Note

Comparison of interactions between warfarin and cephalosporins with and without the *N*-methyl-thio-tetrazole side chain

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YT conceptualized and coordinated the trial. SI was the chief investigator and responsible for the data analysis. SK, KM, HK, YS, TM, and MS designed the trial and analyzed the data. All authors contributed to the writing of the final manuscript.

Abstract

Cephalosporins with an N-methyl-thio-tetrazole (NMTT) side chain interact with warfarin by reducing the production of blood clotting factors. However, cephalosporins without the NMTT side chain also enhance the effects of warfarin. Thus, we aimed to compare the effects of warfarin modified by cephalosporins with and without the NMTT side chain, using a Japanese health insurance claims database. The inclusion criteria were patients who (1) intravenously received second- or third-generation cephalosporins between April 2010 and March 2017 and (2) received warfarin during cephalosporin therapy. Patients were administered either cephalosporins with the NMTT side chain (NMTT group) or those without NMTT (non-NMTT group). After matching patient data by propensity score, the following outcomes were compared between the two groups: (1) proportion of patients administered vitamin K, (2) proportion of bleeding events, and (3) changes in the daily dose of warfarin. Among 203 patients, 100 patients (50 per group) were matched by the propensity score. The proportion of patients administered vitamin K was 6.0% in both groups. These patients intravenously received a single dose of menatetrenone; no bleeding was observed. The proportion of patients subjected to a reduction in the daily dose of warfarin was 6.5% and 4.3% in the NMTT and non-NMTT groups, respectively. As our study had a small sample size, we could not determine whether the risk of over anticoagulation of warfarin is affected by cephalosporins with or without NMTT side chain. However, we showed the bleeding risk was sufficiently low regardless of the presence/absence of the NMTT side chain.

Keywords: cephalosporin, claims database, drug–drug interaction, bleeding, warfarin

Concomitant use of antibiotics is considered a risk factor for warfarin-induced over-anticoagulation and bleeding, because antibiotics disrupt the intestinal flora that synthesizes vitamin K [1]. Additionally, studies have reported that cephalosporins with an *N*-methyl-thio-tetrazole (NMTT) side chain interact with warfarin by reducing the production of blood clotting factors [2–4]. Although the interaction between warfarin and cephalosporins with the NMTT side chain has been established, cephalosporins without the NMTT side chain have also been reported to enhance the effects of warfarin [5–6]. Thus, information regarding the clinical importance of the presence or absence of the NMTT side chain in cephalosporins in their interaction with warfarin is limited.

Intravenous infusion of second- and third-generation cephalosporins is used for various infections, including pneumonia, acute cholangitis, and cholecystitis [7–8]. Some of these antibiotics have an NMTT side chain and some do not. Therefore, for appropriate drug selection, it is important to elucidate the difference between cephalosporins with and without NMTT in terms of their influence on the effect of warfarin. However, it is often difficult to enroll enough patients in a single medical center.

Recently, medical big-data sources such as claims data have been employed for research purposes. In Japan, large health insurance claims data have been compiled in the Japanese health insurance claims database maintained by JMDC, Inc. (Tokyo, Japan) [9]. The database consists of data of approximately 5.6 million insured individuals, covering approximately 5% of the Japanese population. This database also includes employment medical claims of patients under 75 years of age. Therefore, the JMDC claims database could be used to solve the above-mentioned clinical question regarding the NMTT side chain.

Here, we conducted epidemiological research to compare the influence of intravenous infusions of second- and third-generation cephalosporins with and without the NMTT side chain on the effect of warfarin.

We employed the JMDC claims database [9]. The inclusion criteria were patients who (1) intravenously received second- or third-generation cephalosporins between April 2010 and March 2017 and (2) received warfarin during cephalosporin therapy.

Data on second- and third-generation cephalosporins were collected and divided into two groups—(1) cephalosporins with the NMTT side chain (NMTT) group: cefotiam (CTM), cefmetazole (CMZ), cefmenoxime (CMX), cefoperazone-sulbactam (SBT-CPZ), and cefoperazone (CPZ) and (2) cephalosporins without the NMTT side chain (non-NMTT) group: ceftriaxone (CTRX), cefotaxime (CTX), and ceftazidime (CAZ).

