Association of furosemide or hydrochlorothiazide use with risk of atrial fibrillation post pacemaker implantation among elderly patients

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Background: Atrial fibrillation (AF) induced by artificial pacing is directly related to atrial remodeling. Previous basic research has shown that furosemide aggravates pathologic myocardial remodeling while hydrochlorothiazide alleviates it. However, whether furosemide or hydrochlorothiazide plays a role in developing AF after pacemaker implantation remains unknown. The study aims to investigate the association between oral furosemide or hydrochlorothiazide and the risk of developing AF after pacemaker implantation.

Methods: After a review of electronic medical records, elderly patients with pacemaker implantation and without a known baseline history of AF were included and information on their use of daily oral furosemide or hydrochlorothiazide was extracted. New incident AF cases were confirmed via the records of outpatient visits. A Cox proportional-hazards model was used to evaluate the association between daily oral furosemide or hydrochlorothiazide and risk of developing AF after pacemaker implantation, after adjustment for potential confounders.

Results: Among a total of 551 patients aged more than 65 years, 157 AF cases were identified after pacemaker implantation during a maximum follow up of 3.0±1.6 years. Of these, 242 had used furosemide and 97 had used hydrochlorothiazide therapy. Patients taking daily oral furosemide had a relatively higher risk of AF after pacemaker implantation [hazard ratio (HR): 1.507, 95% confidence interval (CI): 1.036–2.192; P=0.032] after being adjusted for related disease and prescribed medications, while oral taking of hydrochlorothiazide was shown to be a non-effective factor (HR: 0.666, 95% CI: 0.413–1.074), which had no statistical significance.

Conclusions: Daily oral furosemide might increase the risk of developing AF after pacemaker implantation in elderly patients, while hydrochlorothiazide has no detrimental effect.

Keywords: Furosemide; hydrochlorothiazide; atrial fibrillation (AF); pacemaker implantation; elderly patients

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Introduction

Pacemaker implantation is currently a common and effective method to treat many types of bradycardia arrhythmias (1,2). However, a significant amount of research including the MOST study and CTOPP study has shown that the incidence of atrial fibrillation (AF) in pacemaker implanted populations increases from 3% to 15–30% (3-5). AF induced by artificial pacing is widely considered to be directly related to atrial pathologic remodeling, which includes structural pathologic remodeling and electrical remodeling. In addition, sympathetic activation, inflammation, and pacing mode are associated with the risk of developing AF after pacemaker implantation (6,7). While much attention has recently been paid to the effects of commonly used cardiovascular drugs, such as ACEI, ARB, and statins in the occurrence of AF in patients implanted with a permanent pacemaker, few studies have focused on the effect of diuretics (8,9).

In keeping with clinical guidelines, a significant proportion of elderly patients are taking diuretics daily to regulate blood pressure, reduce the burden on the heart, and eliminate edema to counter the impacts caused by hypertension (HTN), heart failure (HF), abnormal renal and liver function, and other diseases (10,11). Furthermore, elderly individuals are prone to undergo pacemaker implantation for bradycardia arrhythmias resulting in a higher risk of AF (12). Therefore, the potential association between diuretics use and the occurrence of AF after pacemaker implantation in the elderly deserves further investigation.

Thiazides, loop diuretics, and potassium-sparing diuretics make up the main composition of diuretics, among which furosemide and hydrochlorothiazide are the most used. By removing excess liquid from the body, daily oral furosemide and hydrochlorothiazide can help reduce blood pressure, decrease the burden on heart, and alleviate chronic HF. However, previous basic research has suggested that these medications may play different roles in the development of AF (13). Furosemide enhances plasma renin, angiotensin II (Ang II) and aldosterone, activates sympathetic nerves, and reduces the level of serum magnesium, promoting the development of AF (14). Conversely, hydrochlorothiazide reduces the serum level of Ang II, thereby inhibiting the transforming growth factor (TGF)-β/Smads signaling pathway to alleviate heart structural pathologic remodeling (15). These mechanisms may be strongly associated with the development of AF after pacemaker implantation in the elderly. Therefore, it is of great significance to explore the effects of diuretics on the development of AF after pacemaker implantation in the clinically real world and gain evidence for diuretic selection in elderly pacing patients. This study aims to evaluate the association of furosemide or hydrochlorothiazide use with the risk of AF after pacemaker implantation among elderly patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-1792).

