BMC Cardiovascular Disorders

RESEARCH

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Anticoagulation therapy and related outcomes among Asian patients after bioprosthetic valve replacement

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Abstract

Importance An inadequate number of studies focused on Asian populations have investigated the safety of warfarin usage among Asian patients with tissue valve aortic valve replacement (AVR) or mitral valve replacement (MVR).

Objective This study aimed to identify the optimal international normalized ratio (INR) range for Asian patients during a 1-year follow-up after tissue valve replacement.

Design, setting, participants We conducted a retrospective cohort study of patients who underwent tissue valve AVR, MVR, and double valve replacement (DVR) between January 1, 2001, and December 31, 2018. Data were sourced from the Chang Gung Research Database, an electronic structured medical database covering 4 regional hospitals and 3 medical centers. The exposure of interest was INR level.

Main outcomes and measures The outcomes of primary and secondary interest were composite thromboembolic events and bleeding events during the 1-year follow-up, respectively. The relationship between INR level and the risk of thromboembolic events was explored using a logistic regression model in which the INR value was treated as a flexible restricted cubic spline. Because having atrial fibrillation (AF) greatly would greatly affect the INR control result, the analysis was stratified by AF status.

Results A total of 1059 participants were eligible for this study. The mean patient age was 65.5 (11.9) years; 592 (55.9%) participants were men, and 467 (44.1%) were women. A total of 447 had AF and 612 did not. The lowest bleeding risk was observed at an INR level around 1.9 to 2.0. An INR level of 1.84 (hazard ratio [HR], 0.49; 95% confidence interval [CI]: 0.36–0.67) and 1.7 (HR, 0.78; 95% CI: 0.62–0.99) corresponded to the lowest risk of thromboembolic events in patients with pre-existing AF and those without, respectively. The INR level corresponding to the lowest risk of thromboembolic events was approximately 1.7 in patients without AF but with MVR, DVR, or isolated AVR.

Conclusions and relevance For patients who underwent tissue valve replacement, the bleeding risk was elevated when the INR was greater than 2.0, but the risk of thromboembolic event increased only when the INR was lower than 1.84 in the AF group and 1.7 in the non-AF group, regardless of whether the patient received AVR, MVR, or DVR.

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Key points

Question: Is a low international normalized ratio (INR) target associated with a low complication rate among Asian patients who underwent bioprosthetic valve replacement?.

Findings: One thousand fifty-nine patients with tissue valve replacement were recruited for this study. During the 12-month follow-up, a total of 5480 INR records were generated. We correlated complication events such as bleeding and thromboembolism with each INR level to analyze complication rates. In patients with or without atrial fibrillation, both aortic and mitral valve replacement cohorts exhibited the lowest complication rates as evident in an INR range of 1.5 to 2.5, which is below the recommended threshold in the current American College of Cardiology/American Heart Association guidelines.

Meaning: Among the Asian population who underwent bioprosthetic valve replacement, a low INR target was associated with low bleeding risk without an increase in the thromboembolic event rate.

Tweet: For the Asian population, during the 12 months after bioprosthetic valve replacement, the preferred INR target is recommended to be 0.5 lower than that suggested in the current American College of Cardiology/American Heart Association guidelines.

Keywords INR, Warfarin, Bioprosthetic valve replacement

Introduction

Valvular disease affects approximately 41 million people worldwide. Due to humans living increasingly long times, the prevalence of valvular heart disease has been growing, with the majority of cases attributable to rheumatic heart disease in low-income countries and functional degeneration in high-income countries [1].

Guidelines released by the American College of Cardiology, Washington D.C., U.S.A. (ACC) and the American Heart Association, Dallas, Texas, U.S.A. (AHA) in 2020 recommend the use of tissue valves for aortic valve replacement (AVR) in patients who are over 50 years old and for mitral valve replacement (MVR) in patients who are over 65 years old [2].

Tissue valve replacement has become an increasingly common intervention. Despite the higher reoperation risk and the fact that bioprosthetic valves are intended for older patients, an increasing number of relatively young people are opting for tissue valves over mechanical valves. This decision is influenced by an unwillingness to commit to a lifelong regimen of oral anticoagulants and concerns over the drug–food interactions of vitamin K antagonists (VKAs) [3, 4].

According to the 2020 AHA/ACC guideline, the goal VKA anticoagulation international normalized ratio (INR) is 2.5 for both MVR and AVR tissue valve replacements (bioprosthetic valve replacements), but this guideline is based on a low level of evidence (Class 2a). Patients who undergo tissue valve replacement are required to take anticoagulants for 3 to 6 months following surgery. During this period, it is crucial to reach the optimal INR to prevent thromboembolic and bleeding events. However, the AHA/ACC guideline is based on limited data from Western studies and cannot be generalized to Asian populations because racial and ethnic background influences VKA dosage. In contrast to Caucasians, Asians are prone to bleeding under the effect of warfarin, which increases the risk of intracranial hemorrhage [5].

The largest study on the optimal INR for Asians with nonvalvular atrial fibrillation (AF) was conducted in Japan, and its findings suggested an INR left shift of 0.5 is preferred for Asian patients [6]. A recent study by our group revealed that an INR left shift is recommended for Asian patients after mechanical valve replacement [7].

However, to date, no evidence has been presented showing the INR safety range for Asian patients following tissue valve replacement, and the optimal INR for Asian patients also remains unclear.

Therefore, in this study, we utilized a multicenter medical database and focused on patients who underwent tissue valve replacement. We analyzed the correlation between their INR and risk of bleeding or thromboembolic events. We also compared the optimal INR for those with and without AF because this single factor has a significant effect on thromboembolic risk. Our objective was to identify the optimal INR for Asians with or without AF undergoing MVR or AVR tissue valve replacement.

Method

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplemental Table 1).

Data source

Data were collected from the Chang Gung Research Database (CGRD) of Chang Gung Memorial Hospital

(CGMH). Founded in 1976, CGMH has been expanding for almost half a century and now comprises 3 medical centers and 4 regional hospitals. It is one of the largest medical groups in Asia, with over 9000 beds in Taiwan and serving 30 000 outpatients daily. Structured digital medical records have been widely used for the past 2 decades; detailed patient data are encoded, well encrypted, and delabeled for research use. For data generated before 2015, we used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), whereas for data generated after 2016, both the *ICD-9-CM* and the *Tenth Revision* (*ICD-10-CM*) were applied. More information about CGRD has been published elsewhere [8, 9]. Because of personal privacy issues, informed consent was waived by the Institutional Review Board of CGMH (approval number: 202100124B0), but personal medical information was required to be encrypted.

