Real-world outcomes of anticoagulant prescription in anticoagulant-naïve octogenarian patients with non-valvular atrial fibrillation

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Abstract

Background and objectives: The clinical practice of anticoagulation in anticoagulant-naïve octogenarians with non-valvular atrial fibrillation (NVAF) has not been established in a real-world setting. We aimed to investigate the real-world prescription for anticoagulation and to compare the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin vs. no anticoagulation in anticoagulant-naïve octogenarian NVAF patients.

Subjects and methods: From January 1, 2013 to August 31, 2015, we identified 89 consecutive newly detected NVAF patients aged ≥80 years. We retrospectively reviewed medical records until May 31, 2017 according to the differences in anticoagulation prescription (no anticoagulation, 39 patients; NOACs, 17; warfarin, 33). The efficacy outcome was stroke or systemic embolism. The safety outcome was total and major bleeding.

Results: Stroke incidence did not differ significantly among the prescriptions (no anticoagulation, 2.41; NOACs, 3.55; and warfarin, 1.28 per 100 patient-years). Considerable incidence of major bleeding was observed in the anticoagulation groups (no anticoagulation, no events; NOACs, 12.11; and warfarin, 4.30 per 100 patient-years, p = 0.570). Total bleeding tended to be high in the NOAC and warfarin groups compared to no anticoagulation (no anticoagulation, 10.76 per 100 patient-years, p = 0.054). In the multivariable Cox proportional hazard model, previous bleeding history, warfarin and NOACs treatment were significant predictors for total bleeding.

Conclusion: The occurrence of total and major bleeding was excessively high in the anticoagulation groups (NOACs or warfarin) compared to the no anticoagulation group. Future study is required to optimize anticoagulant regimen in octogenarian subjects.

Introduction

The prevalence of Non-Valvular Atrial Fibrillation (NVAF) increases with age and reaches 10% or more in octogenarians [1–3]. Patients with NVAF have increased risk of stroke, and the incidence of NVAF-related stroke is also increasing with age [4]. Octogenarian patients with NVAF are at increased risk of thromboembolism. Current guidelines recommend adequate anticoagulation using warfarin or Non-vitamin K Antagonist Oral Anticoagulants (NOACs) for these elderly patients [5,6]. However, many physicians hesitate to prescribe anticoagulants to octogenarian patients because they increase the risk of bleeding. Warfarin was the only available oral anticoagulant until 2009; it has been clearly shown to effectively prevent thromboembolic events in patients with NVAF, especially in elderly patients [7–9]. However, warfarin therapy requires periodic blood monitoring and interacts with numerous drugs and foods; it is often underused in elderly patients because of a higher risk of bleeding and poor tolerability [10].
Recently, NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown to be non–inferior or even superior to warfarin for long-term stroke prevention in patients with NVAF [11-14]. Recent meta-analysis also supported the efficacy of NOACs, which had a favorable risk-benefit profile: they significantly reduced the incidence of stroke than that of warfarin, and their effect on major bleeding was similar to that of warfarin in elderly patients (≥75 years) [15,16]. Subgroup analysis of major clinical trials in Asian populations showed that NOACs had better results compared to warfarin in terms of bleeding complications [17,18]. As societies worldwide have aged, the efficacy and safety of NOACs in octogenarians have emerged as an important area of research. Kwon and Kim et al. reported recently that NOACs and warfarin were highly effective for prevention of stroke, but major bleeding occurred in a considerable number of Korean octogenarian patients in both anticoagulant groups [19]. Therefore, the present study aimed to investigate real-world anticoagulant prescription and to evaluate the efficacy (prevention of stroke or systemic embolism) and safety (risk of total and major bleeding) of NOACs and warfarin compared to no anticoagulation in anticoagulant-naïve Korean octogenarian patients with newly detected NVAF.