Methods

A single-center, retrospective, observational study was conducted to assess the association of furosemide or hydrochlorothiazide use with the subsequent risk of developing AF in elderly patients who were implanted with pacemakers.

Study subject

After the de-identification of personal information, patients aged more than 65 years and without a known baseline history of AF who received pacemaker implantation in the Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from 2012 to 2018 were included based on a review of their electronical medical records (EMR), and information on their daily use of oral furosemide or hydrochlorothiazide was extracted. The exclusion criteria for the study were any of the following: (I) severe liver and renal dysfunction, (II) abnormal thyroid function (hyperthyroidism), (III) congenital heart disease, (IV) past history of heart surgery history, (V) severe valvular heart disease, (VI) patients diagnosed with AF before the index date, either paroxysmal or permanent. Patients who were diagnosed with AF within 3 months after pacemaker implantation were also excluded, since it is widely accepted that at least 3 months are needed for cardiac remodeling to induce AF and this protocol has also been adopted in (16). Ethical approval was granted by the Medical Ethics Committee of the Xinhua Hospital Chongming Branch (CMEC-2020-KT-14) and obeyed the principles of the Declaration of Helsinki (as revised in 2013). Besides, the study was waived the need for informed consent due to the observational character of the study.

Medication information collection

The main exposure of interest was daily oral furosemide

or hydrochlorothiazide, which could be identified from prescription records.

Primary outcomes

AF cases were defined by checking the EMR for evidence of a diagnosis made by a professional physician at any ambulatory visit, at discharge, or during post-operation follow-up based on the International Classification of Diseases, 10th Revision, diagnosis code (ICD-10: I48).

Covariates

A retrospective review using EMR and database information was conducted for evidence of HTN, diabetes mellitus (DM), or HF. The left ventricular ejection fraction (LVEF) and NYHA Functional Classification of each patient was then determined, and as these factors are commonly accepted as closely related to the development of AF, they were defined as covariates. Data on other prescribed related medications including ACEI/ARB, β-blockers, calcium-channel blockers (CCBs), statins, diuretics except furosemide (DEF), and diuretics except hydrochlorothiazide (DEH) were also identified.

Statistical analysis

Continuous variables were expressed as mean values ± SD, whereas categorical variables were expressed as frequencies between subjects with and without taking furosemide or hydrochlorothiazide. Associations between categorical variables were tested by Pearson's χ^2 test and Kolmogorov-Smirnov test was used to examine whether the data were normally distributed. Comparisons for the continuous data showing normal distribution were performed using the Student's *t*-test or otherwise by the Mann-Whitney U test. Cox proportional models were established to calculate the hazard ratio (HR) and 95% confidence interval (CI) for evaluating the association between oral furosemide or hydrochlorothiazide and AF after pacemaker implantation with adjustment for potential confounders, including age, gender, documented comorbidities, and concomitant medications. Kaplan-Meier survival analysis was used to indicate the AF-free survival in furosemide and hydrochlorothiazide groups. Statistical processes were completed by STATA 15.1 software.

Results

Patient characteristics

A total of 551 patients aged more than 65 years who met the study inclusion criteria were included for analyses and 157 AF cases were identified after pacemaker implantation during a follow up of 3.0±1.6 years. Among all the enrolled individuals, 309 (56.1%) subjects received furosemide therapy while 97 (17.6%) took hydrochlorothiazide. The baseline characteristics of all subjects are summarized in *Tables 1* and *2*. The rate of occurrence of AF after pacemaker implantation in those who received furosemide was significantly higher than in those without it (37.2% *vs.* 21.7%, P<0.001), and they were markedly older (83.8±5.9 *vs.* 81.4±7.5, P<0.001). In addition, compared with those not taking it, patients prescribed with furosemide were more likely to receive cardioprotective medications including ACEI (43.0% *vs.* 34.0%, P=0.031) and other diuretics except furosemide (94.6% *vs.* 55.3%, P<0.001). The furosemide group also had a higher rate of HTN (77.3% *vs.* 66.9%, P=0.029), HF (63.6% *vs.* 27.8, P<0.001), and diabetes (28.5% *vs.* 19.4%, P=0.012) (*Table 1*). Subjects who received hydrochlorothiazide therapy were more likely to use ACEI (52.6% *vs.* 34.8%, P=0.001), ARB (87.6% *vs.* 55.9%, P<0.001), CCB (79.4% *vs.* 59.0%, P<0.001), and statins (73.2% *vs.* 57.7%, P=0.005), and had a higher risk of developing HTN (88.7% *vs.* 69.2%, P<0.001) than those not taking daily oral hydrochlorothiazide (*Table 2*).

