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Prescribing Trends of Fixed-Dose Combination Antibiotics Not Recommended by the WHO (FNRs) for ICU Patients in Six Major Areas of China During a Seven-Year Period

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Objective: To evaluate the prescribing trends of fixed-dose combination antibiotics not recommended by the WHO (FNRs) for intensive care unit (ICU) patients in six major areas of China from 2013 to 2019.

Methods: A descriptive analysis was conducted using the pharmacy prescription data. Prescription data for patients admitted to the ICU were extracted from the Hospital Prescription Analysis Cooperative Project. Trends in FNR use were analyzed over a seven-year period, and the trends were further analyzed at the specific drug and hospital levels.

Results: A total of 15,596,620 prescriptions were eligible for analysis, and 1,492,793 patients were included. Among these patients, 91,515 (6.13%) received FNRs. The annual number of ICU patients who received FNR showed an increasing trend (P=0.007), but the percentage per year did not (P=0.764). The FNR use was usually higher in male patients than in female patients (P<0.001). Patients aged > 60 years had the highest percentage of patients who received FNRs (P<0.001). Among the eight FNRs identified in this study, cefoperazone/sulbactam was the most commonly used FNR in both patient numbers and prescribed hospitals, followed by piperacillin/sulbactam. The use of cefotaxime/sulbactam was less common but showed an increasing trend. There were significant differences among the regions.

Conclusion: This study investigated the national landscape of FNR use among ICU patients. Attention should be given to the frequent use of FNRs in these patients. Data on the real-world effectiveness and safety of FNRs are urgently required.

Keywords: antibiotic use, fixed-dose combination, irrational, prescription, cefoperazone, sulbactam

Introduction

Antibiotics play a pivotal role in combating infectious diseases, necessitating their rational use. Severe infections are prevalent in patients admitted to intensive care units (ICUs), and antibiotics are commonly administered to these patients.[1] The rational use of antibiotics is paramount for preserving drug efficacy, minimizing adverse effects, conserving medical resources, and safeguarding the health of patients.[2–5] Conversely, inappropriate use of antibiotics has led to decreased effectiveness, emergence of drug-resistant bacteria, and increased costs.[6,7] Therefore, rational use of antibiotics is crucial for ICU infection management.[2,8,9]

Among all antibiotics, fixed-dose combination antibiotics (FDCAs) have become increasingly widespread.[10–12] These drugs combine multiple active ingredients in a fixed ratio to improve treatment convenience, compliance, and potential synergistic effects.[13,14] However, pharmacokinetic mismatches, insufficient evidence-based support, individual differences and regulatory and compliance issues may render certain FDCAs inappropriate for use in specific clinical

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scenarios.[3,15] The WHO listed 103 combinations of FDCAs not recommended (FNR) in the 2021 AWaRe classification. These FNRs are not evidence-based or recommended by international guidelines, and concerns are raised about their efficacy, safety and emergence of antimicrobial resistance (AMR).[10,16–18] Despite these potential disadvantages, multiple FNRs have been approved and widely used in various countries, including China.[16,19] There is little data regarding the use of FNR in ICU patients, which is important for antimicrobial stewardship. This study aimed to provide national data on FNR use in ICU patients for a seven-year period utilizing a comprehensive prescription database, and the results will be helpful for clinical practice, pharmacovigilance, and regulation.

Methods

Study Design

This study was designed as a retrospective descriptive study based on prescription data. Ethical approval was obtained from the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (Reference Number KEYAN2023-0209). The requirement for informed consent was waived as part of the study. The patients' personal information was confidential to the researchers, and the study was conducted in compliance with the Declaration of Helsinki.

Data Source

Prescription data were extracted from the database of the Hospital Prescription Analysis Cooperative Project in China. The database contains prescription information of participating hospitals on 40 randomized days per year, and has been widely used in Chinese pharmacoepidemiology studies.[20–25]

In this study, prescription data from 66 hospitals in Beijing, Hangzhou, Chengdu, Guangzhou, Shanghai, and Tianjin were selected because these hospitals participated in the program continuously from 2013 to 2019 and were located in the north, west, south, and east, thus covering a wide area of China. Brief hospital information is shown in Table S1.

