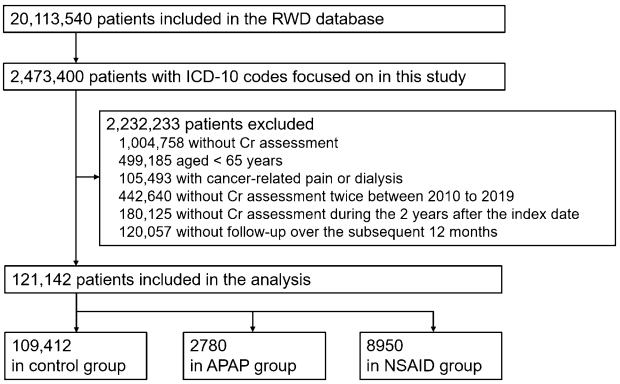

Fig. 2 Study flow diagram. Several individuals met two or more criteria for exclusion

The clinical backgrounds of the study participants are shown in Table 1. The median age (range) of the population was 78.0 (65–101) years, and 47.8% ($n=57,867$) were men. There were 2780 individuals in the APAP group, 8950 in the NSAID group, and 109,412 in the control group. The most common diagnosis among all groups was spinal osteoarthrosis (68.4–85.9%). More than half of the patients had hypertension (71.9–82.6%) and/or hyperuricemia (73.7–84.0%) as comorbidities.

Baseline renal function was measured at eGFR ≤ 60 (mL/min/1.73 m^2) in 52.1% ($n=63,102$) of the population. The eGFR was ≤ 30 (mL/min/1.73 m^2) in 9.6% ($n=266$) of patients in the APAP group, 2.8% ($n=250$) in the NSAID group, and 4.2% ($n=4550$) in the control group, indicating that APAP was prescribed significantly more frequently in the low renal function group ($P<0.001$). Among the groups, 43.1% ($n=11,198$) of patients in the APAP group, 37.0% ($n=3313$) in the NSAID group, and 39.8% ($n=43,525$) in the control group had 30 < eGFR ≤ 60 (mL/min/1.73 m^2). The prescription rate of APAP was higher than that of NSAIDs each year ($P<0.001$; Fig. 3). This trend was observed in those aged 75 years and above ($P<0.001$).

The changes in 1/SCr during the follow-up period are shown in Fig. 4. The median annual changes (IQR) were − 0.038 (− 0.182 to 0.101) in the APAP group, − 0.040 (− 0.187 to 0.082) in the NSAID group, and − 0.025 (− 0.142 to 0.079) in the control group ($P<0.001$; Table 2). These changes were not significantly different among the

Table 1 Clinical backgrounds of the study participants

	Control group	NSAID group	APAP group
N	109,412	8950	2780
Median age (range)	78 (65, 101)	77 (65, 101)	81 (65, 101)
Male sex (%)	53,446 (48.8)	3469 (38.8)	952 (34.2)
Chronic pain disease, *n* (%)			
Headache	18,060 (16.5)	2315 (25.9)	915 (32.9)
Rheumatoid arthritis	9419 (8.6)	1820 (20.3)	464 (16.7)
Chronic pain	9981 (9.1)	1253 (14.0)	595 (21.4)
Peripheral neuropathy	41,133 (37.6)	4499 (50.3)	1492 (53.7)
Muscle-related pain	5551 (5.1)	584 (6.5)	230 (8.3)
Spinal stenosis	27,024 (24.7)	3675 (41.1)	1022 (36.8)
Osteoarthritis of the spine	74,872 (68.4)	7265 (81.2)	2389 (85.9)
Shoulder	28,695 (26.2)	3599 (40.2)	965 (34.7)
Knee	31,970 (29.2)	4056 (45.3)	1211 (43.6)
Hip	9666 (8.8)	1302 (14.5)	433 (15.6)
Other	6244 (5.7)	925 (10.3)	277 (10.0)
Comorbidities, *n* (%)			
Hypertension	78,712 (71.9)	7090 (79.2)	2296 (82.6)
Dyslipidemia	58,597 (53.6)	4924 (55.0)	1532 (55.1)
Diabetes	31,949 (29.2)	2555 (28.5)	914 (32.9)
Hyperuricemia	80,627 (73.7)	7236 (80.8)	2334 (84.0)
eGFR (mL/min/1.73 m^2), *n* (%)			
90 < eGFR	8549 (7.8)	939 (1.5)	244 (8.7)
60 < eGFR ≤ 90	52,788 (48.2)	4448 (49.7)	1072 (38.6)
30 < eGFR ≤ 60	43,525 (39.8)	3313 (37.0)	11,198 (43.1)
eGFR ≤ 30	4550 (4.2)	250 (2.8)	266 (9.6)

APAP acetaminophen, *eGFR* estimated glomerular filtration rate, *NSAID* nonsteroidal anti-inflammatory drug