Outcome: AF after pacemaker implantation

The median duration of follow-up of the entire retrospective cohort was 2.9 years. By using multivariate Cox hazard regression analysis, daily oral furosemide use demonstrated stable association with a raised risk of developing new AF after pacemaker implantation, when compared with subjects not taking it (HR: 1.507; 95% CI: 1.036–2.192, P=0.032) and this remained statistically significant after adjustment for other clinical covariates including age, gender, smoking and drinking, medication use (ACEI, ARB, β-blocker, CCB, statins, DEF, DEH), and a history of chronic disease (HTN, NYHA functional class, ischemic stroke). In contrast receiving hydrochlorothiazide therapy was shown to be a non-effective factor (HR: 0.666; 95% CI: 0.413–1.074, P=0.095), with no statistical significance (*Table 3*).

Table 1 Characteristics of furosemide users and non-users

Characteristics	Furosemide user, n=242	Non-user, n=309	P value
Male	129 (53.3%)	156 (50.5%)	0.510
Age (year), mean (SD)	83.6±5.9	81.4±7.5	<0.0001
Smoking	49 (20.2%)	65 (21.0%)	0.820
Drinking	13 (5.4%)	22 (7.1%)	0.400
HTN	187 (77.3%)	213 (68.9%)	0.029
HF	154 (63.6%)	86 (27.8%)	<0.001
NYHA functional class			<0.001
1	88 (36.4%)	223 (72.2%)	
2	76 (31.4%)	61 (19.7%)	
3	21 (6.8%)	21 (6.8%)	
4	17 (7.0%)	4 (1.3%)	
DM	69 (28.5%)	60 (19.4%)	0.012
ACEI	104 (43.0%)	105 (34.0%)	0.031
ARB	156 (64.5%)	183 (59.2%)	0.210
β-blocker	170 (70.2%)	195 (63.1%)	0.079
CCB	158 (65.3%)	187 (60.5%)	0.250
DEF	229 (94.6%)	171 (55.3%)	<0.001
Statins	150 (62.0%)	183 (59.2%)	0.510
LVEF, mean ± SD	60.3±11.7	62.5±7.7	0.043
AF	90 (37.2%)	67 (21.7%)	<0.001
TFPAP (month), mean ± SD	28.9±17.5	26.4±15.8	0.330
Follow-up (month), mean ± SD	36.9±18.5	35.5±18.6	0.390

HTN, hypertension; HF, heart failure; NYHA, New York Heart Association; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; DEF, diuretic except furosemide; AF, atrial fibrillation; TFPAP, time from pacemaker implantation to atrial fibrillation occurrence.

Kaplan-Meier survival analysis indicated that patients taking furosemide were also associated with worse AF-free survival after pacemaker implantation (*Figure 1*), while a trend of preventing the development of AF after pacemaker implantation by using hydrochlorothiazide failed to reach clinical or statistical significance (P=0.095) (*Figure 2*).

Discussion

AF induced by artificial pacing is considered directly related to atrial pathologic remodeling, which includes structural pathologic remodeling, and electrical remodeling. Sympathetic activation, inflammation, and pacing mode are also associated with the occurrence of AF after pacemaker implantation. On the other hand, some elderly patients undergo pacemaker implantation for bradycardia arrhythmias. As an independent risk factor for the development of AF, aging may inevitably lead to myocardial hypertrophy and fibrosis, sympathetic activation, and decreased renal function, which may promote the development of AF (17,18). Therefore, factors that influence myocardial remodeling may affect the development of AF in patients with a permanent pacemaker, especially in elderly individuals.