Patient identification

Patients who received AVR and/or MVR with bioprosthetic valves between January 1, 2001, and December 31, 2018, and survived to discharge were included in this study. The date of discharge was defined as the index date. The exclusion criteria were as follows: age less than 20 years, no available INR data, and use of a non-VKA oral anticoagulant (NOAC) during the 1-year follow-up period after discharge. Due to fundamentally different treatment strategies for INR control in patients with and without AF, we divided the cohort into 2 groups: pre-existing AF and non-AF (Fig. 1A). The performance of valve replacement, type of surgery, and type of prosthesis were ascertained by examining the operation notes of 2 authors (TY Liu and SW Chen). The details of validation are provided in the recent work [7]. The existence of pre-existing AF was identified using *ICD* diagnostic codes, an approach which has been validated in previous studies [10, 11].

Follow-up

Each patient was followed from the first INR examination date after the index date until the 365th day after discharge. The data unit of follow-up for each patient was the number and interval of INR examinations. The data unit for each patient was the period from a prior INR examination to the next one. For example, there were 5 rows of data units when the patient had 6 INR examinations within 365 days after discharge. All INR records from outpatient visits were analyzed, whereas only the first record was utilized when multiple INR records for the same emergency department visit or admission were recorded [7].

Covariates

The covariates were age, sex, height, body weight, body surface area, smoking, left ventricular ejection fraction, type of valvular disease, comorbidities, event history, concurrent medications at baseline, and preoperative laboratory data. Surgical characteristics such as etiology, valve brand, valve size, concomitant surgery, and operation time were also extracted from operation notes and discharge notes. If patients had at least 2 outpatient *ICD* diagnoses or 1 inpatient *ICD* diagnosis before the index valve surgery, they were counted as having comorbidities. If there was at least 1 inpatient diagnosis history before INR examination, they were counted as having an event history. Preoperative laboratory data were collected. Medications taken 3 months before the index surgery were also extracted from the pharmacy database. Details concerning the covariates are listed in Table 1.

Outcomes

The outcome of primary interest in the study was composite thromboembolic events, which consisted of ischemic stroke, acute myocardial infarction, systemic thromboembolism, lower extremity systemic thromboembolism, and bowel ischemia. The outcome of secondary interest was composite bleeding events, which were any of the following: hemorrhagic stroke, gastrointestinal bleeding, genitourinary bleeding, and major bleeding. The outcome occurrence was captured in the inpatient setting and defined as 1 day before to 7 days after the date of each INR examination [7]. Each patient was allowed to have multiple episodes of an outcome; however, only 1 episode was recorded for each INR interval [7].

Statistical analysis

The baseline characteristics, surgical characteristics, and follow-up information of patients with and without pre-existing AF were compared using a chi-square test for categorical variables, independent sample t test for continuous variables, and Mann–Whitney U test for apparently skewed continuous variables (ie, aspartate aminotransferase). The relationship between INR level and the risk of events was explored using a logistic regression model in which the INR value was treated as a flexible restricted cubic spline (RCS). Multiple events per patient were allowed due to the data structure accommodating multiple measurements per patient. The location of knots was set as the 5th, 35th, 65th, and 95th percentiles while exploring the possibility of nonlinearity. The within-subject correlation among multiple INR records of the same patient was determined using bootstrap estimates (using 200 bootstrap samples), substituting cluster sampling with replacement for the usual simple sampling with replacement. R version 4.0.2 (R Project for Statistical Computing) and the package "rms" version 5.1 to 3.1 was applied for RCS modeling. SAS version 9.4 (SAS

