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Vasodilator agents improve hemodialysis vascular access patency

A population-based study from Korea

Do Hyoung Kim, MD, PhD[a], Donghoon Han, MD[b,*], Jaehwan Kim, BD[c], Hayne Cho Park, MD[a], Young-Ki Lee, MD, PhD[a], Dong Geum Shin, MD[b], Min-Kyung Kang, MD, PhD[b], Jung Rae Cho, MD, PhD[b], Seonghoon Choi, MD[b], Namho Lee, MD, PhD[b]

Abstract

Vascular access (VA) failure is an important problem for patients undergoing hemodialysis, and maintaining VA patency is challenging. In this study, we used a nationwide database to investigate the effects of nitrate, as a vasodilator, on VA failure in hemodialysis patients.

We investigated the Korean insurance claims data of hemodialysis patients who underwent angioplasty for VA failure between January 2012 and December 2017. The patients were divided into 2 groups: those not receiving vasodilator therapy (controls) and those receiving any vasodilator administration (vasodilator treatment, VDT). The primary endpoint was VA primary patency, defined as the time between arteriovenous dialysis access creation and the first percutaneous transluminal angioplasty (PTA).

During the study period, a total of 6350 patients were recruited, 409 (6.4%) patients assigned to the VDT group and 5941 (93.6%) controls. PTA was performed in 998 patients (15.7%), including 8 in the VDT group and 990 controls. The VA site PTA rate was significantly lower in the VDT group (2.0%) than in the control group (16.7%, $P < .001$). In the subgroup analysis, the patency rates associated with the different vasodilators were similar ($P = .736$). All vasodilators, except molsidomine, improved the patency rate by approximately 20%.

In this large national database study, vasodilator administration was associated with higher VA primary patency, compared with controls, in hemodialysis patients. VDT may have a beneficial effect on maintaining VA patency in patients undergoing hemodialysis.

Abbreviations: AVF = arteriovenous fistula, AVG = arteriovenous graft, ESRD = end-stage renal disease, HIRA = the Health Insurance Review and Assessment Service, PTA = percutaneous transluminal angioplasties, VA = vascular access, VDT = vasodilator treatment.

Keywords: hemodialysis, primary patency, vascular access, vasodilators

1. Introduction

Vascular access (VA) is essential for patients with end-stage renal disease (ESRD) undergoing hemodialysis. The survival and quality of life of these patients depend on the adequacy of dialysis via a well-functioning VA.[1] However, creating and maintaining a well-functioning VA is a critical challenge. A VA can be obtained using a native (autologous) arteriovenous fistula (AVF), arteriovenous graft (AVG) connecting artery and vein with a prosthetic graft, or a central venous catheter,[2,3] with most patients undergoing hemodialysis receiving an AVF or AVG. After VA creation, the shear stress on venous endothelial cells, due to increasing flow, induces venous vascular remodeling and vascular dilatation, leading to VA maturation.[4–6]

However, if only vascular remodeling occurs, without dilatation, myofibroblasts are activated and infiltrate into the intima and differentiate into smooth muscle cells.[7,8] After the proliferation and migration of smooth muscle cells, the AVF endothelial intima may develop neointimal hyperplasia, leading to AVF stenosis and dysfunction.[5,7–9] Thus, venous stenosis at the vein-artery anastomosis, in AVF, or at the vein-graft anastomosis, in AVG, is the main cause of VA failure.[10,11]

Nitrates and molsidomine, nitric oxide group-containing vasodilators, affect dilatation of systemic and coronary vascular beds[12]; nicorandil, another vasodilator, causes arterial, and venous dilatation.[13] Although these vasodilators have demonstrated systemic or coronary artery vasodilation effects, there is

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The data that support the findings of this study are available from a third party, 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 available from the authors upon reasonable request and with permission of the third party.

[a] Division of Nephrology, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea, [b] Division of Cardiology, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea, [c] Data Science Team, Hanmi Pharm. Co., Ltd., Seoul, Korea.

[*] Correspondence: Donghoon Han, Division of Cardiology, Department of Internal medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea, 1, Shingil-ro, Yeongdeungpo-gu, Seoul 07247, Republic of Korea (e-mail: magnox@hallym.or.kr, dhhan.cardio@gmail.com).