Basic research has shown that furosemide aggravates myocardial remodeling via increasing the serum level

Table 2 Characteristics of hydrochlorothiazide users and non-users

Characteristics	Hydrochlorothiazide user, n=97	Non-user, n=454	P value
Male	53 (54.6%)	232 (51.1%)	0.530
Age (year), mean ± SD	82.2±7.2	82.4±6.9	0.840
Smoking	28 (28.9%)	86 (18.9%)	0.029
Drinking	11 (11.3%)	24 (5.3%)	0.026
HTN	86 (88.7%)	314 (69.2%)	<0.001
HF	46 (47.4%)	194 (42.7%)	0.400
NYHA functional class			0.530
1	51 (52.6%)	260 (57.3%)	
2	27 (27.8%)	110 (24.2%)	
3	17 (17.5%)	65 (14.3%)	
4	2 (2.1%)	19 (4.2%)	
DM	23 (23.7%)	106 (23.3%)	0.940
ACEI	51 (52.6%)	158 (34.8%)	0.001
ARB	85 (87.6%)	254 (55.9%)	<0.001
β-blocker	72 (74.2%)	293 (64.5%)	0.067
CCB	77 (79.4%)	268 (59.0%)	<0.001
DEF	70 (72.2%)	316 (69.6%)	0.620
Statins	71 (73.2%)	262 (57.7%)	0.005
LVEF, mean ± SD	60.8±8.9	61.6±10.1	0.570
AF	22 (22.7%)	135 (29.7%)	0.160
TFPAP (month), mean ± SD	27.5±18.0	27.9±6.7	0.920
Follow-up (month), mean ± SD	38.6±18.8	35.5±18.5	0.140

HTN, hypertension; HF, heart failure; NYHA, New York Heart Association; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; DEH, diuretic except hydrochlorothiazide; AF, atrial fibrillation; TFPAP, time from pacemaker implantation to atrial fibrillation occurrence.

of Ang II and aldosterone (19). The activating effect of furosemide on the renin-angiotensin-aldosterone system (RAAS) is also evidenced by significantly greater serum Ang II and aldosterone, as shown in a previous study (20). Ang II is a powerful promoter of fibrosis, which increases collagen content and fibroblast proliferation, which in turn disturbs heart conduction velocity and induces regional conduction blocks, resulting in ideal conditions for the occurrence of AF. Elevated plasma and myocardial aldosterone levels are also widely reported to be highly associated with the development of cardiac fibrosis (21). Myocardium and interstitial fibrosis are marked by an increase in atrial connective tissue growth factor (CTGF) and plasma Interleukin-6 (IL-6) levels, while aldosterone induces their expression through their activation of the NF-κB (22). Thus, abnormal electrical excitability and atrial morphological structure changes induced by pacemaker implantation may lead to increased Ang Ⅱ and aldosterone levels, and daily oral furosemide may exacerbate these effects. Loop diuretics, including furosemide, have been reported to trigger sympathetic nervous system activation (23) and one study demonstrated that furosemide can directly activate the renal sympathetic nervous system, independent from the RASS (24). This phenomenon may well be elicited by a change in the local micro-environment of the afferent nerve endings in the renal interstitium, which

Table 3 Associations between furosemide or hydrochlorothiazide use and risk of atrial fibrillation after pacing among Chinese patients

Variables	Case/N	Cox model	
		HR (95% CI)	P value
Furosemide			
Use	90/242	1.507 (1.036, 2.192)	0.032
Non-user	67/309	0.664 (0.456, 0.965)	0.032
Hydrochlorothiazide			
Use	22/97	0.666 (0.413, 1.074)	0.095
Non-user	135/454	1.501 (0.931, 2.420)	0.095

Model adjustment: age, gender, smoking and drinking, medication use (ACEI, ARB, βblocker, CCB, statins, DEF or DEH), history of chronic diseases (HNT, NYHA functional class, and ischemic stroke). HR, hazard ratio; NYHA, New York Heart Association; HNT, hypertension. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; DEF, diuretic except furosemide; DEH, diuretic except hydrochlorothiazide.