Subjects and methods

Study patients

Between January 2013 and August 2015, 173 patients aged between 80 and 89 years were newly diagnosed with AF at the Konkuk University Medical Center (Seoul, Korea). Patients with prior anticoagulant treatment (n = 15), follow-up duration < 1 month, including follow-up loss or death (n = 57), calculated estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m² (n= 6), anticoagulation contraindications including liver cirrhosis, hepatocellular carcinoma, and thrombocytopenia (n= 1), and valvular AF (n = 5) were excluded from analysis. Valvular AF was defined as rhythm disturbance in the presence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair [20]. After exclusion, a total of 89 patients remained in the study. Study patients were divided into three groups based on anticoagulant prescription (no anticoagulation, NOACs, and warfarin). The no–anticoagulation group was defined as patients with antiplatelet or no treatment. Types (rivaroxaban, dabigatran, or apixaban) and doses (low dose or common dose) of NOACs were prescribed at the discretion of the attending physicians. The target international normalized ratio (INR) intensity in the warfarin group was decided by the attending physician because Japanese guidelines recommend INR control between 1.6 and 2.6 in patients who are ≥70 years old and low–intensity warfarin therapy (INR, 1.6–2.6) has been reported to be favorable in elderly Korean patients with NVAF [21,22]. We retrospectively reviewed electronic medical records of study patients until May 2017. This study was approved by the Institutional Review Board of the Konkuk University Medical Center (protocol no. KUH1010905). The requirement for informed consent was waived as de-identified information was retrieved retrospectively.

Definitions of variables

The eGFR was assessed by using the abbreviated MDRD equation: eGFR (mL/min/1.73 m²) = \[186.3 \times (\text{serum creatinine in mg/dL} \times (\text{age} – 0.203)) \times 1 \times 1 \times 1\] (male) or 0.742 (female) [23]. The CHA₂DS₂-VASc score was defined as a cumulative score of congestive heart failure/left ventricular ejection fraction of <40%, hypertension, age (≥75 years or ≥65 years), diabetes, stroke, vascular disease (history of myocardial infarction, aortic plaque, or peripheral artery disease), and sex (female). The HAS-BLED score was defined as a cumulative score of hypertension (uncontrolled, >160 mmHg systolic), abnormal renal and liver function (dialysis, transplant, Cr >2.3 mg/dL, cirrhosis, bilirubin level twice the normal, liver enzyme thrice the normal), stroke, bleeding, labile INRs, elderly (e.g., age ≥65 years), antiplatelet and nonsteroid anti-inflammatory drugs, and alcohol.

Efficacy and safety outcomes

The efficacy outcome was the composite of stroke or systemic embolism. Stroke was defined as the sudden onset of a focal neurological deficit lasting at least 24 h. Systemic embolism was defined as acute vascular occlusion of an extremity or major organ documented at the time of autopsy, angiography, or vascular imaging.

The safety outcome was the incidence of total and major bleeding. Major bleeding was defined as (1) fatal bleeding, (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intracranial, retroperitoneal, intrarticular, or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of ≥2 g/dL or requiring transfusion of ≥2 units of whole blood or red cells [24]. Minor bleeding was defined as all other clinically overt bleedings that did not meet the criteria for major bleeding [24]. Total bleeding was composite incidence of major and minor bleedings.

Two investigators (S. Park and C. H. Kwon) reviewed all medical records of the study patients during the follow-up and adjudicated all stroke, systemic embolism, and bleeding events that contributed to the pre-specified outcomes. The efficacy and safety outcomes for no anticoagulation, NOACs, and warfarin groups were compared. Event rates are presented as event numbers per 100 patient-years of follow-up.

Statistical analysis

Statistical analyses were performed using SPSS 17 software (SPSS Inc., Chicago, IL, USA). The data are expressed as the mean ± SD (continuous variables) or as frequency (categorical variables). When comparing baseline variables between the no anticoagulation, NOACs, and warfarin groups, continuous variables were compared using the One–way ANOVA test or Kruskal–Wallis test, and categorical variables were compared using the chi-square test or Fisher’s exact test. The association of clinical variables with stroke or total bleeding was assessed using univariable and multivariable Cox proportional hazard models. All variables were included in the multivariable analysis. A backward-elimination multivariable stepwise
A regression model was used to test the independent correlations of these variables with stroke or total bleeding. The Kaplan–Meier method was used to estimate the survival rates after stroke and major or total bleeding, and death rate. Additionally, the survival rates were compared using the log–rank test. A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study patients are listed in Table 1. The mean age was 84.3 ± 3.5 years, and 69.7% of the patients were female. The median follow-up duration for the study population was 24 months (interquartile range, 14–36 months). Among the 89 patients, 4 (4.5%) had previous stroke history and 22 (24.7%) presented with NVAF and a newly developed stroke. Of the 26 patients with a previous or newly developed stroke, 3 (11.5%) were prescribed anti-platelet treatment, 8 (30.8%) received NOACs, and 15 (57.7%) received warfarin. Previous stroke/systemic embolism history was significantly higher in the NOACs (n = 8, 47.1%) and warfarin groups (n = 15, 45.5%) compared to the no anticoagulation group (n = 3, 7.7%) (p < 0.001). The CHA2DS2–VASC score was significantly higher in the warfarin group (5.1 ± 1.1) than in the NOACs (4.1 ± 1.2) (p = 0.001), but not higher significantly than in NOACs (4.8 ± 1.3) (p = 0.983).