Prescription Inclusion and Data Extraction

Prescriptions meeting the following criteria were included in the analysis: (1) prescriptions written during 2013 and 2019, (2) prescriptions from the aforementioned hospitals, and (3) prescriptions written for patients admitted to the ICU. The following information about prescriptions was extracted: patient code, sex, age, date, location, diagnosis, and the generic name and price of antibiotics. Prescriptions with missing data were excluded. Patient codes were reorganized in the dataset so that individual participants could not be identified. The study was conducted between October 2023 and January 2024.

Analysis

The main results were the yearly proportion of patients who received FNRs and their trends. Any drug within the FDCAs not recommended by the WHO was defined as an FNRs. The yearly number of ICU patients was calculated using the patient code in the extracted prescriptions, and the yearly number of patients who received FNR was calculated by counting the number of patients who had at least one FNR prescription. The characteristics of the patients who received FNRs are descriptively presented. The proportion of patients receiving FNRs each year was calculated using the following equation, and the overall trends of FNR use were described for the 7-year observation period: trends in FNR use according to sex, region, and specific FNR were evaluated.

$$\text{The proportion of patients receiving FNRs} = \frac{\text{The number of ICU patients who received FNRs}}{\text{The number of ICU patients}} \tag{1}$$

Subgroup analyses by age, sex, specific drugs and geographical religion were conducted. Four age groups were set to determine whether the trends in FNR use were driven by a particular age group. The four age groups were children and adolescents (2–17 years), young adults (18–45 years), middle-aged adults (46–59 years), and older adults (60 years and older).

The data were processed using Access software (Microsoft, Redmond, WA, United States). The chi-square test was used to compare patients in males vs females in each year, and the Mann–Kendall trend test was used to assess trends in prescribed drugs. A log-linear test was used to assess trends in proportions. All the statistical analyses were carried out using R V4.0.5 software. Statistical significance was set at a P value < 0.05.

Results

Characteristics and Overall Trends of FNR of Included Prescriptions

A total of 15596620 prescriptions were eligible for analysis, and 1492793 patients were included. Among these patients, 91515 (6.13%) received FNRs. As shown in Figure 1, the yearly number of ICU patients who received FNRs showed an increasing trend (P=0.007), while the percentage of these patients did not show a significant trend over 7 years (P=0.764). The demographic characteristics of the patients and those who received FNR treatment are shown in Table 1. The number of male patients was usually greater than that of female patients (chi-square test, P<0.001). Patients aged > 60 years had the highest percentage of patients who received FNRs (chi-square test, P<0.001). However, the proportion of FNR users among patients aged 18–45 years increased during the study period (P= 0.035).

Trends in Specific Drugs

Eight FNRs were identified in the present study, seven of which were compound preparations of β-lactams and enzyme inhibitors. The prescription trends for each FNR were analyzed. As shown in Figure 2, the use of cefoperazone/sulbactam ranked first, followed by piperacillin/sulbactam, cefoperazone/tazobactam, mezlocillin/sulbactam, cefotaxime/sulbactam, ceftriaxone/tazobactam, and amoxicillin/sulbactam. Detailed data regarding the total amount of each medication used and the proportion of ICU patients using the medication are shown in Table 2. The use of cefoperazone/sulbactam and mezlocillin/sulbactam significantly increased prescription volume (both P <0.05). Concurrently, a notable decrease was observed in the proportion of piperacillin/sulbactam users (P=0.07), whereas a substantial increase in the proportion of cefotaxime/sulbactam users was detected (P=0.048).

Table 3 shows the number and proportion of hospitals providing each FNR. Cefoperazone/sulbactam is the most widely used treatment, followed by piperacillin/sulbactam. Other FNRs were prescribed in fewer than 30% of the hospitals, while cefotaxime/sulbactam showed an increasing trend (P=0.011).

Trends by Geographical Religions

The prescription trends of FNR were further analyzed according to different geographical regions. As shown in Table 4 and Table S2, significant differences exist among the regions. The proportion of patients receiving FNR was greater in Guangzhou (17.2%, chi-square test, P<0.001), while the proportions in Hangzhou and Chengdu were lower (3.82% and 3.83%, chi-square test, P<0.001). The number of patients receiving FNRs increased in three regions (Hangzhou, Tianjin, and Guangzhou) (all P<0.05), which calls for special attention.