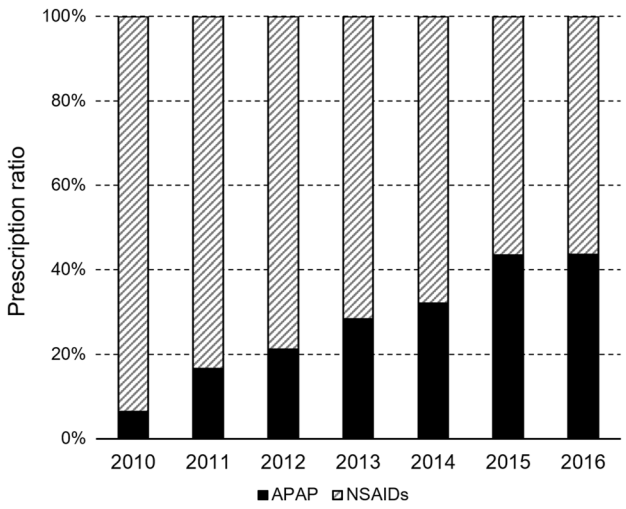

Fig. 3 Prescription ratio of APAP and NSAIDs

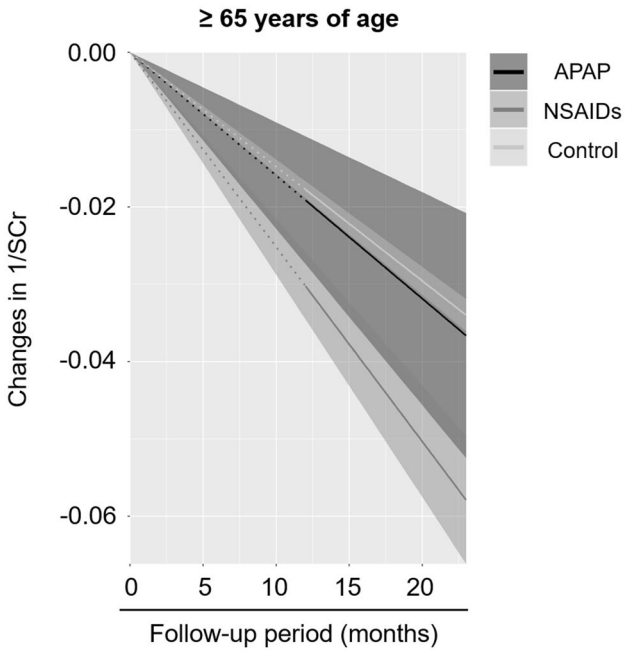

Fig. 4 Changes in 1/SCr during the 2-year follow-up period

patients with a low renal function, with 0.003 (− 0.066 to 0.113) in the APAP group, 0.000 (− 0.089 to 0.090) in the NSAID group, and − 0.009 (− 0.086 to 0.089) in the control group ($P = 0.327$). During the 2-year follow-up period, the regression coefficient of the APAP group (− 0.027) was similar to that of the control group (− 0.026) and smaller than that of the NSAID group (− 0.044). The slopes were significantly different among the groups ($P < 0.001$); both APAP and NSAID groups differed from the control group ($P = 0.003$ and $P < 0.001$, respectively).

The changes in 1/SCr in patients aged 75 years and above are shown in Fig. 5. The median annual change in 1/SCr (IQR) was − 0.036 (− 0.182 to 0.105) in the APAP group, − 0.039 (− 0.189 to 0.091) in the NSAID group, and − 0.026 (− 0.147 to 0.083) in the control group ($P < 0.001$; Table 2). As with the total population, these changes were not significantly different among the patients with a low renal function with eGFR ≤ 30, and they were 0.001 (− 0.069 to 0.111) in the APAP group, − 0.011 (− 0.101 to 0.089) in the NSAID group, and 0.008 (− 0.088 to 0.092) in the control group ($P = 0.445$). The regression coefficient during the 2-year follow-up period was also similar between the APAP group (− 0.018) and control group (− 0.024) but higher in the NSAID group (− 0.040). The slopes were significantly different among the groups ($P < 0.001$). The NSAID group was significantly different from the control group ($P < 0.001$), but the APAP group was not ($P = 0.021$).

Discussion

We assessed the influence of long-term exposure to APAP on renal function using a real-world database. APAP was prescribed significantly more frequently than NSAID in individuals with a poor renal function, suggesting that physicians may avoid the clinical use of NSAIDs for such individuals, likely because of their well-documented long-term renal toxicity [13, 16]. Furthermore, the rate of APAP prescription significantly increased each year.