Among the 89 enrolled patients, 50 patients (56.2%) were prescribed NOACs (n = 17, 19.1%) or warfarin (n = 33, 37.1%). The no anticoagulation group included 9 patients with no treatment and 30 patients with antiplatelet treatment. Of the 17 patients who received NOACs, 8 patients received rivaroxaban (3 received a commonly used dose (20 mg once daily) and 5 a low dose (15 mg once daily)), 7 received apixaban (4 received a common dose (5 mg twice a day) and 3 a low dose (2.5 mg twice a day)), and 2 received a low dose of dabigatran (110 mg twice a day). Mean INR in patients of the warfarin group was 1.89 ± 0.76 at the last follow-up.

Efficacy and safety outcomes

Table 2 and Figure 1 show the efficacy and safety outcomes according to treatment groups. None of the study patients experienced transient ischemic events. Stroke events occurred in 4 patients during the follow-up period (2 in the no anticoagulation group and 1 each in the NOACs and warfarin groups). The incidence rates of stroke and systemic embolic events were low in both anticoagulant groups, with no significant differences between the treatment groups.

Major bleeding events occurred in 6 patients treated with NOACs or warfarin (5 in the gastrointestinal tract and 1 in the intracranial area). However, there was no major bleeding event in the no anticoagulation group (Table 2). The rate of total bleeding was not significantly different among the three treatment groups.

Table 1: Baseline characteristics of patients according to different anticoagulation treatment groups.

|                        | No anticoagulation (n = 39) | NOACs (n = 17) | Warfarin (n = 33) |
|------------------------|-----------------------------|----------------|------------------|
| Follow-up duration (months) | 23.0 (8.0–27.0) | 20.0 (7.0–28.8) | 20.0 (19.0–27.0) |
| Age (years)            | 84.5 ± 3.4                  | 84.8 ± 3.6     | 84.4 ± 5.5       |
| Female                 | 8 (88.9)                    | 5 (50.0)       | 4 (57.1)         |
| Body mass index (kg/m²)| 19.4 ± 8.1                  | 21.2 ± 3.9     | 21.9 ± 3.5       |
| Type of arrhythmia     |                            |                |                  |
| Paroxysmal atrial fibrillation | 6 (66.7)          | 5 (50.0)       | 8 (24.2)         |
| Persistent atrial fibrillation | 3 (33.3)         | 5 (50.0)       | 24 (72.7)        |
| Congestive heart failure | 2 (22.2)              | 3 (30.0)       | 12 (36.4)        |
| Hypertension           | 6 (66.7)                    | 8 (80.0)       | 27 (81.8)        |
| Diabetes mellitus      | 2 (22.2)                    | 3 (30.0)       | 15 (45.5)        |
| Previous stroke/SE     | 1 (11.1)                    | 3 (30.0)       | 9 (27.3)         |
| Vascular disease       | 0 (0.0)                     | 0 (0.0)        | 1 (3.0)          |
| Previous bleeding      | 1 (11.1)                    | 0 (0.0)        | 1 (3.0)          |
| CHA2DS2–VASC score     | 4.2 ± 1.3                   | 4.5 ± 1.0      | 5.1 ± 1.5        |
| HAS-BLED score         | 2.1 ± 0.9                   | 2.4 ± 0.6      | 3.1 ± 1.0        |
| Creatinine (mg/dL)     | 0.86 ± 0.19                 | 0.99 ± 0.27    | 0.96 ± 0.29      |
| eGFR (mL/min/1.73 m²)  | 67.7 ± 15.8                 | 65.1 ± 16.9    | 64.7 ± 16.8      |
| Hemoglobin (g/dL)      | 12.1 ± 1.0                  | 12.1 ± 1.5     | 12.4 ± 1.7       |

Values are expressed as the mean ± SD, median (interquartile range), or number (percentage).