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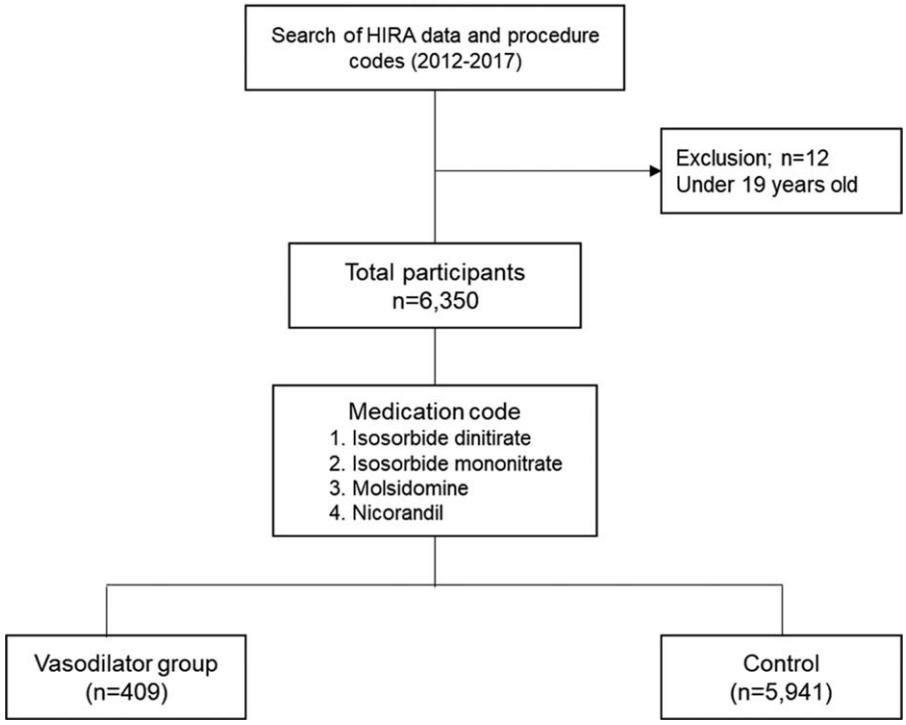

Figure 1. Study flow chart.

limited evidence about their effects on VAs. Thus, we investigated a large, nationwide, population-based database to determine the effects of vasodilators on VA patency.

2. Methods

2.1. Study design and participants

This retrospective cohort study used information from the National Health Insurance Service–National Health Screening Cohort and the Health Insurance Review and Assessment Service (HIRA). The National Health Insurance Program covers nearly 100% of the Korean population, and the NHIS- HEALS is a representative sample cohort that was randomly selected from the total eligible Korean population, for 1 year; we merged the one-year NHIS- HEALS data sets from 2012 to 2017. Further, the HIRA data, such as age group, sex, comorbidity, prescription information, surgical history, and treatment procedure(s), were included. The cohort's representation of the general population has been previously described.[14]

2.2. Data collection

The International Classification of Diseases, 10th revision, codes were used to identify patients >19 years old, with newly diagnosed ESRD (N185 or N189) and undergoing hemodialysis (N189 and V001). Thereafter, we selected patients who underwent VA operations, using procedure codes such as AVF or AVG, from 2012 to 2017; the specific procedure codes examined were: O2011 (external arteriovenous shunt for hemodialysis), O2012 (internal arteriovenous shunt for hemodialysis), O2081 (fistula formation-autologous vein (hemodialysis)), and O2082 (fistula formation-artificial vein (hemodialysis)). In addition, we extracted the data for patients who underwent percutaneous transluminal angioplasties (PTAs), including the diagnosis codes T823 (mechanical complication of other vascular grafts), and M6597 (percutaneous transluminal angioplasty (others)), with the claim dates defined as the procedure dates.

Vasodilator prescription data were extracted from the HIRA. The vasodilator agents included isosorbide mononitrate, isosorbide dinitrate, molsidomine, and nicorandil (detailed medication codes are included in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A537). According to the data, the patients were assigned to either the vasodilator treatment (VDT) or control group (Fig. 1).