Pharmaceutical reference guidelines state that APAP is appropriate for "careful administration" to individuals with

Table 2 Annual changes in 1/SCr

	Control	NSAID group	APAP group	*P* value
	$n = 109{,}412$	$n = 8950$	$n = 2780$	
All	− 0.025 (− 0.142, 0.079)	− 0.040 (− 0.187, 0.082)	− 0.038 (− 0.182, 0.101)	< 0.001
	$n = 77{,}116$	$n = 5517$	$n = 2204$	
Age ≥ 75 years	− 0.026 (− 0.147, 0.083)	− 0.039 (− 0.189, 0.091)	− 0.036 (− 0.182, 0.105)	< 0.001

Values indicate median (IQR)

APAP acetaminophen, *eGFR* estimated glomerular filtration rate, *NSAID* nonsteroidal anti-inflammatory drug, *SCr* serum creatinine

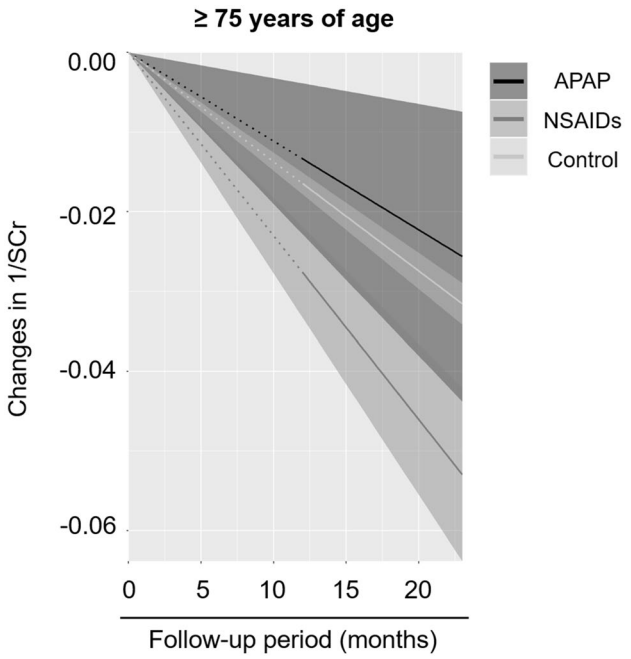

Fig. 5 Changes in 1/SCr among those aged ≥ 75 years

renal dysfunction and contraindicated for individuals with severe renal dysfunction [3]; therefore, it should be prescribed considering the condition of each individual. Our results demonstrated that the long-term use of APAP did not negatively affect the renal function during the 2-year follow-up period in patients with a severe renal dysfunction. The annual changes in 1/SCr were significantly different among the groups, but the changes were only − 0.025 to − 0.040 in the total population and not significant among individuals with a low renal function. This trend was also observed in older individuals.

During the 2-year follow-up period, the regression coefficient of the APAP group was similar to that of the control group, and it was smaller than that of the NSAID group. This was the trend among all those surveyed and those of older age. In the aged population, the slope of the NSAID group was significantly different from that of the control group, but from that of the APAP group, indicating that long-term use of APAP may have less influence on renal function than NSAIDs in elderly patients.

The number of SCr measurements could mean that physicians should carefully prescribe APAP according to laboratory test results. SCr was measured approximately 1.5 times more often in the APAP group than in the control group, to control individuals with eGFR ≤ 30.

In this clinical situation, APAP is unlikely to exacerbate poor renal function among individuals with renal dysfunction, and it may therefore be a reasonable treatment for controlling chronic pain in such patients.

There are certain limitations to this study. First, we could not consider the dosage of APAP and NSAIDs using the dataset, which limits the conclusions that can be drawn. Further investigation is needed to address this concern. Second, the validity of the ICD-10 codes used in this study should also be clarified in the future. Nonetheless, our study has several strengths. This is the first study to evaluate the influence of long-term exposure to APAP on renal function using a real-world database. The database used in this study covered 185 hospitals with 20 million patients, and thus, the generalizability of the results is high. Overall, the results of this study will be useful for clinicians in selecting analgesic or antipyretic drugs.

Conclusion

Physicians tended to select APAP for individuals with a low renal function, and it appears to be appropriate based on our finding that long-term use of APAP does not negatively affect renal function in a clinical setting. As such, when selecting analgesic or antipyretic drugs for individuals with a low renal function, APAP may be an appropriate choice.

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Author contributions KI designed the research, interpreted the results, and wrote the paper. TF designed the research and collected and analyzed the data. NS provided suggestions to conduct the study and interpreted the results. HT designed the research and collected and analyzed the data. All authors have read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest Kazuki Ide and Takashi Fujiwara received a consulting fee from the Real World Data, Co., Ltd (Kyoto, Japan). Hironobu Tokumasu is a Director of Real World Data, Co., Ltd (Kyoto, Japan). Other authors declare no conflicts of interest.

Ethics approval This study was approved by the Ethics Committee of Kurashiki Central Hospital (No. 3247) and conducted according to the Declaration of Helsinki.

Consent to participate The need for additional informed consent from the study participants was waived according to the guidelines.

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