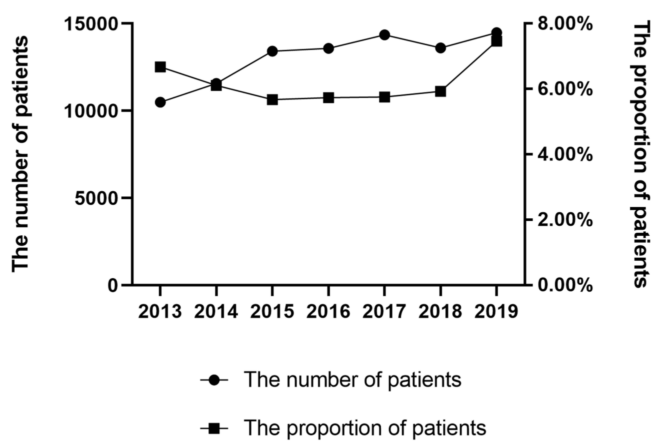

Figure 1 Trends in the yearly number and proportion of patients using FNRs.

Table 1 Demographic Characteristics of Included Patients from 2013 to 2019

			Total	2013	2014	2015	2016	2017	2018	2019	P
ICU patients	Age	2–17	58,088	6305	6629	8569	8452	9718	9445	8970	0.072
		18–45	227,598	26,994	31,095	36,329	36,816	35,509	31,267	29,588	>0.999
		46–59	301,704	34,097	36,874	44,321	47,380	50,043	47,884	41,105	0.133
		>60	905,403	89,725	114,930	147,076	144,077	154,264	140,907	114,424	0.764
	Sex	Male	932525	96,234	116,817	146,752	149,677	156,735	146,790	119,520	0.230
		Female	560268	60,887	72,711	89,543	87,048	92,799	82,713	74,567	0.548
	Total		1492793	157,121	189,528	236,295	236,725	249,534	229,503	194,087	0.368
ICU patients using FNRs	Age	2–17	2585	250	229	412	401	398	464	431	0.133
		18–45	10,991	1230	1334	1630	1693	1653	1639	1812	0.035
		46–59	15,058	1631	1842	2021	2190	2309	2312	2753	0.003
		>60	62,881	7378	8169	9352	9303	9999	9194	9486	0.133
	Sex	Male	59292	6772	7536	8660	8732	9212	8893	9487	0.007
		Female	32223	3717	4038	4755	4855	5147	4716	4995	0.072
	Total		91515	10,489	11,574	13,415	13,587	14,359	13,609	14,482	0.006
Proportion	Age	2–17	4.45%	3.97%	3.45%	4.81%	4.74%	4.10%	4.91%	4.80%	0.230
		18–45	4.83%	4.56%	4.29%	4.49%	4.60%	4.66%	5.24%	6.12%	0.016
		46–59	4.99%	4.78%	5.00%	4.56%	4.62%	4.61%	4.83%	6.70%	0.548
		>60	6.95%	8.22%	7.11%	6.36%	6.46%	6.48%	6.52%	8.29%	0.764
	Sex	Male	6.36%	7.04%	6.45%	5.90%	5.83%	5.88%	6.06%	7.94%	>0.999
		Female	5.75%	6.10%	5.55%	5.31%	5.58%	5.55%	5.70%	6.70%	0.44
	Overall		6.13%	6.68%	6.11%	5.68%	5.74%	5.75%	5.93%	7.46%	0.764

Notes: P-value for trend in number and proportion of patients were assessed by Mann–Kendall trend test and log-linear test, respectively. The proportion is defined as the number of patients using FNRs divided by the total number of ICU patients.