2.3. Study outcomes

The primary endpoint was the VA primary patency rate after the AV shunt operation. The period from the AV operation day to the first PTA event was defined as the primary patency duration of the AV shunt. Primary endpoint was compared according to VDT.

2.4. Statistical analysis

Continuous variables are presented as means with standard deviations; categorical variables are presented as numbers with percentages. Categorical variables were analyzed using the χ^2 test or Fisher exact test. Differences between the VDT and control groups were analyzed using Student *t*-test. The observed patency rate was estimated using the Kaplan–Meier method. A Cox proportional hazards model, which included all of the baseline variables and vasodilators for the between-group comparison, was used to determine the relationship between the clinical

Table 1

Baseline characteristics of the vasodilator and control groups of patients undergoing hemodialysis.

	Total (n = 6350)	Vasodilator group (n = 409)	Control group (n = 5941)	*P* value
Age (yr)	62.9 ± 13.3	67.0 ± 10.9	62.6 ± 13.4	<.001
Male (n, %)	3819 (60.1)	238 (58.2)	3581 (60.3)	.405
Underlying disease (n, %)				
Hypertension	1164 (18.3)	59 (14.4)	1150 (19.4)	.035
Diabetes	2297 (36.2)	168 (41.1)	2129 (35.8)	.033
MI	203 (3.2)	43 (10.5)	160 (2.7)	<.001
Dyslipidemia	93 (1.5)	13 (3.2)	80 (1.4)	.003
Stroke	558 (9.3)	47 (11.5)	511 (8.6)	.046
PAD	107 (1.7)	11 (2.7)	96 (1.6)	.103
Medication (n, %)				
Aspirin	4026 (63.4)	338 (82.6)	3688 (62.1)	<.001
Clopidogrel	2049 (32.3)	253 (61.9)	1796 (30.2)	<.001
Statin	3413 (53.8)	300 (73.4)	3113 (52.4)	<.001
Patients undergoing PTA (n, %)	998 (15.7)	8 (2.0)	990 (16.7)	<.001

Data are presented as number (%) or mean ± SD.

MI = myocardial infarction, PAD = peripheral artery disease, PTA = percutaneous transluminal angioplasty.

variables and primary patency. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated according to sex (male), older age (>65 years old), past medical history (hypertension, diabetes, myocardial infarction, dyslipidemia, stroke, and peripheral artery disease), and medication history (particularly aspirin, clopidogrel, and statin use). Furthermore, we analyzed and compared VA patency rate among each vasodilator. All statistical analyses were performed using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) and SAS (SAS Enterprise Guide 7.1; SAS Institute, Cary, NC, USA). *P* value <.05 was considered statistically significant.

2.5. Data sharing statement

HIRA data are third-party data not owned by the authors. HIRA data are available upon visit or by mail upon direct, email or fax submission of the data set request form and declaration of data use that is downloadable from the "HIRA" website (http://www.hira.or.kr/dummy.do?pgmid=HIRAA070001000450) and upon payment of the transfer of data request fee (300 000 KRW per data set).

2.6. Ethics approval

The study protocol was approved by the Institutional Review Board at Hallym University Kangnam Sacred Heart Hospital (approval number: 2019-12-015-001), and all procedures were performed in accordance with the tenets of the Declaration of Helsinki.

3. Results

3.1. Baseline characteristics

A total of 6350 patients (mean age, 69.9 years; 3819 (60.1%) males) were included in this study. As shown in Table 1, 409 (6.4%) patients were assigned to the VDT group and 5941 (93.6%) comprised the control group. The patients in the VDT group were older than those in the control group. In the VDT group, the proportions of patients with histories of diabetes mellitus, myocardial infarction, dyslipidemia, and stroke were higher than in the control group; however, hypertension was more prevalent in the control group. In addition, aspirin, clopidogrel, and statins were prescribed significantly more frequently in the VDT group (Table 1).