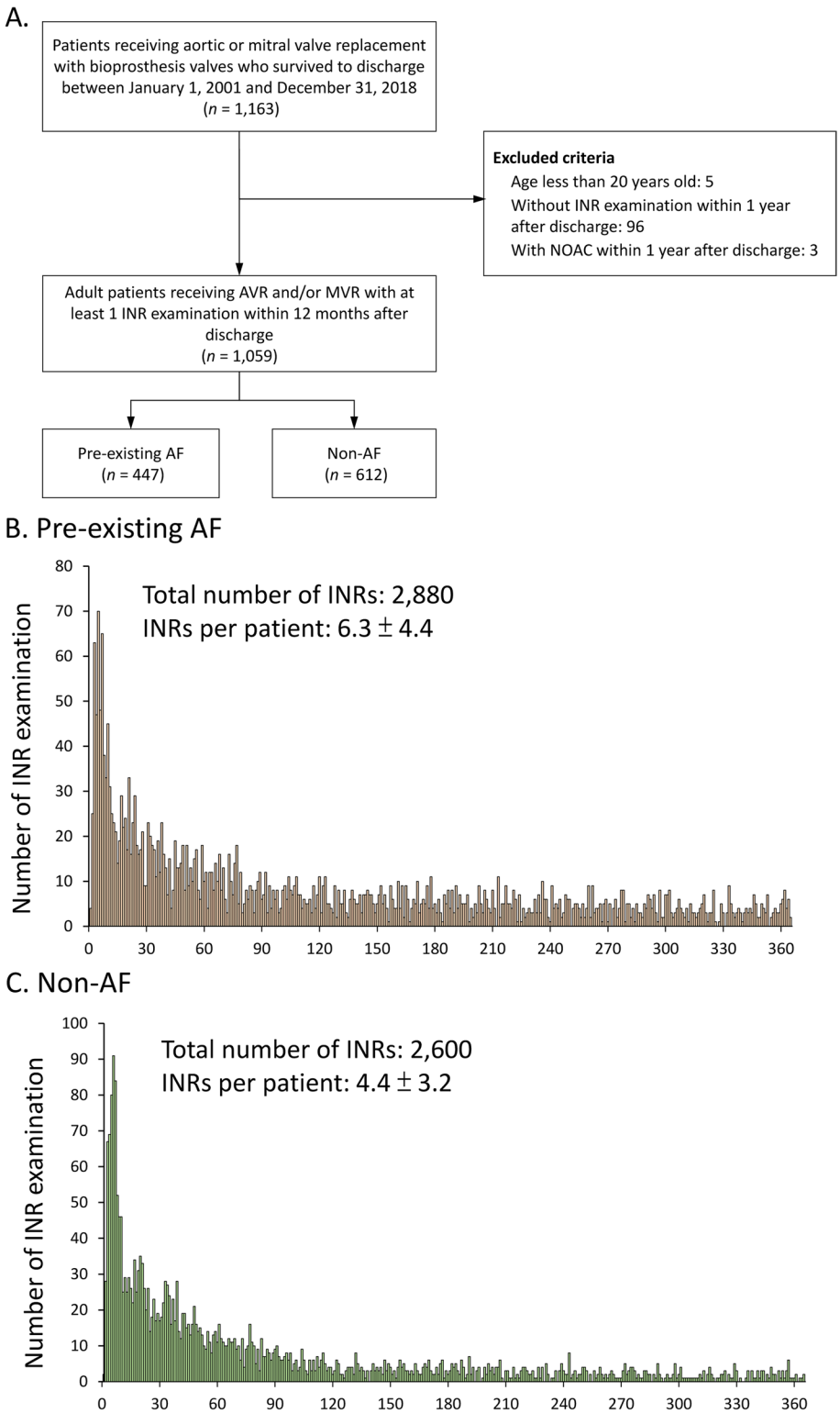

Fig. 1 Flowchart for the inclusion and exclusion of the study patients (**A**) and the number and interval of INR examinations in patients with pre-existing AF (**B**) and without AF (**C**). AF, atrial fibrillation; AVR, aortic valve replacement; INR, international normalized ratio; MVR, mitral valve replacement; NOAC, non-vitamin K antagonist oral anticoagulant

Table 1 Baseline characteristics of patients according to pre-existing diagnosis of atrial fibrillation

Variable	Available number	Total ($n=1,059$)	AF ($n=447$)	Non-AF ($n=612$)	*P*
Age, years	1,059	65.5 ± 11.9	66.9 ± 9.2	64.4 ± 13.5	0.001
Male sex	1,059	592 (55.9)	221 (49.4)	371 (60.6)	< 0.001
Height, cm	982	159.5 ± 11.4	158.6 ± 11.2	160.2 ± 11.6	0.036
Body weight, kg	1,034	58.9 ± 12.3	57.0 ± 11.7	60.2 ± 12.5	< 0.001
Body surface area, m^2	982	1.61 ± 0.20	1.58 ± 0.20	1.63 ± 0.19	< 0.001
Smoking	1,059	228 (21.5)	88 (19.7)	140 (22.9)	0.212
Left ventricular ejection fraction, %	1,030	58.4 ± 14.7	57.8 ± 14.1	58.8 ± 15.2	0.281
Surgical type	1,059				< 0.001
Single arterial valve replacement		614 (58.0)	160 (35.8)	454 (74.2)	
Single mitral valve replacement		312 (29.5)	209 (46.8)	103 (16.8)	
Double valve replacement		133 (12.6)	78 (17.4)	55 (9.0)	
Valvular disease					
Aortic stenosis	1,059	471 (44.5)	152 (34.0)	319 (52.1)	< 0.001
Aortic regurgitation	1,059	337 (31.8)	121 (27.1)	216 (35.3)	0.005
Mitral stenosis	1,059	205 (19.4)	179 (40.0)	26 (4.2)	< 0.001
Mitral regurgitation	1,059	416 (39.3)	213 (47.7)	203 (33.2)	< 0.001
Tricuspid regurgitation	1,059	266 (25.1)	203 (45.4)	63 (10.3)	< 0.001
Comorbid conditions					
Chronic obstructive pulmonary disease	1,059	176 (16.6)	89 (19.9)	87 (14.2)	0.014
Chronic liver disease	1,059	234 (22.1)	97 (21.7)	137 (22.4)	0.791
Chronic kidney disease	1,059	285 (26.9)	133 (29.8)	152 (24.8)	0.075
Hypertension	1,059	602 (56.8)	253 (56.6)	349 (57.0)	0.890
Hyperlipidemia	1,059	312 (29.5)	145 (32.4)	167 (27.3)	0.069
Diabetes	1,059	278 (26.3)	111 (24.8)	167 (27.3)	0.370
Infective endocarditis	1,059	152 (14.4)	30 (6.7)	122 (19.9)	< 0.001
Rheumatic heart disease	1,059	405 (38.2)	271 (60.6)	134 (21.9)	< 0.001
Lung edema	1,059	90 (8.5)	47 (10.5)	43 (7.0)	0.044
Gout	1,059	157 (14.8)	77 (17.2)	80 (13.1)	0.060
Peripheral artery disease	1,059	206 (19.5)	68 (15.2)	138 (22.5)	0.003
Malignancy	1,059	84 (7.9)	24 (5.4)	60 (9.8)	0.008
History of event					
Old ischemic stroke	1,059	134 (12.7)	77 (17.2)	57 (9.3)	< 0.001
Old myocardial infarction	1,059	65 (6.1)	20 (4.5)	45 (7.4)	0.054
History of gastrointestinal bleeding	1,059	161 (15.2)	68 (15.2)	93 (15.2)	0.994
History of intracranial hemorrhage	1,059	48 (4.5)	22 (4.9)	26 (4.2)	0.603
History of major bleeding	1,059	66 (6.2)	31 (6.9)	35 (5.7)	0.419
Heart failure hospitalization	1,059	233 (22.0)	134 (30.0)	99 (16.2)	< 0.001
Concurrent medication at baseline					
Statins	1,059	149 (14.1)	54 (12.1)	95 (15.5)	0.112
Antiplatelet	1,059	409 (38.6)	150 (33.6)	259 (42.3)	0.004
Aspirin	1,059	325 (30.7)	109 (24.4)	216 (35.3)	< 0.001
Clopidogrel	1,059	192 (18.1)	72 (16.1)	120 (19.6)	0.144
Ticagrelor	1,059	24 (2.3)	6 (1.3)	18 (2.9)	0.084
Amiodarone	1,059	220 (20.8)	131 (29.3)	89 (14.5)	< 0.001
Beta-blocker	1,059	587 (55.4)	239 (53.5)	348 (56.9)	0.272
ACEi/ARBs	1,059	572 (54.0)	259 (57.9)	313 (51.1)	0.028
NSAIDs	1,059	159 (15.0)	50 (11.2)	109 (17.8)	0.003
Proton pump inhibitor	1,059	187 (17.7)	74 (16.6)	113 (18.5)	0.421