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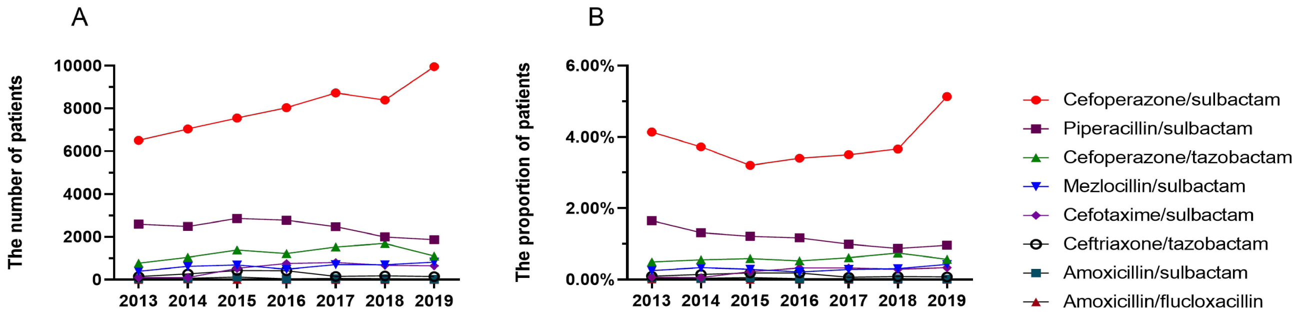

Figure 2 Trends in use of each FNR. (**A**) The number of patients. (**B**) The usage proportion trends by drug.

Discussion

To our knowledge, this study is the first to analyze trends in the use of FNR over time at the national level using surveillance data. As the sample was large and covered six areas of China, the results are nationally representative. More than 6% of ICU patients have used FNR, and this proportion has been increasing in general (7.46% in 2019). The proportion of elderly patients using FNR was always greater than the average. Eight FNRs were identified in this study. Cefoperazone/sulbactam and piperacillin/sulbactam are frequently and widely used. The use of cefotaxime/sulbactam has also increased.

Currently, there are limited data available on the use of FNRs at the national level. The available information primarily pertains to the consumption of FDC antibiotics, and only a few literature reports mention the use of specific FNR.[10,26–30] According to a previous report that analyzed antibiotic usage in 76 countries from 2000 to 2015, FNR antibiotics were employed in 20 (26.3%) countries.[29] The contribution of FNR use to overall antibiotic consumption was less than 3%. However, the usage of specific countries, such as Egypt, India, and Pakistan, were significantly higher, at 9.6%, 7.5%, and 4.0%, respectively.[29] Another study had reviewed global antibiotic sales data and identified 119 FDC antibiotics. The majority (92%) of these FDCs were not approved by the FDA and comprised 5.1% of total sales. China had the second highest FDC count (25/119). Although only 8 FNRs were identified in this study, more than 6% of the ICU patients had received FNR. This percentage was high compared with existed reports. Thus, special attention should be given to the better management of FNRs.

Cefoperazone/sulbactam was the most frequently used FNR in this study, as it has shown good clinical effectiveness and is recommended as a first-line empirical antibiotic in multiple anti-infection guidelines in China.[31] A meta-analysis of 110 studies on the effectiveness and cure rate of cefoperazone/sulbactam showed that the effectiveness rate of cefoperazone/sulbactam was 80.3%, and the cure rate was 50.1% for the treatment of clinical infections.[32] An in vitro study showed that the addition of sulbactam to cefoperazone could enhance the antibacterial activity of cefoperazone against carbapenem-resistant *Acinetobacter baumannii* but had no effect on carbapenem-resistant *Pseudomonas aeruginosa*.[33] A literature review showed that if the combination of cefoperazone/sulbactam could achieve pharmacokinetic optimization in human serum, its clinical application could be expanded.[34] The major concern regarding cefoperazone/sulbactam is its potential relationship with coagulopathy and bleeding events, but recent studies have shown that the risk is acceptable.[35,36] Therefore, it is necessary to obtain more convincing data to support or discourage the use of cefoperazone/sulbactam.