3.2. Vascular access patency rate

During the study period, 998 patients (15.72%) underwent PTAs. The incidence of PTAs involving the VA site was significantly lower in the VDT group (1.96%) than in the control group (16.66%, $P < .001$; Table 1). The VA one-month patency rates were similar between the 2 groups; however, in the Kaplan–Meier analysis, the 1-year patency of the hemodialysis VA site was significantly higher in the VDT group (Fig. 2A).

3.3. Related factors and subgroup analysis

To compare patency rates in patients prescribed different vasodilators, a subgroup analysis was performed. When baseline variables and the vasodilators were included in the univariate Cox regression analysis examining potential AV stenosis risk factors, the patency rates were similar for the different vasodilators (Fig. 2B). The patency rate for males was about 20% greater than that for females (HR, 0.80; 95% CI, 0.71–0.91; $P = .001$; Table 2). The risk of PTA was higher among elderly (>65 years old) patients (HR, 1.01; 95% CI, 1.01–1.02; $P < .001$) and in those with diabetes mellitus (HR, 1.33; 95% CI, 1.18–1.51; $P < .001$), but there was no association between PTA risk and the other comorbidities. A history of aspirin (HR, 1.23; 95% CI, 1.08–1.41; $P = .002$), clopidogrel (HR, 1.39; 95% CI, 1.23–1.58; $P < .001$), or statin (HR, 1.16; 95% CI, 1.03–1.12; $P = .018$) use was associated with a higher PTA risk than for patients not using these medications. On the contrary, a medication history involving the use of any of the examined vasodilators was associated with a lower PTA rate and improved VA patency, compared to patients not taking vasodilators (HR, 0.13; 95% CI, 0.06–0.25; $P < .001$; Table 2); all the vasodilators, except molsidomine, were associated with patency rate improvements of approximately 20% (Table 3).

In the multivariate Cox regression analysis, a history of vasodilator administration was associated with a lower risk of PTA, compared with patients not receiving a vasodilator (HR, 0.15; 95% CI, 0.06–0.40; $P < .001$). Further, the PTA risk was

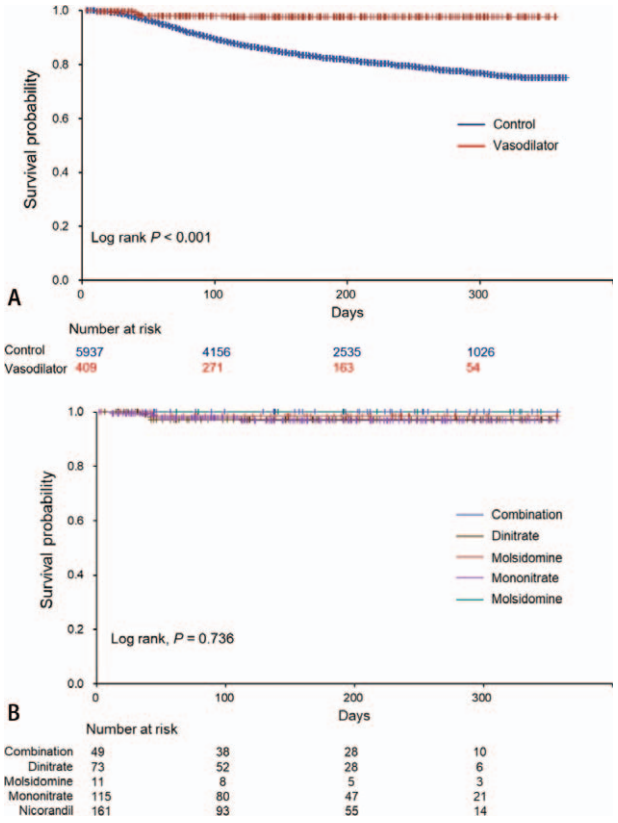

Figure 2. Kaplan–Meier survival plots of PTA events in patients undergoing hemodialysis. (A) Kaplan–Meier curve of PTA events. (B) Kaplan–Meier curve of PTA events according to the administration of each vasodilator. PTA = percutaneous transluminal angioplasty.

significantly lower among men than among women. The use of aspirin and statins was not related to PTA risk; however, clopidogrel use was associated with a significantly increased PTA risk (Table 2).