P values were calculated by using One-way ANOVA test, Kruskal–Wallis test, chi-square test, or Fisher’s exact test among the three treatment regimens (no anticoagulation, NOACs, and warfarin).

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bleeding events also tended to be higher in patients with NOACs or warfarin treatment (20.91 and 10.76 per 100 patient-years, respectively) than in the no-anticoagulation group (1.21 per 100 patient-years). Kaplan–Meier analysis showed a significant difference in the incidence of major and total bleeding according to treatment groups (Figure 1B & 1C). Three major bleeding events in the NOACs group were all gastrointestinal bleeding and occurred in patients who received dabigatran (110 mg).

Table 2: Efficacy and safety outcomes according to treatment groups.

|                      | No anticoagulation (n = 39) | NOACs (n = 17) | Warfarin (n = 33) | P value |
|----------------------|-----------------------------|----------------|------------------|---------|
|                      | No. of events | Event rate (No./100 patient-years) | No. of events | Event rate (No./100 patient-years) | No. of events | Event rate (No./100 patient-years) |
| **Efficacy**         |              |                                 |              |                                 |              |                                 |
| Stroke or systemic embolism | 2          | 2.41                           | 1            | 3.55                           | 1            | 1.28                           | 0.822 |
| Stroke               | 2            | 2.41                           | 1            | 3.55                           | 1            | 1.28                           | 0.822 |
| Systemic embolism   | 0            | –                              | 0            | –                              | 0            | –                              |         |
| **Safety**           |              |                                 |              |                                 |              |                                 |         |
| Total bleeding       | 5            | 20.91                          | 7            | 10.76                          |              |                                 | 0.054 |
| Major bleeding       | 3            | 12.11                          | 3            | 4.30                           |              |                                 | 0.570 |
| ICH                  | 0            | –                              | 1            | 5.73                           |              |                                 | 0.193 |
| GI bleeding          | 0            | –                              | 3            | 10.79                          |              |                                 |         |
| Minor bleeding       | 0            | –                              | 3            | 6.74                           |              |                                 | 0.396 |
| Death                |              |                                 |              |                                 |              |                                 |         |
| All cause death      | 2            | 6.74                           | 3            | 4.03                           |              |                                 |         |
| Cardiac death        | 1            | 1.21                           | 0            | 0                              |              |                                 |         |
| Non-cardiac death    | 2            | 1.21                           | 1            | 1                              |              |                                 |         |

GI, gastrointestinal; ICH, intracranial hemorrhage; No., number; NOACs, non-vitamin K antagonist oral anticoagulants.

P values between treatment groups were calculated for the overall follow-up duration by using the univariable Cox regression model.

Figure 1: Kaplan-Meier curves for stroke (A), major bleeding (B), total bleeding (C), and death (D).
rivaroxaban (15 mg), and rivaroxaban (20 mg). Among major bleeding events in the warfarin group, 2 were gastrointestinal bleeding and 1 was intracranial hemorrhage. The mean INR value at the event time in the warfarin group was 1.89 ± 0.68 (range, 1.33–2.64).

A total of 6 patients died during the follow-up period: 1 in the no anticoagulation group, 2 in the NOACs group, and 3 in the warfarin group. The causes of deaths included of cardiac death (1 case in the no anticoagulation and 2 in the warfarin group), 1 malignancy (in the NOACs group), and 2 cases of septic shock (in the NOACs and warfarin groups). Cumulative incidence of death did not differ significantly among groups (Figure 1D).

Predictors of the incidence of stroke and total bleeding

In the Cox proportional hazard model, previous stroke history and impaired renal function tended to be associated with stroke incidence, but this association was not statistically significant (Table 3). On the other hand, previous bleeding history, warfarin and NOACs treatments were significant predictors for total bleeding (Table 4).