Table 1 (continued)

Variable	Available number	Total ($n=1,059$)	AF ($n=447$)	Non-AF ($n=612$)	*P*
Pre-operative laboratory data					
Creatinine, mg/dL	1,050	1.22 ± 0.98	1.14 ± 0.72	1.28 ± 1.13	0.027
eGFR, ml/min/1.73m^2	1,050	76.0 ± 35.6	73.5 ± 31.1	77.8 ± 38.5	0.054
Hemoglobin, g/dL	1,053	10.6 ± 1.7	10.5 ± 1.7	10.6 ± 1.7	0.589
WBC, 1000/μL	1,045	13.0 ± 5.5	12.4 ± 4.7	13.4 ± 5.9	0.004
Platelet, 1000/μL	1,045	143.2 ± 53.1	135.9 ± 47.4	148.5 ± 56.3	< 0.001
Bilirubin, mg/dL	429	1.60 ± 1.07	1.79 ± 1.21	1.46 ± 0.93	0.002
AST, U/L	672	55.0 [39.0, 82.0]	66.0 [42.0, 97.0]	50.0 [37.0, 72.0]	< 0.001
ALT, U/L	372	22.0 [16.0, 35.0]	23.5 [16.0, 34.0]	22.0 [16.0, 36.0]	0.671
BUN, mg/dL	1,013	20.1 ± 12.4	19.5 ± 10.3	20.5 ± 13.7	0.238
INR	959	1.30 ± 0.22	1.33 ± 0.22	1.28 ± 0.21	0.001
Albumin, g/dl	418	3.36 ± 0.60	3.42 ± 0.58	3.32 ± 0.61	0.096
HbA1C, %	563	6.3 ± 1.0	6.2 ± 0.8	6.3 ± 1.1	0.060

Data were presented as frequency (percentage), mean ± standard deviation or median [25th percentile, 75th percentiles]

Abbreviations: AF atrial fibrillation, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *NSAID* non-steroidal anti-inflammatory drug, *eGFR* estimated Glomerular filtration rate, *WBC* white blood count, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BUN* blood urea nitrogen, *INR* international normalized ratio, *HbA1C* glycated hemoglobin

Institute) was applied for other statistical analyses. A 2-sided *P* value was considered statistically significant.

Results

Inclusion of patients

This study included a total of 1163 patients who received AVR or MVR with bioprosthetic valves between January 1, 2001, and December 31, 2018, and survived to discharge. After applying exclusion criteria, 1059 adult patients with MVR who had received at least 1 INR examination within 12 months after discharge were analyzed. In this group, 447 (42.2%) patients had pre-existing AF and 612 (57.8%) did not (Fig. 1A). During the 12-month follow-up, a total of 5480 INR records were generated; 2880 from the AF group and 2600 from the non-AF group. The mean number of INR examinations was 6.3 and 4.4 in the AF and non-AF groups, respectively (Fig. 1B-C).

Baseline characteristics

The baseline characteristics are detailed in Table 1. The mean age was 65.5 years (standard deviation [SD] = 11.9 years). The patient population consisted of 592 (55.9%) men and 467 (44.1%) women. The AF group comprised 160 patients (35.8%) who received AVR alone and 287 who received MVR and DVR combined surgery (64.2%). In the non-AF group, 454 (74.2%) received AVR alone, and 158 (25.8%) received MVR and DVR combined surgery. Compared with the non-AF patients, those with pre-existing AF were older; were less likely to be male; had smaller body surface area; had less aortic stenosis and aortic regurgitation; had more mitral stenosis, mitral regurgitation, and tricuspid regurgitation; had higher prevalence of chronic obstructive pulmonary disease, rheumatic heart disease, and lung edema; had lower prevalence of infective endocarditis, peripheral artery disease, and malignancy; had more historical events of ischemic stroke and heart failure hospitalization; had more prescriptions for amiodarone and Angiotensin-converting enzyme inhibitors or Angiotensin receptor blockers and had fewer prescriptions for antiplatelet and nonsteroidal anti-inflammatory drugs (Table 1).

Surgical characteristics

Detailed surgical characteristics, such as etiology, valve brands, valve size, concomitant surgery, and operation time, are listed in Table 2. The most common aortic valve etiology was degeneration (49.3%), followed by bicuspid aortic valve (13.4%) and rheumatic heart disease (10.4%). The most common mitral valve etiology was degeneration (29.3%), followed by rheumatic heart disease (23.7%) and ischemia (22.5%). The most common valve brand was St. Jude Epic for both AVR and MVR. Compared with the non-AF patients, those with pre-existing AF were more likely to have concomitant maze surgery and tricuspid valve; were less likely to have concomitant CABG, bentall, and aortic repair or replacement; and had longer operation times (Fig. 2).

Follow-up information

The follow-up information and events of interest during follow-up are presented in Table 3. The mean INRs at

Table 2 Surgical characteristics of patients according to pre-existing diagnosis of atrial fibrillation