If a patient was administered multiple rounds of cephalosporins, only the first administration was included. The exclusion criteria were: (1) patients who were newly prescribed other antibiotics during the 7-day period before cephalosporin therapy until the end of treatment, (2) patients who underwent surgery during the 7-day period before cephalosporin therapy until the end of treatment, (3) patients aged under 18 years, (4) patients in whom the duration of treatment with second- or third-generation cephalosporins was under 3 days, and (5) outpatients. We excluded patients who underwent surgery because: (1) it was difficult to determine whether bleeding events were caused by warfarin or surgery and (2) there was a high possibility that warfarin was stopped pre-operation; we considered that preoperational cessations were not reflected by prescriptions in claims database.

As the JMDC claims database does not contain laboratory data (i.e., the PT-INR value), we compared the following outcomes between the NMTT and non-NMTT groups: (1) proportion of patients administered vitamin K during cephalosporin therapy, (2) proportion of bleeding events during cephalosporin therapy, and (3) changes in the daily dose of warfarin at the start and end of cephalosporin therapy (among patients who did not meet criteria (1) and (2) and did not discontinue warfarin therapy during cephalosporin administration).

For data collection, drugs and diagnoses were identified using the Anatomical Therapeutic Chemical (ATC) system and International Classification of Diseases, 10th Revision (ICD-10), respectively.

For the primary analysis, warfarin, second- and third-generation cephalosporins, and vitamin K preparations were identified by their ATC codes (Supplementary Table 1). Additionally, to identify patients who were newly prescribed other antibiotics, the ATC code of J01 and ATC codes shown in Supplementary Table 1 were used. Patients who underwent surgery were identified by the Japan-specific standardized procedure code of

S1-21. Bleeding events were defined as both diagnosis of bleeding events in the month of cephalosporin administration and discontinuation of warfarin prescription during cephalosporin therapy. Diagnoses of bleeding events were identified by ICD-10 codes (Supplementary Table 2) [10].

To evaluate patient characteristics, we collected baseline data of age, sex, concomitant medications, concomitant antibiotics, underlying diseases, types of diseases requiring warfarin use, types of infections, warfarin therapy duration, and cephalosporin therapy duration. The concomitant medications were evaluated based on a previous study [11], and the details including concomitant antibiotics are presented in Supplementary Table 3. The underlying diseases and types of diseases requiring warfarin use were evaluated during the 12 months before cephalosporin therapy initiation (Supplementary Table 4) [11]. The types of infections were identified by text codes and classified as pneumonia, cholangitis and cholecystitis, bacteremia, gastroenteritis, pancreatitis, febrile neutropenia, infectious endocarditis, and other infections. Treatment duration was evaluated as the total number of prescription days. Concomitant medications were detected by overlapping the prescription periods. The duration of warfarin therapy was classified as >120, 121–180, and 181+ days.

The propensity score-matching method was employed to minimize confounding. We analyzed potential factors affecting the selection of cephalosporins with or without the NMTT side chain (age, sex, concomitant medications, concomitant antibiotics, underlying diseases, types of diseases requiring warfarin use, types of infections, warfarin therapy duration, and cephalosporin therapy duration) using a multivariate logistic model. We then calculated the propensity score using the significant factors. Pairs of patients from the NMTT and non-NMTT groups were matched using the nearest neighbor pair-matching algorithm within a specified caliper (standard deviation of the logit of the propensity score = 0.2) [12]. After confirming statistical balance between the two groups, we evaluated the above-mentioned outcomes. A standardized difference of <0.1 indicated an adequate variable balance [13].

For comparison, Mann–Whitney U test was used for continuous variables because they were confirmed to be non-normally distributed by the Shapiro–Wilk test. Categorical variables were compared using Pearson’s chi-square or Fisher’s exact test.

Results with a *P*-value of <0.05 were considered statistically significant. Statistical analyses were performed using JMP 14® software (SAS Institute, Inc., Cary, NC, USA).

Due to data anonymity, the institutional review board of the Faculty of Pharmaceutical Sciences of Hokkaido University waived informed consent.