Discussion

The present study is a retrospective analysis to compare NOACs and warfarin therapy to no anticoagulation treatment for stroke prevention in anticoagulant-naïve Korean octogenarian patients with NVAF. Our major findings are as follows: (1) prescription rate of appropriate anticoagulation (NOACs or warfarin) was 56.2%; (2) many patients (n = 22, 24.7%) were diagnosed with NVAF and presented a newly developed stroke; (3) the incidence rates of stroke and systemic embolism were low, and there was no significant difference in the efficacy outcomes (stroke or systemic embolism) among treatments (2.41% for no anticoagulation, 3.55% for NOACs, and 1.28% for warfarin per 100 patient-years, p = 0.822); (4) the incidence rate of major bleeding tended to be higher in NOACs or warfarin treatment than in the absence of anticoagulation (no events for NOACs and warfarin per 100 patient-years, 2.41% for no anticoagulation, 3.55% for NOACs, and 1.28% for warfarin per 100 patient-years, p = 0.570); (5) previous bleeding history, NOACs and warfarin treatments were significant predictors of total bleeding events.

Recent studies in Asian populations reported similar rates of stroke or systemic embolism, ranging from 1.26% to 2.6% per year with NOACs and from 2.61% to 3.4% per year with warfarin [17,18,25]. The mean age of populations in these studies was around 70 years. A recent meta-analysis of elderly patients (>75 years) reported that the incidence of stroke or systemic embolism was significantly lower with NOACs than with warfarin therapy (3.3% vs. 4.7%; odds ratio = 0.65; 95% confidence interval = 0.48–0.87) [15]. In addition, Kwon and Kim et al. reported the real-world outcomes of different anticoagulation regimens in Korean octogenarian patients (mean age, 81.7 years) [19]. They reported that stroke events were relatively low in patients treated with NOACs (1.16% per year) or warfarin (2.98% per year) [19]. In our present study, the incidence of stroke events was similar to that in this previous study. However, the present study was performed in anticoagulant-naïve octogenarian patients and evaluated the efficacy of not only appropriate anticoagulation treatment

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**Table 3**: Univariable and multivariable Cox proportional hazards models for the incidence of stroke during follow-up

|                     | Univariable analysis | Multivariable analysis* |
|---------------------|----------------------|-------------------------|
|                     | HR (95% CI)          | p value                 | HR (95% CI)          | p value                 |
| Age (years)         | 0.919 (0.645–1.310)  | 0.640                   | 0.919 (0.645–1.310)  | 0.640                   |
| Female              | 1.479 (0.154–14.237) | 0.735                   | 1.479 (0.154–14.237) | 0.735                   |
| Body mass index     | 1.020 (0.903–1.152)  | 0.754                   | 1.020 (0.903–1.152)  | 0.754                   |
| Congestive heart failure | 0.541 (0.056–5.201) | 0.594                   | 0.541 (0.056–5.201)  | 0.594                   |
| Hypertension        | 1.142 (0.119–10.991) | 0.908                   | 1.142 (0.119–10.991) | 0.908                   |
| Diabetes mellitus   | 1.162 (0.121–11.184) | 0.897                   | 1.162 (0.121–11.184) | 0.897                   |
| Previous stroke     | 2.581 (0.363–18.334) | 0.343                   | 3.328 (0.447–24.774) | 0.240                   |
| Previous bleeding   | 1.960 (0.898–1.026)  | 0.225                   | 0.952 (0.887–1.022)  | 0.174                   |
| Type of anticoagulation |                |                         |                       |                         |
| No anticoagulation  | 1.0                  | –                       | 1.0                  | –                       |
| Warfarin            | 0.574 (0.052–6.332)  | 0.650                   | 0.574 (0.052–6.332)  | 0.650                   |
| NOACs               | 1.379 (0.123–15.504) | 0.795                   | 1.379 (0.123–15.504) | 0.795                   |

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants.