Variable	Available number	Total ($n=1,059$)	AF ($n=447$)	Non-AF ($n=612$)	*P*
Aortic valve replacement etiology	749				< 0.001
Infective endocarditis		72 (9.6)	9 (3.8)	63 (12.4)	
Pre-failure		22 (2.9)	11 (4.6)	11 (2.2)	
Rheumatic heart disease		78 (10.4)	58 (24.3)	20 (3.9)	
Bicuspid aortic valve		100 (13.4)	16 (6.7)	84 (16.5)	
Aortic aneurysm or dissection		75 (10.0)	15 (6.3)	60 (11.8)	
Degeneration		369 (49.3)	120 (50.2)	249 (48.8)	
Others		33 (4.4)	10 (4.2)	23 (4.5)	
Mitral valve replacement etiology	876				< 0.001
Infective endocarditis		147 (16.8)	23 (5.7)	124 (26.2)	
Redo		40 (4.6)	22 (5.5)	18 (3.8)	
Rheumatic heart disease		208 (23.7)	161 (40.0)	47 (9.9)	
Ischemia		197 (22.5)	62 (15.4)	135 (28.5)	
Degeneration		257 (29.3)	113 (28.1)	144 (30.4)	
Others		27 (3.1)	21 (5.2)	6 (1.3)	
Aortic valve replacement valve brand	747				0.186
Hancock II		156 (20.9)	60 (25.2)	96 (18.9)	
St Jude Epic		328 (43.9)	94 (39.5)	234 (46.0)	
SAV		62 (8.3)	18 (7.6)	44 (8.6)	
Trifecta		114 (15.3)	33 (13.9)	81 (15.9)	
Mosaic		50 (6.7)	20 (8.4)	30 (5.9)	
Magna Ease / Perimount		30 (4.0)	12 (5.0)	18 (3.5)	
Others		7 (0.9)	1 (0.4)	6 (1.2)	
MVR valve brand	445				0.010
Hancock II		122 (27.4)	74 (25.8)	48 (30.4)	
St Jude Epic		198 (44.5)	130 (45.3)	68 (43.0)	
Mosaic		44 (9.9)	36 (12.5)	8 (5.1)	
Magna Ease / Perimount		56 (12.6)	37 (12.9)	19 (12.0)	
Others		25 (5.6)	10 (3.5)	15 (9.5)	
AV valve size	544				0.841
19		21 (3.9)	4 (2.4)	17 (4.5)	
21		213 (39.2)	65 (39.6)	148 (38.9)	
23		191 (35.1)	60 (36.6)	131 (34.5)	
25		102 (18.8)	30 (18.3)	72 (18.9)	
27		17 (3.1)	5 (3.0)	12 (3.2)	
MV valve size	291				0.694
23		1 (0.3)	0 (0.0)	1 (1.0)	
25		2 (0.7)	1 (0.5)	1 (1.0)	
27		57 (19.6)	36 (18.8)	21 (21.2)	
29		88 (30.2)	60 (31.3)	28 (28.3)	
31		112 (38.5)	76 (39.6)	36 (36.4)	
33		31 (10.7)	19 (9.9)	12 (12.1)	
Concomitant surgery					
CABG	1,059	162 (15.3)	55 (12.3)	107 (17.5)	0.021
Maze	1,059	147 (13.9)	143 (32.0)	4 (0.7)	< 0.001
MV repair	1,059	129 (12.2)	63 (14.1)	66 (10.8)	0.104
TV surgery	1,059	250 (23.6)	196 (43.8)	54 (8.8)	< 0.001
Bentall (root)	1,059	79 (7.5)	12 (2.7)	67 (10.9)	< 0.001
Aortic repair or replacement	1,059	96 (9.1)	27 (6.0)	69 (11.3)	0.003
Operation time					
Total bypass time, min	1,014	177.5 ± 67.3	190.0 ± 69.9	168.4 ± 63.9	< 0.001
Aortic cross clamp time, min	1,013	130.9 ± 60.6	138.3 ± 63.8	125.4 ± 57.6	0.001

Data were presented as frequency (percentage) or mean ± standard deviation

Abbreviations: AF atrial fibrillation, *AV* aorta valve, *MV* mitral valve, *CABG* coronary artery bypass graft, *TV* tricuspid valve

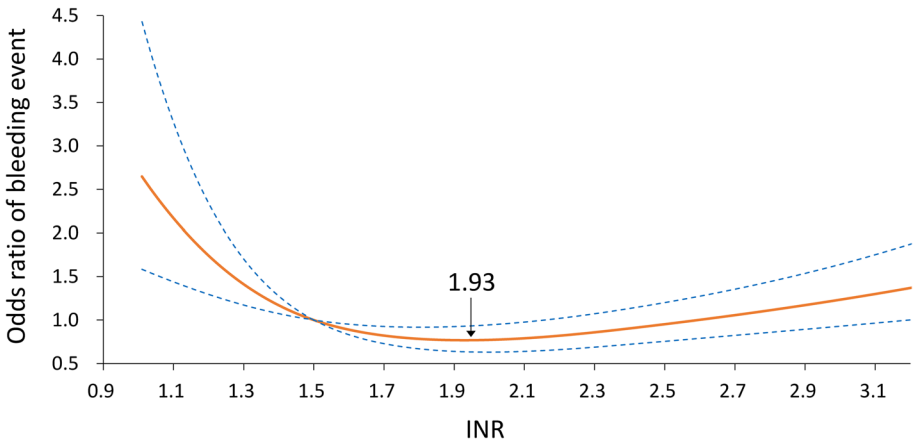

Fig. 2 Relationship between INR level and the risk of composite bleeding events in patients who underwent valve replacement surgery. INR, international normalized ratio

discharge, the first INR, the last INR, and the mean INR during 1-year follow-up were 1.65, 1.30, 1.47, and 1.59, respectively. During the 1-year follow-up, the number of patients who experienced any thromboembolic event or bleeding event was 53 (5%) and 67 (6.3%), respectively. Compared with the non-AF patients, those with pre-existing AF had higher INR levels at all time points, higher frequency of INR examinations, and more thromboembolic events (mainly driven by ischemic stroke). However, the bleeding risk was not significantly different between the AF and non-AF groups (6% vs 6.5%). During the first year of follow-up period, 31 (2.9%) patients died

Table 3 Follow up information and events of interested during the follow up according to pre-existing diagnosis of atrial fibrillation