As shown in Fig. 1, 203 patients were classified into the NMTT (*n* = 73) and non-NMTT groups (*n* = 130). No significant differences were observed between the NMTT (*n* = 50) and non-NMTT (*n* = 50) groups after propensity score matching (Table 1). Standardized difference of <0.1 was obtained for almost all variables, except for three variables. In each group, the number of eligible patients for each antibiotic before and after propensity score matching was as follows: the NMTT group - CTM (*n* = 13 and 9), CMZ (38 and 27), and SBT-CPZ (22 and 14); and the non-NMTT group - CTRX (110 and 42), CTX (6 and 3), and CAZ (14 and 5). Patients who received CPZ did not meet the inclusion criteria.

The proportion of patients administered vitamin K during cephalosporin therapy was 6.0% in both groups after propensity score matching (Table 2). These patients received a single-dose intravenous administration of menatetrenone, 3–12 days after starting cephalosporins. No patient exhibited bleeding events. Among patients who did not receive vitamin K preparations and did not discontinue warfarin during the cephalosporin therapy (*n* = 46, in both groups), the proportion of patients subjected to a reduction in the daily dose of warfarin was 6.5% and 4.3% in the NMTT and non-NMTT groups, respectively.

Although a standardized difference of <0.1 was not obtained for only three variables, the statistical balance between the NMTT and non-NMTT groups was also confirmed by propensity score matching (Table 1) [13]. The proportion of patients administered vitamin K was the same (Table 2, both 6%). All patients received a single-dose intravenous administration of menatetrenone, probably for warfarin reversal. Additionally, the proportion of patients subjected to warfarin dose reduction was also similar between the two groups. These results partially suggest that the risk of over-anticoagulation by cephalosporins does not differ with or without the NMTT side chain. Furthermore, bleeding events were not observed; however, several studies that assessed bleeding events demonstrated a relatively higher proportion of bleeding events [10–11].

For this reason, we excluded patients who had undergone surgery. Furthermore, the JMDC claims database contains data of only patients under 75 years of age. Additionally, we explored the occurrence of bleeding events only during the cephalosporin therapy, whereas previous studies had a follow-up period of several months [10–11]. Thus, our results suggest that the bleeding risk is low in both groups; this information is important in clinical practice. Even without the concomitant use of warfarin, cephalosporins with the NMTT side chain cause hypoprothrombinemia [14]. Therefore, if the PT-INR values could be evaluated, a higher proportion may be recorded in the NMTT group. This was partially consistent with our finding that the number of patients in the non-NMTT group in whom the warfarin dose was increased was slightly higher (Table 2).

Our study had some limitations. First, as we evaluated the use of warfarin according to the total number of prescription days, the actual use of warfarin could not be evaluated. There is a possibility that warfarin discontinuation or dose reduction could not be detected. Second, the accuracy of diagnoses (i.e., their ICD-10 codes), such as underlying diseases and types of infections, was not determined. Third, the effects of warfarin are influenced by various factors [1–2, 10–11], some of which could not be evaluated (e.g., cephalosporin dose). Finally, 50 patients were secured per group after propensity score matching; however, the sample size was not large enough. For example, 89 patients were required in each group if the proportion of patients administered vitamin K had been set at 6.0% in the non-NMTT group and the non-inferiority test was performed comparing values with the NMTT group values under the following conditions: (1) power (1-beta) = 80%, (2) alpha level for the one-sided test = 0.025, and (3) margin of non-inferiority = 10% [15]. Furthermore, we could not calculate sample size in beforehand because there was no evidence to estimate the proportion of bleeding events.

With these limitations, we could not determine whether the risk of over-anticoagulation is affected by the presence or absence of the NMTT side chain. However, as described above, we showed the proportion of bleeding events was sufficiently low regardless of the presence/absence of the NMTT side chain in the second- and third-generation cephalosporins administered with warfarin at least in

patients who did not undergo surgery and those under 75 years old. These findings will help make decisions with respect to drug selection during warfarin therapy.

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Figure legend

Fig. 1. Flowchart of patient selection.

NMTT: *N*-methyl-thio-tetrazole.

Tables

Table 1. Comparison of the Characteristics of Patients Before and After Propensity Score Matching.