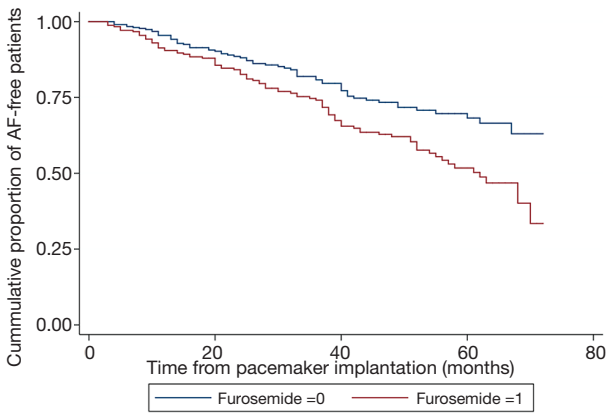

Figure 1 Kaplan-Meier curves showing cumulative 72-month atrial fibrillation after pacemaker implantation in the furosemide group.

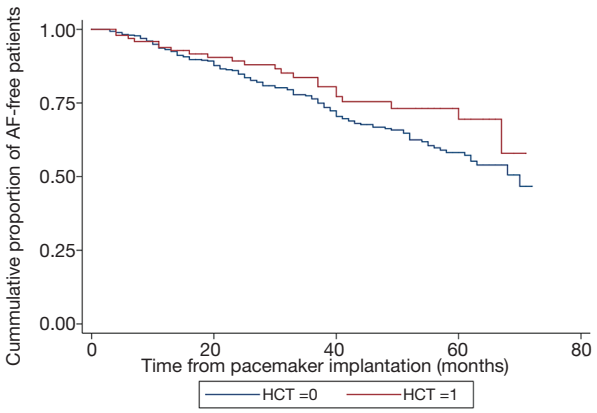

Figure 2 Kaplan-Meier curves showing cumulative 72-month atrial fibrillation after pacemaker implantation in the hydrochlorothiazide group. HCT, hydrochlorothiazide.

have been found to promote cardiac sympathetic meridian activation and increase the occurrence of arrhythmias. Right ventricular pacing and double-chamber pacing were capable of strongly increasing sympathetic tone (25), and abnormal excitement of autonomic nerves brought by artificial pacing may also lead to AF. Therefore, daily oral furosemide after artificial pacing may give rise to AF risk in the elderly via activating sympathetic nerves. Furosemide also plays a role in decreasing the level of magnesium in vivo. It is well established that renal magnesium reabsorption mainly takes place in the loop of Henle, and furosemide may induce substantial magnesium losses (26). The depletion of intracellular magnesium stores and hypomagnesaemia have been held responsible for a variety of cardiovascular abnormalities including AF, and the mechanism might be underpinned by the enhanced electrical instability of the atrial and ventricular myocardium induced by intracellular magnesium depletion (27). In addition, the reduction of serum magnesium contributes to an inflammatory reaction in the heart, and the resultant interstitial fibrosis may serve as a substrate for development of AF. In summary, research suggests furosemide may induce pathologic remodeling of heart structure, activate sympathetic nerves, and reduce the level of serum magnesium, thereby potentially promoting the development of AF in elderly patients. These findings are consistent with the results of our study which show a higher risk of AF in the elderly population after pacemaker

implantation relates to daily oral furosemide.

Hydrochlorothiazide may reduce heart pathologic structural remodeling via several mechanisms. Thiazide-type diuretics can reduce left ventricular hypertrophy and drawdown pathologic heart remodeling (13), and hydrochlorothiazide has been shown to decrease plasma proinflammatory cytokine levels and inhibit the TGF-β/Smads signaling pathway in rats, thereby improving their cardiac function reducing cardiac fibrosis (14,28). In addition, because TGF-β acts downstream of Ang II, hydrochlorothiazide probably works through regulating the Ang II/TGF-β cascade and research has shown that artificial pacing induces abnormal electrical excitability and hemodynamic changes, which may lead to increased serum Ang II levels. These findings suggest hydrochlorothiazide should be clinically preferred in elderly individuals as it decreases serum levels of Ang II and reduces the risk of AF after pacemaker implantation, and supports the results of our study which show hydrochlorothiazide provides a slight protective effect against AF after pacemaker implantation.