Variable	Valid *N*	Total (*n* = 1,059)	AF (*n* = 447)	Non-AF (*n* = 612)	*P*
Follow up information					
INR at discharge	1,046	1.65 ± 0.48	1.70 ± 0.49	1.62 ± 0.47	0.005
The first INR after discharge	959	1.30 ± 0.22	1.33 ± 0.22	1.28 ± 0.21	0.001
The last INR before 365th day after discharge	1,059	1.47 ± 0.65	1.54 ± 0.56	1.42 ± 0.70	0.002
Mean INR during follow up	1,059	1.59 ± 0.46	1.66 ± 0.43	1.53 ± 0.48	< 0.001
Number of INR examination per patient	1,059	5.2 ± 3.9	6.3 ± 4.4	4.4 ± 3.2	< 0.001
Follow up duration at the end of study, years	1,059	4.0 ± 3.1	4.1 ± 3.2	3.9 ± 3.0	0.328
The first event during the follow-up					
Thromboembolic events					
Ischemic stroke	1,059	33 (3.1)/ 8.0	24 (5.4)/ 13.8	9 (1.5)/ 3.8	< 0.001
Acute myocardial infarction	1,059	11 (1.0)/ 2.6	5 (1.1)/ 2.8	6 (1.0)/ 2.5	0.827
Systemic thromboembolism	1,059	13 (1.2)/ 3.1	3 (0.7)/ 1.6	10 (1.6)/ 4.2	0.160
Lower extremity systemic thromboembolism	1,059	7 (0.7)/ 1.7	1 (0.2)/ 0.6	6 (1.0)/ 2.5	0.133
Ischemia bowel	1,059	3 (0.3)/ 0.7	1 (0.2)/ 0.6	2 (0.3)/ 0.8	0.755
Any thromboembolic event	**1,059**	**53 (5.0)/ 13.1**	**31 (6.9)/ 18.1**	**22 (3.6)/ 9.4**	**0.014**
Total bleeding events					
Hemorrhagic stroke	1,059	6 (0.6)/ 1.4	3 (0.7)/ 1.6	3 (0.5)/ 1.3	0.698
Gastrointestinal bleeding	1,059	61 (5.8)/ 15.2	24 (5.4)/ 13.9	37 (6.1)/ 16.2	0.641
Genitourinary bleeding	1,059	3 (0.3)/ 0.7	1 (0.2)/ 0.6	2 (0.3)/ 0.8	0.755
Major bleeding	1,059	27 (2.6)/ 6.5	8 (1.8)/ 4.4	19 (3.1)/ 8.0	0.180
Any bleeding event	**1,059**	67 (6.3)/ 16.7	**27 (6.0)/ 15.7**	**40 (6.5)/ 17.5**	**0.743**
All-cause death	**1,059**	**31 (2.9)/ 32.1**	**15 (3.4)/ 37.1**	**16 (2.6)/ 28.6**	**0.480**

Data were presented as frequency (percentage)/ incidence density or mean ± standard deviation

Incidence density: number of events per 1,000 person-years

Abbreviations: *AF* atrial fibrillation, *INR* international normalized ratio

in our hospitals with an incidence rate of 32.1 deaths per 1,000 person-years.

Relationship between INR level and thromboembolic or bleeding events

The RCS model indicated that an INR level of approximately 2.0 (1.93 in Fig. 2) corresponded to the lowest risk of bleeding events. INR levels of 1.84 (hazard ratio [HR], 0.49; 95% confidence interval [CI]: 0.36–0.67) and 1.7 (HR, 0.78; 95% CI: 0.62–0.99) corresponded to the lowest risk of thromboembolic events in patients with pre-existing AF (Fig. 3A) and those without (Fig. 3B). We additionally identified the association between INR level and risk of thromboembolic event in the 162 patients who developed postoperative AF (Supplemental Fig. 1). The results demonstrated a linear relationship, indicating that higher INR levels were correlated to a lower thromboembolic risk. Further analysis was conducted on patients without pre-existing AF according to surgical type. The results demonstrated that the INR level corresponding to the lowest risk of thromboembolic events was approximately 1.7 in patients with isolated AVR (Fig. 4A) and in patients with combined MVR and DVR (Fig. 4B).

Discussion

Utilizing a multicenter medical database, we conducted a large-scale in-hospital cohort study to determine the optimal INR level for patients undergoing tissue valve replacement in Taiwan. More than 5000 INR records were analyzed, including comprehensive covariates and surgical details. For Asian patients, the overall likelihood of a bleeding event is significantly elevated when the INR is greater than 2.0. In patients whose condition is complicated with AF, the likelihood of thromboembolic events is significantly increased when the INR is less than 1.84; for the non-AF group, the risk is increased for an INR less than 1.7. In the non-AF group, there was no significant difference between patients who received AVR alone and those who underwent a combined MVR and DVR. The risks of thromboembolic events in these 2 groups were