Description	Before propensity score matching				After propensity score matching			
	NMTT group (*n* = 73)	Non-NMTT group (*n* = 130)	*P*-value	Std diff	NMTT group (*n* = 50)	Non-NMTT group (*n* = 50)	*P*-value	Std diff
Age (years), median (IQR) [range]	59 (48.5–63) [30–73]	61 (50–67) [24–74]	0.057 †	0.224	59 (50–63.5) [30–73]	60 (47–66) [24－74]	0.646 †	0.018
Sex (male), n (%)	51 (69.9)	84 (64.6)	0.447 ‡	0.112	33 (66.0)	32 (64.0)	0.834 ‡	0.042
Sex (female), n (%)	22 (30.1)	46 (35.4)			17 (34.0)	18 (36.0)		
Concomitant medications, n (%)								
Antiplatelet agents	19 (26.0)	33 (25.4)	0.920 ‡	0.015	10 (20.0)	8 (16.0)	0.603 ‡	0.104
Histamine H_2-receptor antagonists	16 (21.9)	18 (13.8)	0.139 ‡	0.212	8 (16.0)	8 (16.0)	1.000 ‡	0.000
Proton-pump inhibitors	28 (38.4)	60 (46.2)	0.282 ‡	0.158	20 (40.0)	19 (38.0)	0.838 ‡	0.041
Azole antifungals	1 (1.37)	1 (0.77)	1.000 §	0.058	0 (0.0)	0 (0.0)	—	—
Concomitant antibiotics, n (%)								
Macrolides	1 (1.37)	6 (4.62)	0.425 §	0.191	1 (2.00)	1 (2.00)	1.000 §	0.000
Tetracyclines	0 (0.0)	1 (0.77)	1.000 §	0.125	0 (0.0)	0 (0.0)	—	—
Other beta-lactam antibiotics	4 (5.48)	4 (3.08)	0.462 §	0.119	2 (4.00)	3 (6.00)	1.000 §	0.092
Quinolones	4 (5.48)	5 (3.85)	0.725 §	0.078	3 (6.00)	3 (6.00)	1.000 §	0.000
Beta-lactam antibacterials, penicillins	0 (0.0)	4 (3.08)	0.299 §	0.252	0 (0.0)	0 (0.0)	—	—

Sulfamethoxazole-trimethoprim	2 (2.74)	1 (0.77)	0.294 [§]	0.151	2 (4.00)	1 (2.00)	1.000 [§]	0.117
Aminoglycosides	1 (1.37)	3 (2.31)	1.000 [§]	0.070	0 (0.0)	0 (0.0)	—	—
Anti-MRSA agents	0 (0.0)	4 (3.08)	0.299 [§]	0.252	0 (0.0)	0 (0.0)	—	—
Underlying diseases, n (%)								
Heart failure	40 (54.8)	84 (64.6)	0.168 [‡]	0.201	28 (56.0)	26 (52.0)	0.688 [‡]	0.080
Hypertension	44 (60.3)	100 (76.9)	0.012 [‡, *]	0.365	31 (62.0)	32 (64.0)	0.836 [‡]	0.041
Diabetes mellitus	36 (49.3)	93 (71.5)	0.002 [‡, *]	0.467	29 (58.0)	29 (58.0)	1.000 [‡]	0.000
Prior stroke or transient ischemic attack	27 (37.0)	46 (35.4)	0.820 [‡]	0.033	18 (36.0)	19 (38.0)	0.836 [‡]	0.041
Renal dysfunction	11 (15.1)	32 (24.6)	0.110 [‡]	0.241	10 (20.0)	10 (20.0)	1.000 [‡]	0.000
Gastrointestinal dysfunction	48 (65.8)	68 (52.3)	0.063 [‡]	0.276	32 (64.0)	30 (60.0)	0.680 [‡]	0.082
Type of diseases for warfarin use, n (%)								
Atrial fibrillation	37 (50.7)	67 (51.5)	0.907 [‡]	0.017	27 (54.0)	25 (50.0)	0.689 [‡]	0.080
Venous thromboembolism	20 (27.4)	32 (24.6)	0.663 [‡]	0.063	14 (28.0)	14 (28.0)	1.000 [‡]	0.000
After a valve replacement	8 (11.0)	13 (10.0)	0.830 [‡]	0.031	4 (8.00)	6 (12.0)	0.505 [‡]	0.134
Others	16 (21.9)	28 (21.5)	0.950 [‡]	0.009	10 (20.0)	11 (22.0)	0.806 [‡]	0.049
Type of infections, n (%)								
Pneumonia	13 (17.8)	44 (33.8)	0.015 [‡, *]	0.373	12 (24.0)	14 (28.0)	0.648 [‡]	0.091
Cholangitis and cholecystitis	10 (13.7)	6 (4.62)	0.025 [‡, *]	0.319	5 (10.0)	6 (12.0)	0.749 [‡]	0.064
Bacteremia	3 (4.11)	27 (20.8)	0.001 [‡, *]	0.522	3 (6.00)	2 (4.00)	1.000 [§]	0.092
Gastroenteritis	11 (15.1)	12 (9.23)	0.208 [‡]	0.179	6 (12.0)	5 (10.0)	0.749 [‡]	0.064
Pancreatitis	8 (11.0)	3 (2.31)	0.019 [§, *]	0.353	2 (4.00)	2 (4.00)	1.000 [§]	0.000