Piperacillin/sulbactam, the second most frequently used FNR, has successfully addressed the issues of high chemical cost and frequent penicillin allergic reactions associated with piperacillin/tazobactam by replacing tazobactam with sulbactam. According to an in vitro experiment,[37] the antibacterial activities of the two are similar for gram-positive bacteria. However, for gram-negative bacteria, especially *Escherichia coli* and *Proteus vulgaris*, the antibacterial activity of piperacillin/sulbactam was significantly higher than that of piperacillin/tazobactam. The antibacterial effects of other Enterobacteriaceae and *Pseudomonas aeruginosa* strains were comparable. Notably, for *Stenotrophomonas maltophilia*, the activity of piperacillin/sulbactam was greater. A randomized, single-blind, controlled clinical trial in China showed that piperacillin/sulbactam can be used as a suitable substitute for piperacillin/tazobactam for the treatment of

Table 2 Number of ICU Patients with a Specific FNR from 2013 to 2019

	Total	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**P1**	**P2**
Cefoperazone/sulbactam	56229(3.77%)	6512(4.14%)	7050(3.72%)	7553(3.20%)	8041(3.40%)	8730(3.50%)	8393(3.66%)	9950(5.13%)	0.007	0.764
Piperacillin/sulbactam	17077(1.44%)	2597(1.65%)	2490(1.31%)	2866(1.21%)	2777(1.17%)	2481(0.99%)	1994(0.87%)	1872(0.96%)	0.072	0.007
Cefoperazone/tazobactam	8754(0.59%)	767(0.49%)	1044(0.55%)	1388(0.59%)	1222(0.52%)	1532(0.61%)	1698(0.74%)	1103(0.57%)	0.133	0.133
Mezlocillin/sulbactam	4410(0.30%)	399(0.25%)	621(0.33%)	684(0.29%)	486(0.21%)	703(0.28%)	693(0.30%)	824(0.42%)	0.035	0.368
Cefotaxime/sulbactam	3586(0.24%)	93(0.06%)	97(0.05%)	527(0.22%)	752(0.32%)	801(0.32%)	667(0.29%)	649(0.33%)	0.133	0.048
Ceftriaxone/tazobactam	1740(0.12%)	149(0.09%)	271(0.14%)	430(0.18%)	418(0.18%)	151(0.06%)	178(0.08%)	143(0.07%)	0.548	0.45
Amoxicillin/sulbactam	395(0.026%)	57(0.036%)	64(0.034%)	125(0.053%)	37(0.016%)	50(0.020%)	44(0.019%)	18(0.009%)	0.133	0.071
Amoxicillin/flucloxacillin	48(0.003%)	10(0.006%)	29(0.015%)	9(0.004%)	—	—	—	—	—	—

Notes: Data were presented by number (percentage) of patients. P1-value for trend in number of patients which were assessed by Mann–Kendall trend test; P2- value for trend in proportions, which is defined as the number of patients using FNRs divided by the total number of ICU patients.

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Table 3 Number and Proportion of Hospitals Providing Specific FNR from 2013 to 2019

	Total	2013	2014	2015	2016	2017	2018	2019	P1	P2
Cefoperazone/Sulbactam	64(100%)	56(87.5%)	61(95.3%)	58(87.9%)	58(90.6%)	62(96.9%)	63(98.4%)	62(96.9%)	0.065	0.048
Piperacillin/Sulbactam	32(50.0%)	26(40.6%)	27(42.2%)	28(42.4%)	29(45.3%)	24(37.5%)	24(37.5%)	23(35.9%)	0.287	0.288
Cefoperazone/Tazobactam	13(20.3%)	10(15.6%)	11(17.2%)	12(18.20%)	9(14.10%)	11(17.2%)	10(15.6%)	10(15.6%)	0.751	0.751
Mezlocillin/Sulbactam	20(31.3%)	13(20.3%)	14(21.9%)	12(18.2%)	11(17.2%)	15(23.4%)	13(20.3%)	11(17.2%)	0.538	0.539
Cefotaxime/Sulbactam	11(17.2%)	2(3.1%)	5(7.8%)	8(12.1%)	8(12.5%)	8(12.5%)	10(15.6%)	10(15.6%)	0.011	0.006
Ceftriaxone/Tazobactam	6(9.38%)	3(4.69%)	6(9.38%)	5(7.58%)	5(7.81%)	5(7.81%)	4(6.25%)	3(4.69%)	0.341	0.539
Amoxicillin/Sulbactam	5(7.81%)	2(3.13%)	4(6.25%)	4(6.06%)	2(3.13%)	2(3.13%)	1(1.56%)	1(1.56%)	0.076	0.057
Amoxicillin/Flucloxacillin	3(4.69%)	3(4.69%)	2(3.13%)	1(1.52%)	—	—	—	—	—	—

Notes: P1-value for trend in number of hospitals which FNR were prescribed, which were assessed by Mann–Kendall trend test; P2- value for trend in proportions, which is defined as the number of hospitals using FNRs divided by the total number of hospitals in specific year.