4. Discussion

In this study, vasodilator use was associated with improved VA performance in patients undergoing hemodialysis. Although there were no differences in the VA patency rates among the examined vasodilator drugs, patients receiving vasodilators had fewer PTAs and higher VA patency rates than those not receiving these drugs. In addition, male patients and patients with histories of myocardial infarctions and strokes tended to have reduced PTA risks. However, clopidogrel use was associated with a higher PTA risk than was observed for other patients undergoing hemodialysis.

Venous stenosis at the vein-artery anastomoses in AVFs or the vein-graft anastomoses in AVGs is the most common cause of VA failure. The venous stenosis is caused by vascular intimal hyperplasia and thrombosis, which is triggered by platelet activation, endothelial cell injury, and vascular smooth muscle cell proliferation.[10,11] Every year, AV stenosis leads to AV dysfunction and causes 20% to 30% of hemodialysis patients to require inpatient treatment; it also results in higher patient mortality rates.[15,16] Therefore, improving the prognoses of hemodialysis patients by preventing narrowing or blockage of the blood vessels that can lead to AV fistula dysfunction is important.[9] To solve this problem, various interventional procedures, such as using drug-eluting balloons or stents, for reducing AV fistula stenosis are being performed; medical treatment for preventing stenosis and obstruction is also being considered.[17–19]

Systemic medical therapies involving the use of antiplatelet agents (aspirin and clopidogrel), omega-3 polyunsaturated fatty acids (fish oils), and statins reduce VA failure by promoting VA maturation and reducing stenosis and thrombosis through antiproliferative, antiaggregatory, anti-inflammatory, and vasodilatory effects.[20–22] In our report, aspirin use was not associated with VA patency, similar to the results from other

Table 3

Cox proportional analysis for primary patency of each vasodilator agent.

	HR	95% CI	*P* value
Isosorbide dinitrate	0.09	0.01–0.64	.020
Isosorbide mononitrate	0.17	0.05–0.52	.002
Molsidomine	0	0–0	.950
Nicorandil	0.183	0.07–0.49	<.001

CI = confidence interval, HR = hazard ratio.

Table 2

Cox proportional analysis for primary patency in patients undergoing hemodialysis.

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (yr)	1.01	1.01–1.02	<.001	1.01	1.00–1.01	<.001
Sex (male)	0.80	0.71–0.91	<.001	0.81	0.71–0.91	<.001
Hypertension	0.96	0.81–1.14	.676			
Diabetes mellitus	1.33	1.18–1.51	<.001	1.16	0.92–1.46	.212
MI	0.77	0.52–1.15	.204			
Dyslipidemia	0.58	0.29–1.16	.123			
Stroke	0.91	0.72–1.15	.429			
PAD	1.41	0.93–2.16	.108			
Aspirin	1.23	1.08–1.41	.002	1.12	0.95–1.33	.183
Clopidogrel	1.39	1.23–1.58	<.001	1.43	1.25–1.65	<.001
Statin	1.16	1.03–1.32	.018	1.06	0.92–1.23	.403
Any vasodilator	0.13	0.06–0.25	<.001	0.15	0.06–0.40	<.001

CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, PAD = peripheral artery disease.

studies. For example, Kim et al reported a large-scale prospective study in which aspirin did not show a protective effect on vascular patency.[23] In addition, the effect of clopidogrel for VA patency did not affect functional AV fistula significantly. Otherwise, the patients prescribed clopidogrel was associated with higher PTA risk in this study.[24] A research documented that clopidogrel was more prescribed to the patients who have cardiovascular risk factors as postcoronary intervention therapy in the clinical field. We considered that clopidogrel might be more prescribed for patients with severe comorbidity, and that could affect the result.[25] However, a systematic review reported that antiplatelet agents, including aspirin, prevented VA blockage.[26] Thus, despite some studies showing the expected effects, these results are not universal. As a result, the effects of these drugs remain unclear and subject to debate.[17]