*4A backward-elimination multivariable stepwise regression model was used.
(NOACs or warfarin), but also no anticoagulation (anti-platelet treatment or no treatment). Surprisingly, the incidence of stroke events was low not only in patients with adequate anticoagulation, but also in those with no anticoagulation treatment. Also, there was no significant difference in the incidence of stroke events between anticoagulant regimens. These results may be explained by selection bias because the study populations were relatively small, and absolute numbers of stroke events were also very low in all study groups. In addition, because the CHA2DS2-VASc scores were significantly lower in the no anticoagulation group than in the anticoagulation groups, stroke events in no anticoagulation group may be similar to other anticoagulation groups in our results. Therefore, further study is required to establish which anticoagulant regimen (including only anti-platelet therapy) would be needed in Asian octogenarian patients.

Previous results for the risks of major bleeding in octogenarians treated with warfarin were inconsistent. One study found that the cumulative incidence of major hemorrhages was 13.1 per 100 patient-years [10]. However, another prospective observational study reported a low rate of major bleeding (1.87 per 100 patient-years) [26]. In recent sub-analyses of randomized trials, the risk of major bleeding was 4.37–4.40 per 100 patient-years in patients aged ≥75 years treated with warfarin [27,28]. A recent Korean study that enrolled octogenarian patients showed that the incidence of major bleeding was 12.46% per year in patients treated with warfarin, which was not consistent with our result (4.30% per year) [19]. Bleeding risks in octogenarian patients taking NOACs have not been previously reported. Previous sub-analyses in elderly patients (≥75 years) treated with NOACs showed that the incidence of major bleeding was 4.43–5.10 per 100 patient–year [27,28]. In Asian patients (mean age, ~70 years) treated with NOACs, the risk of major bleeding was reported to be 2.99–3.59 per 100 patient–years [17,18,25], but was about twice as high (8.96% per year) in Korean octogenarian patients [19]. Our study also showed excessively a high incidence of major bleeding in patients treated with NOACs. Given that the results of previous and our present study for Korean octogenarian patients were obtained in the real-world setting, the risk of major bleeding in these patients seems to be markedly high with both NOACs and warfarin. A previous study that enrolled Korean octogenarian patients did not include the patients without adequate anticoagulation [19], but the present study included those patients. Therefore, our study has revealed the ‘real-world’ practice of anticoagulation in Korean octogenarians, especially in anticoagulant-naïve patients, and has shown that anticoagulation therapy with NOACs or warfarin is a significant predictor for total bleeding events.

Our present study had several limitations. First, our analysis was retrospective. Second, the number of study patients and events were too small to lead to the conclusion. Statistical insignificance of stroke and death despite with large hazard ratios might be due to β-error. Therefore, this study has limited to demonstrate the benefit of anticoagulation for the prevention of stroke/systemic embolism. Third, different kinds and doses of NOACs were prescribed. Thus, we could not compare the efficacy and safety between different NOACs. Fourth, we could not test patients’ adherence to prescribed anticoagulant regimen. Finally, we did not calculate the time-in-therapeutic range for the warfarin group, and thus could not evaluate the appropriateness of warfarin therapy. Despite the limitations, our study had comparatively long follow-up durations, and largely reflected the current status of ‘real-world’ anticoagulation practice in anticoagulant-naïve octogenarian patients.

**Conclusion**

In conclusion, the incidences of stroke or systemic embolism are low in Korean octogenarian NVAF patients regardless of anticoagulation regimen. On the other hand, major and total bleeding events are excessively high in both anticoagulant groups. Previous bleeding history, NOACs and warfarin therapies are significant predictors for total bleeding events in anticoagulant-naïve octogenarian NVAF patients. In the future, a well-designed and prospective study on the optimal anticoagulant regimen should be conducted in Korean octogenarian NVAF patients.

**Declarations**

**Ethical Approval and Consent to participate**

This study was approved by the Institutional Review Board of the Konkuk University Medical Center (protocol no. KUH1010905). The requirement for informed consent was waived as de-identified information was retrieved retrospectively.

**Consent for publication**

We agree for publication

**Availability of supporting data**

It is available to submit of supporting data

**Authors’ contributions**

Suigeon Park; wrote the methods and the results: contributed to discussion: edited the whole paper

Chang Hee Kwon; developed the hypothesis: wrote the introduction, methods and results: contributed to discussion

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