Table 4 Trends in FNR Use by Geographical Regions from 2013 to 2019

Cities	Total	2013	2014	2015	2016	2017	2018	2019	P1	P2
Shanghai	7183(5.74%)	925(5.33%)	1066(6.35%)	1078(6.13%)	901(5.74%)	1013(6.40%)	990(5.98%)	1210(4.80%)	0.548	0.764
Hangzhou	11533(3.82%)	1305(3.88%)	1469(3.77%)	1653(3.97%)	1716(4.22%)	1765(4.00%)	1720(3.39%)	1905(3.66%)	0.007	0.764
Beijing	14984(8.08%)	2147(7.50%)	1934(7.44%)	2029(7.22%)	2241(8.45%)	2321(9.47%)	2278(8.90%)	2034(7.78%)	0.368	0.368
Tianjin	9303(6.48%)	1031(7.72%)	1001(5.37%)	1127(5.01%)	1160(5.29%)	1788(7.62%)	1500(7.00%)	1696(7.63%)	0.035	0.764
Chengdu	22445(3.83%)	2572(5.28%)	3336(4.63%)	3663(3.41%)	3328(3.00%)	3198(2.73%)	3012(3.38%)	3336(8.31%)	>0.999	0.550
Guangzhou	26067(17.2%)	2509(16.3%)	2768(16.3%)	3865(20.3%)	4241(20.2%)	4274(17.5%)	4109(15.7%)	4301(15.2%)	0.016	0.288

Notes: Data were presented by number (percentage) of patients who received FNRs. P1-value for trend in number of patients, which were assessed by Mann–Kendall trend test. P2- value for trend in proportions, which was assess using log-linear test.

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community-acquired respiratory and urinary tract infections caused by β-lactamase-producing bacteria.[38] In vitro experiments further confirmed that the addition of sulbactam to piperacillin improved the sensitivity of *Pseudomonas aeruginosa* and *Acinetobacter baumannii to piperacillin*.[39]

There are only some in vitro studies but little high-quality evidence-based medical evidence for cefoperazone/tazobactam, mezlocillin/sulbactam, cefotaxime/sulbactam, amoxicillin/sulbactam and amoxicillin/flucloxacillin.[27,40,41]

For drugs that are widely used in clinical settings and demonstrate clear therapeutic benefits, large-scale randomized controlled trials can be conducted to provide higher-level evidence of their efficacy and safety. This will enable a more comprehensive evaluation of drug effectiveness and safety, thereby providing doctors and patients with accurate information. For FNR, which has been proven to have no better clinical efficacy, standardized management systems should be established. These include developing guidelines for their use, limiting unnecessary utilization, promoting safer and more effective drug alternatives, and other measures. Additionally, healthcare facilities should strengthen supervision and management to ensure effective control of FNR.

This study had several limitations. First, our analysis relied solely on prescription data, thereby rendering an evaluation of the adequacy of antimicrobial therapy as well as its outcomes infeasible. Additionally, there is a dearth of data pertaining to indications for prescribing antimicrobials, a subject that merits further exploration in subsequent research.

Conclusion

This study investigated the national landscape of FNR use among ICU patients in China. The overall FNR use in these patients was > 6%, which calls for special attention to rational use and better management. Among the eight FNRs identified in this study, cefoperazone/sulbactam and piperacillin/sulbactam were the most frequently used and widely distributed. Data on the real-world effectiveness and safety of these FNRs are urgently required to support or discourage their use.

Data Sharing Statement

The original contributions presented in this study are included in the article/supplementary material, and further inquiries can be directed to the corresponding authors.

Ethics Approval

Studies involving human participants were reviewed and approved by the Ethics Committee of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University (Reference Number KEYAN2023-0209). Written informed consent for participation was not required for this study, in accordance with national legislation and institutional requirements.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No potential competing interest was reported by the authors.

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