Febrile neutropenia	0 (0.0)	2 (1.54)	0.537 §	0.177	0 (0.0)	0 (0.0)	—	—
Infectious endocarditis	2 (2.74)	7 (5.38)	0.494 §	0.134	0 (0.0)	1 (2.00)	1.000 §	0.202
Other infections	32 (43.8)	50 (38.5)	0.454 ‡	0.109	25 (50.0)	23 (46.0)	0.689 ‡	0.080
Length of warfarin therapy, n (%)								
Less than 120 days	34 (46.6)	66 (50.8)	0.566 ‡	0.084	25 (50.0)	26 (52.0)	0.841 ‡	0.040
121-180 days	4 (5.48)	7 (5.38)	0.977 ‡	0.004	3 (6.00)	2 (4.00)	1.000 §	0.092
181+ days	35 (47.9)	57 (43.8)	0.573 ‡	0.082	22 (44.0)	22 (44.0)	1.000 ‡	0.000
Duration of cephalosporin therapy (IQR) [range]	6 (4–8) [3－21]	7 (4–8.25) [3－42]	0.179 †	0.203	6 (4–8) [3－19]	6 (4–8) [3－14]	0.656 †	0.025

†Mann–Whitney U test, ‡chi-squared test, §Fisher's exact test, *Results with a *P*-value of ≤0.05 were considered statistically significant. Abbreviations: IQR, interquartile range; NMTT, N-methyl-thio-tetrazole; MRSA, methicillin-resistant *Staphylococcus aureus*; Std diff, standardized difference. There are some overlaps in the types of diseases requiring warfarin use and types of infections. A standardized difference of <0.1 suggests adequate variable balance after propensity matching.