In this study, we documented that older patients, those with diabetes, and females had higher PTA risk than patients without these traits. Similar results have been shown in other studies; for example, Wen et al reported that female sex and advanced age were independent risk factors for VA dysfunction.[27] Additionally, Smith et al reported that advanced age and the presence of diabetes are risk factors for VA dysfunction.[28] Age might be associated with an increased PTA risk because of the higher incidence of comorbidities, such as peripheral vascular disease and diabetes, in patients of advanced age. The sex-associated difference in risk may be related to the diameter of women's arteries being smaller than those of men; therefore, lower AVF patency rates in women, compared with men, may be expected.[29,30] However, a single-center, retrospective study revealed no differences in the construction of AVFs for patients in different age groups.[31] In the case of sex, a meta-analysis study documented similar one-year patency rates, maturation, and vessel diameters between males and females.[32,33] Therefore, age and sex, as independent factors of VA patency, continue to be debated.[30] Relative to the impact of diabetes, a systematic review documented that primary patency rates appear to be lower in patients with diabetes than in those without the disease, similar to the results of our study.[34,35]

Although several studies regarding factors affecting VA patency have been reported, there are few studies describing the effects of vasodilators on VA. When an AVF is created, blood flow causes shear stress on the vascular wall and also triggers endothelial cells to produce nitric oxide, which is necessary for vasodilation.[36] Endothelial nitric oxide synthase seems to be essential for vascular maturation and function, but its effect on AVF maturation has not been clearly established. Daniel et al reported that overexpression of the nitric oxide synthase system results in distinct hemodynamic and wall mechanical profiles associated with favorable AVF remodeling, in a mouse model. The authors documented that AVFs in mice overexpressing nitric oxide showed larger lumen areas, inducing smoother blood flow, lower wall shear stress, blood vorticity, inner wall circumferential stretch, and radial wall thinning at the anastomoses.[35,37] We focused on lumen dilatation as a cornerstone to prevent VA stenosis, and analyzed the effect of vasodilators on VA patency in a large-scale study of patients undergoing hemodialysis. As suggested by the mouse model study, we assumed that vasodilator administration triggered dilation of the lumen diameter of the VA, leading to lower shear stress at the vascular wall. Thus, this phenomenon might be associated with the observed VA patency improvements in patients undergoing hemodialysis and being treated with vasodilators.

There are some limitations to our study. The major limitations of this study originate from the inherent features of the the National Health Insurance Service– National Health Screening Cohort cohort.[38] The possibility of misclassification bias exists for the diagnosis of ESRD involving hemodialysis, which was defined using healthcare usage records. In addition, some data may be underestimated due to the following reasons. Second, most patients might have received vasodilators due to cardiovascular disease. If patients undergoing hemodialysis have underlying cardiovascular disease, the mortality rate is increased[39] and some patients might die before the PTA procedure. Since the outcome of this study focused on VA patency, using the PTA code, those who died before being diagnosed with VA stenosis could not be included. Third, we did not include surgical thrombectomy as a treatment for VA stenosis. Fourth, this study is a retrospective study based on NHIS codes. Therefore, we could not confirm the mechanism of vasodilation for VA. Finally, the number of patients was small and mortality data were not available for analysis, even though we enrolled all patients with ESRD and requiring hemodialysis who underwent VA creation during the study period. In addition, we missed the propensity scoring matching analysis due to technical and time limitations. However, the statistically significant improvement in VA patency in the VDT group might be considered to be a meaningful indication of the vasodilator effect.

In conclusion, vasodilator administration might help improve VA patency in patients undergoing hemodialysis. Thus, these results support a potential therapeutic approach involving the use of vasodilators. Moreover, the study provides evidence to support future research into the mechanism and role of these agents in the preservation of hemodialysis VAs.

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Author contributions

Conceptualization: Donghoon Han.
Data curation: Jaehwan Kim.
Formal analysis: Jaehwan Kim.
Investigation: Hayne Cho Park, Young-Ki Lee, Dong-Geum Shin, Min-Kyung Kang, Jung Rae Cho, Seonghoon Choi, Namho Lee.
Methodology: Do Hyoung Kim, Donghoon Han.
Software: Jaehwan Kim.
Validation: Do Hyoung Kim, Donghoon Han.
Writing – original draft: Do Hyoung Kim, Donghoon Han.
Writing – review & editing: Do Hyoung Kim, Donghoon Han.

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