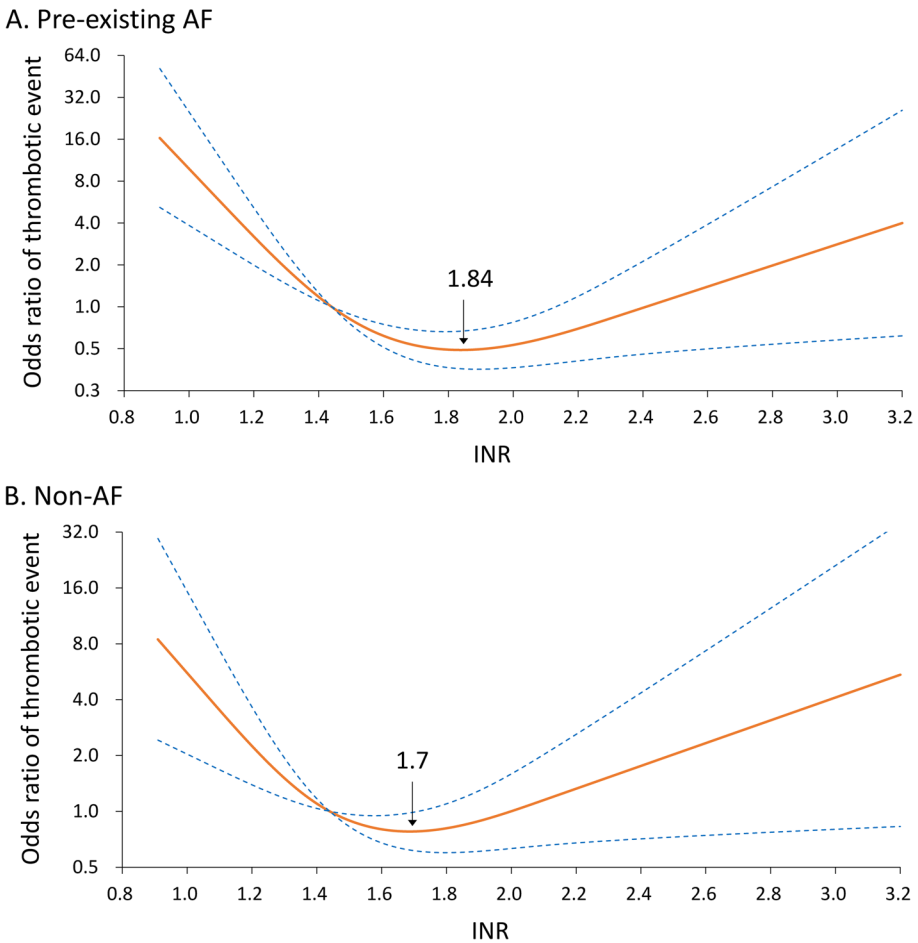

Fig. 3 Relationship between INR level and the risk of composite thrombotic events in patients who underwent valve replacement surgery with pre-existing AF (**A**) and without pre-existing AF (**B**). AF, atrial fibrillation; INR, international normalized ratio

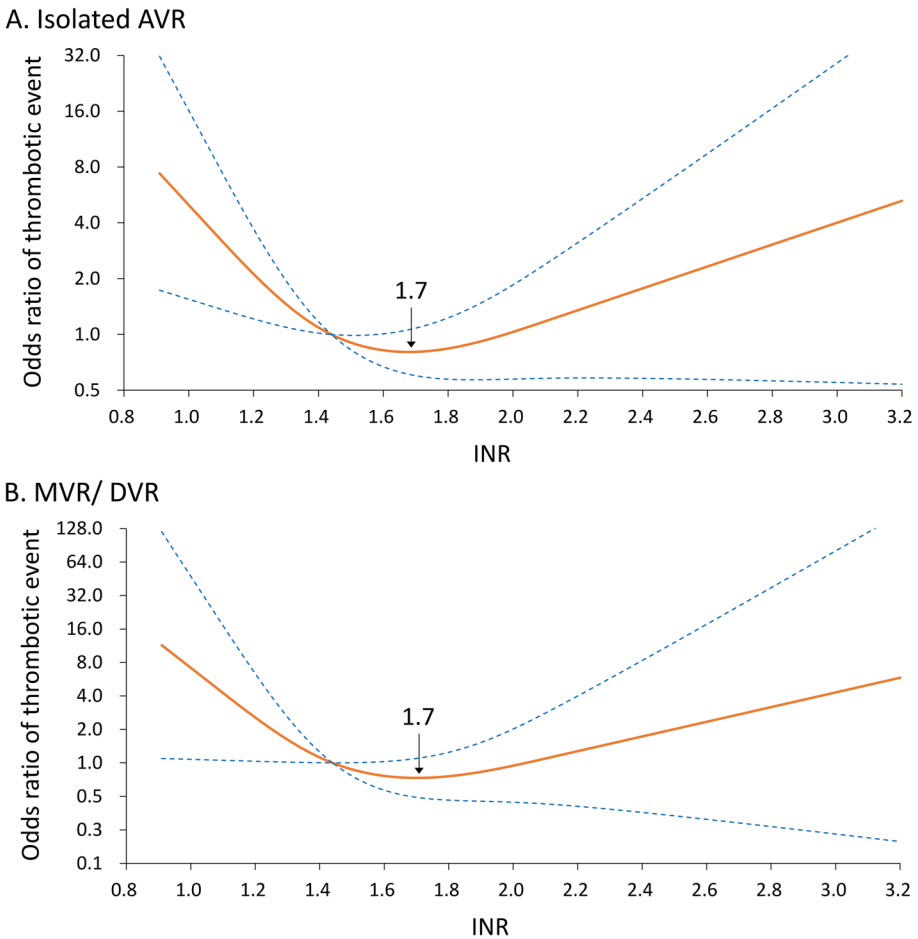

Fig. 4 Relationship between INR level and the risk of composite thrombotic events in patients without pre-existing AF who underwent isolated AVR (A) and MVR or DVR (B). AF, atrial fibrillation; AVR, aortic valve replacement; DVR, double valve replacement; INR, international normalized ratio; MVR, mitral valve replacement

elevated when the INR was less than 1.7. We have also reported the number of patients who developed postoperative AF without preoperative AF and incorporated this variable into the model (Supplemental Fig. 1). However, patients with postoperative AF may require a higher INR due to their very high risk of thromboembolic events.

Because of the lifelong requirement of taking anticoagulants, comparisons between NOACs and warfarin and INR goals for patients with mechanical valves have been intensively studied, and strong evidence has been produced (eg, RE-ALIGN trial and RIWA study) [12, 13]. By contrast, there has been little discussion of bioprosthetic valves, even though tissue valve replacement also represents a viable option for AVR and MVR surgery.

Each year, over 200,000 patients undergo transcatheter AVR (TAVR), and approximately 140,000 patients receive a surgical bioprosthetic valve [14, 15]. As indicated by the observations from the ANSWER registry and ACTION registry [16, 17], it is still difficult to justify universal anticoagulation usage after AVR; however, patients with MVR seem to have a higher risk of thromboembolic events [18]. Thus, a routine anticoagulation regimen remains a Class 2a recommendation in the latest ACC/AHA guideline.

Comparisons of VKAs and NOACs have sparked heated debate in recent years as well. The RE-ALIGN trial (2013) demonstrated that, compared with warfarin, dabigatran was associated with higher risks of thromboembolic and bleeding events [12]. However, a systemic review by Li et al. (2022) demonstrated that, compared with VKAs, NOACs have noninferior outcomes in patients who have indications for oral anticoagulants after TAVR [19]. Further studies comparing the advantages and disadvantages of VKAs, antiplatelet medications, and NOACs are also expected to provide stronger evidence of the quality of life benefits for patients with valvular heart disease.