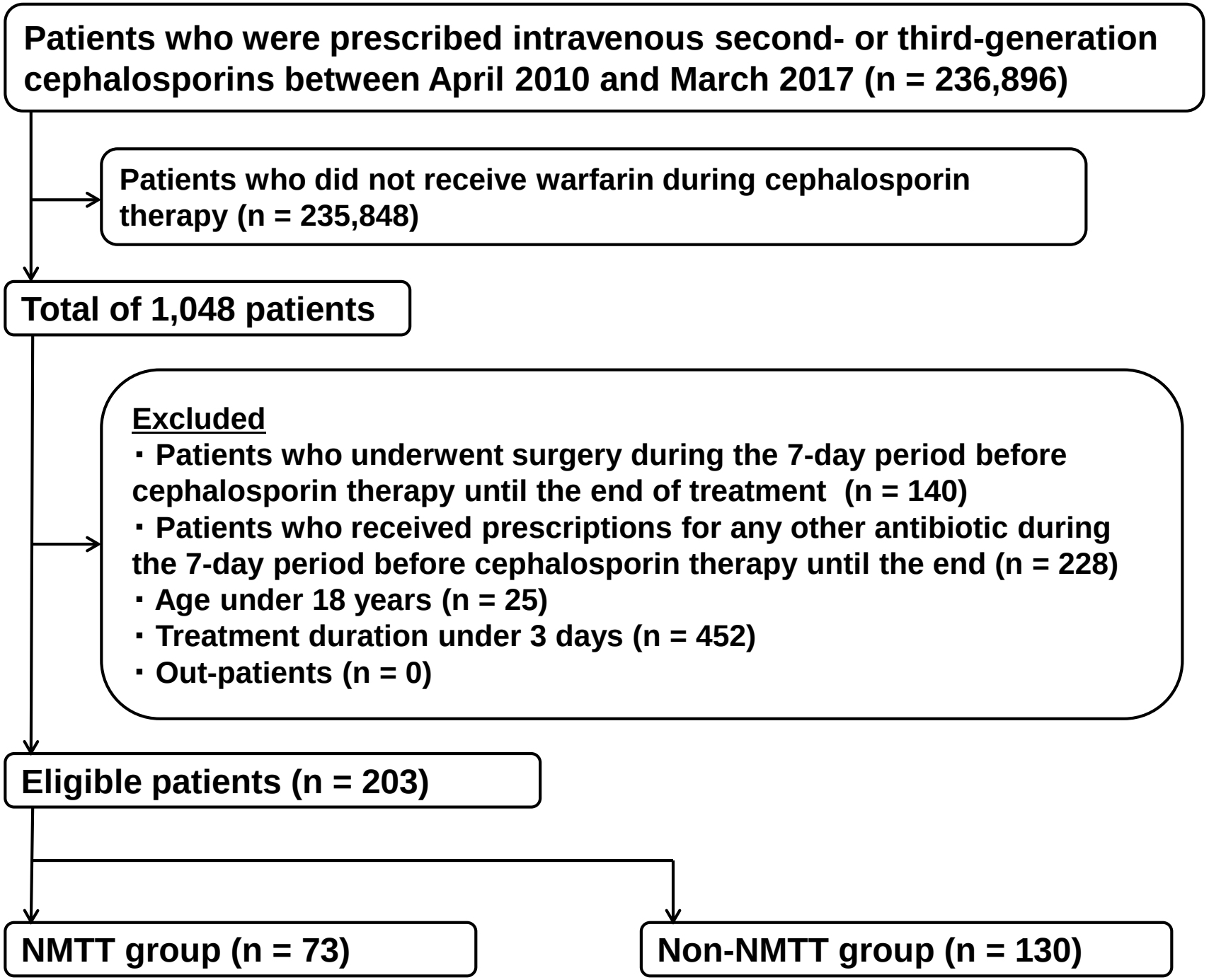
Table 2. Comparison of Changes in the Effects of Warfarin Between the NMTT and Non-NMTT Groups.

Description	NMTT group	Non-NMTT group	*P*-value
Vitamin K administration, n/n (%)	3/50 (6.0)	3/50 (6.0)	1.000 ‡
Bleeding events, n/n (%)	0/50 (0.0)	0/50 (0.0)	—
Daily dose of warfarin			
Start of cephalosporin therapy (mg), median (IQR) [range]	2.5 (2–3.5) [1.0–7.5]	3 (2–3.5) [1–7]	0.859 †
End of cephalosporin therapy (mg), median (IQR) [range]	2.5 (2–3.5) [0.5–7.5]	3 (2–3.75) [1.0–6.5]	0.333 †
Proportion of dose reductions, n/n (%)	3/46 (6.5)	2/46 (4.3)	1.000 ‡
Proportion of dose elevations, n/n (%)	0/46 (0.0)	3/46 (6.5)	0.242 ‡

†Mann–Whitney U test, ‡Fisher's exact test.

Abbreviations: IQR, interquartile range; NMTT, N-methyl-thio-tetrazole. Daily dose of warfarin was analyzed only in patients who did not receive vitamin K administration and did not discontinue warfarin during the cephalosporin therapy.

Fig. 1


Patients who were prescribed intravenous second- or third-generation cephalosporins between April 2010 and March 2017 (n = 236,896)
Patients who did not receive warfarin during cephalosporin therapy (n = 235,848)
Total of 1,048 patients
Excluded
・Patients who underwent surgery during the 7-day period before cephalosporin therapy until the end of treatment (n = 140)
・Patients who received prescriptions for any other antibiotic during the 7-day period before cephalosporin therapy until the end (n = 228)
・Age under 18 years (n = 25)
・Treatment duration under 3 days (n = 452)
・Out-patients (n = 0)
Eligible patients (n = 203)
NMTT group (n = 73)
Non-NMTT group (n = 130)