Daily oral furosemide increases the plasma level of renin/Ang II/aldosterone, activates sympathetic nerves, and reduces the level of serum magnesium, playing an aggregative role in the development of AF among elderly patients with permanent pacemakers. Therefore, maybe spironolactone, ACEI/ARB and magnesium could be used to reduce the side effect of furosemide.

On the contrary, daily oral hydrochlorothiazide reduces serum levels of angiotensin II, thereby inhibiting the TGF-β/Smads signaling pathway to alleviate heart structural remodeling, and finally reduces the risk of AF in elderly patients after pacemaker implantation.

Multiple guidelines have advised that diuretics should be used for elderly patients suffering from HF or HTN (10,11). The 2018 ESC/ESH Guidelines for the management of arterial HTN recommended five major drug classes for the treatment of HTN: ACEIs, ARBs, β-blockers, CCBs, and diuretics, and diuretics are optimally advised especially in old and very old patients (29). While thiazides and related compounds, loop diuretics, and potassium-sparing diuretics are the main diuretics in use, which kind of diuretic to choose remains a controversial topic and should be determined according to the individual status of patients. Clinically, furosemide is widely used for HF, particularly in old individuals with fluid retention and renal failure. But for the old people with a permanent pacemaker, many drugs should be used to counteract the adverse effects.

Conversely, hydrochlorothiazide is recommended as a cornerstone therapy for antihypertension and small doses of it are often used in combination with other antihypertensive drugs like ACEI/ARB for elderly patients with HTN. Imparting a mild diuretic effect, potassium-sparing diuretics serve as adjuvant therapy for HF and HTN in clinical practice. For patients with gout or diabetes who are using hydrochlorothiazide, they could add the use of lowing uric acid drugs at the same time. Besides, another diuretics such as spirolactone would be a better choice for people in that situations. The results of our present study suggest that in elderly patients with a permanent pacemaker, hydrochlorothiazide may be preferable to furosemide by avoiding the risk of AF developing.

Overall, our results demonstrated that elderly individuals who followed daily oral furosemide after pacemaker implantation were associated with a raised risk of developing new AF in comparison to those not using it, which remained statistically significant after adjustment for related clinical covariates. In contrast, receiving hydrochlorothiazide therapy showed a slight protective effect against AF developing in elderly pacing patients. Our findings suggest that the daily use of hydrochlorothiazide is safer than oral furosemide in elderly patients with a permanent pacemaker for reducing the risk of subsequent AF. Our study may provide evidence for the clinical selection of diuretics for elderly pacing individuals.

Limitation

Our study has some limitations. Firstly, we only transferred the retrospective data from a single center based on case records, so the final sample size of the group is small. In addition, the definition of the onset time of AF may have a small range of bias because it is generally difficult to accurately define this by asking patients about their symptoms and medical records must be relied upon. Thirdly, the factors leading to the occurrence of AF are very complex. We have considered the correction factors as much as possible, but it is inevitable that there would still be some omissions. In addition, the pacing mode may also affect the incidence rate of subsequent AF after pacemaker implantation (30), and we did not categorize different pacing modes or conduct subgroup analyses because most of the included individuals received ventricular single chamber

pacing (VVI mode).

Conclusions

Daily oral furosemide might enhance the risk of developing AF after pacemaker implantation in elderly patients. In contrast, hydrochlorothiazide has no detrimental effect and might be clinically preferred when needed.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-1792

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-1792). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All data were anonymized. Individual clinical information could only be identified by using inpatient numbers derived from each participant's identification number before the research team received the data. Ethical approval was granted by the Medical Ethics Committee of the Xinhua Hospital Chongming Branch (CMEC-2020-KT-14), and our study obeyed the principles of the Declaration of Helsinki (as revised in 2013). The study was waived the need for informed consent due to the observational character of the study.

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