The current consensus on anticoagulant usage in the bioprosthetic group is to initiate VKA for 3 to 6 months

postoperatively. Nevertheless, to our best knowledge, retrospective cohort studies seeking to determine an optimal INR goal are rare, and studies suggesting a precise INR target for bioprosthetic valves are even rarer. Compared with Caucasians, Asians are more susceptible to the adverse effects of warfarin, (ie, bleeding events) [20, 21]. A meta-analysis by Liu et al. reviewed nonvalvular AF in East Asian populations, revealing that an INR of 1.5 to 2.5 is preferred to decrease the risk of a bleeding event [22]. In our study, we separated the groups into AF and non-AF out of consideration for the fact that the AF group would have a higher risk of thromboembolic events. Our study also accounted for the fact that Asian populations are more tolerant to lower INR levels but are prone to bleed at an INR greater than 2.5. In 2022, Huang et al. demonstrated that an INR target of 1.5 to 2.5 is more favorable for Asians in the study's mechanical valve group [7]. Synthesizing the findings previously mentioned, we expect a more appropriate INR goal to range between 1.5 and 2.5 for tissue valve replacement postoperatively.

According to the US Census Bureau, the US is home to approximately 23 million Asian Americans (6.9% of the US population). The United States is a country of considerable diversity, and as we have mentioned, the association between race/ethnicity and warfarin dosage should be determined to cover a more comprehensive groups of warfarin usage safety. Further studies on the optimal INR range for different race/ethnic populations that can generate stronger evidence, especially randomized controlled trials, are required to inform more robust guidelines for the optimal anticoagulant usage among patients with bioprosthetic valves. The introduction of NOACs and new types of bioprosthetic valves is also expected to create better outcomes for tissue valve replacement patients.

Limitations

This study has several limitations. First, as our study was entirely reliant on *ICD-9* and *ICD-10* codes to identify types of valvular surgery, there was the potential for code error. To overcome this, we artificially reviewed the etiology for a total of 1163 surgeries in the interest of increasing the accuracy of the operation records and decreasing any inconsistency and potential coding errors. Second, the typical drawback of a retrospective cohort study is that we could only infer correlation but not causation. We were able to find the correlation between the optimal INR level and the risk of adverse events, but based on our results, we are unable to customize a precision medicine regimen for individuals. Another limitation of our study is the inability to determine the exact timing of thromboembolic or bleeding events in relation to INR measurement. Due to the retrospective design, there may be a delay between the onset of complications and the time patients sought medical attention, leading to potential discrepancies in INR values at the time of the actual event. A prospective study with real-time INR monitoring would be required to overcome this limitation and provide a more accurate assessment of the relationship between INR levels and thromboembolic or bleeding risks. At last, bleeding events were not classified according to VARC (Valve Academic Research Consortium) criteria because the study period (2001–2018) largely predates the introduction of VARC-1 in 2011. Despite so, we believe that the identification of bleeding events in our study remains consistent, as all cases were evaluated within the same healthcare system and defined using uniform ICD codes. Finally, as our findings were based on a Taiwanese population, their generalizability to other populations may be limited. Nevertheless, given that CGMH is one of the largest health-care systems in East Asia and maintains a sound and solid database, this study's findings are of value and may be representative in this field. Studies with higher evidence levels should be performed to confirm the validity of this study's findings.

Conclusion

For patients who underwent tissue valve replacement, the bleeding risk was elevated when the INR was greater than 2.0, but the risk of thromboembolic events increased only when the INR was lower than 1.84 in the AF group and 1.7 in the non-AF group, regardless of whether the patient had AVR or MVR and DVR. Based on our study results, a lower INR range may be relatively safe for both AF and non-AF groups in Asian populations. However, further large-scale randomized controlled trials are needed to validate these findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04837-y.

Supplementary Material 1: Supplemental Figure 1. Relationship between INR level and the risk of composite thrombotic events in the 162 patients who developed postoperative AF. AF, atrial fibrillation; INR, international normalized ratio.

Supplementary Material 2: Supplemental Figure 2. Relationship between INR level and the risk of composite bleeding events in patients who underwent valve replacement surgery after excluding observations within the first tertile of yearly INR. INR, international normalized ratio.

Supplementary Material 3: Supplemental Figure 3. Relationship between INR level and the risk of composite thrombotic events in patients who underwent valve replacement surgery with pre-existing AF (A) and without pre-existing AF (B) after excluding observations within the first tertile of yearly INR. AF, atrial fibrillation; INR, international normalized ratio.

Supplementary Material 4: Supplemental Figure 4. Relationship between INR level and the risk of composite thrombotic events in patients without pre-existing AF who underwent isolated AVR (A) and MVR or DVR (B) after excluding observations within the first tertile of yearly INR. AF, atrial fibrillation; AVR, aortic valve replacement; DVR, double valve replacement; INR, international normalized ratio; MVR, mitral valve replacement.

Acknowledgements
This study was based on data from the CGRD provided by the Chang Gung Memorial Hospital administration. However, the interpretation and conclusions in this study belong to the authors. The authors thank the Maintenance Project of the Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Linkou for study design and monitor, data analysis and interpretation. The authors also thank Alfred Hsing-Fen Lin and Zoe Ya-Jhu Syu for their assistance with the statistical analysis.

Authors' contributions
T-YL: Conceptualization, Methodology, Investigation, Writing—Original Draft. Y-HC: Conceptualization, Methodology, Writing—Review & Editing. VC-CW: Methodology, Formal analysis, Software, Validation. D-YC: Data curation, Formal analysis, Software, Validation. K-CH: Formal analysis, Investigation, Resources. F-CH: Conceptualization, Methodology, Investigation. Y-CT: Conceptualization, Methodology, Investigation. C-PL: Data curation, Formal analysis, Validation. P-HC: Conceptualization, Resources, Supervision. S-WC: Conceptualization, Project administration, Validation, Writing-review & editing.All authors give final approval of the version to be submitted and any revised version.

Funding
This work was supported by a grant from Chang Gung Memorial Hospital, [Taiwan CFRPG3M0011, CMRPG3L0101-2 and BMRPD95(SWC)]. This work was also supported by the Ministry of Science and Technology grant [Most 110–2314-B-182A-114 (SWC].

Data availability
The data that support the findings of this study are available from Chang Gung Memorial Hospitals but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Chang Gung Memorial Hospitals. Please contact our corresponding author Dr. Shao-Wei Chen for the required data.

Declarations

Competing interests
The authors declare no competing interests.

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Received: 12 March 2024 Accepted: 8 May 2025
Published online: 28 May 2025

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