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Original Research

Long-term use of proton-pump inhibitor on Alzheimer's disease: a real-world distributed network analysis of six observational Korean databases using a Common Data Model

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Abstract

Background: Dementia has a crucial impact on the quality of life of elderly patients and their caregivers. Proton-pump inhibitors (PPIs) are the most frequently prescribed treatment, but they have been shown to be associated with dementia. The data are inconsistent, however.

Objective: To investigate the association between PPIs use and Alzheimer's disease (AD) or all-cause dementia in six observational Korean databases using a Common Data Model (CDM) and to perform a distributed network analysis.

Methods: Subjects aged over 18 years between 1 January 2004 and 31 December 2020. Among 7,293,565 subjects from 6 cohorts, 41,670 patients met the eligibility criteria. A total of 2206 patients who were included in both cohorts or with a history of dementia were excluded. After propensity matching, 5699 propensity-matched pairs between the PPIs and histamine-2 receptor antagonist (H_2RA) users were included in this study. The primary outcome was the incidence of AD at least 365 days after drug exposure. The secondary outcome was the incidence of all-cause dementia at least 365 days after drug exposure.

Results: In the 1:1 propensity score matching, the risk of AD or all-cause dementia was not significantly different between the PPIs and H_2RA groups in all six databases. In the distributed network analysis, the long-term PPI users (⩾365 days) were unassociated with AD [hazard ratio (HR) = 0.92, 95% confidence interval (CI) = 0.68–1.23; I^2 = 0%] and all-cause dementia (HR = 1.04, 95% CI = 0.82–1.31; I^2 = 0%) compared with H_2RA users.

Conclusion: In the distributed network analysis of six Korean hospital databases using Observational Medical Outcomes Partnership (OMOP)-CDM data, the long-term use of PPI was not associated with a statistically significantly increased risk of AD or all-cause dementia. Therefore, we suggest that physicians should not avoid these medications because of concern about dementia risk.

Keywords: Alzheimer disease, Common Data Model, dementia, H_2 receptor antagonist, proton-pump inhibitors

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Introduction

Proton-pump inhibitors (PPIs) are the most frequently prescribed classes of drugs for the treatment of gastroesophageal reflux disease and peptic ulcers.[1] PPIs are preferred over histamine-2 receptor antagonists (H_2RA) because PPIs have been shown to have superior efficacy at reducing gastric acid compared with H_2RAs.[1,2] In

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fact, PPI use rapidly increased from 0.2% in 1990 to 14.2% in 2018, whereas the usage of H_2RAs has remained relatively low (1.2%–3.4%) in the United Kingdom.[3]

Presumed adverse events of PPIs, however, have been reported in the clinical field including *Clostridium difficile* infection,[4] osteoporosis,[5] chronic renal disease,[6] and dementia.[7] Among these factors, dementia has a crucial impact on the quality of life of elderly patients and their caregivers and is a healthcare-related socioeconomic burden.[8] Vitamin B_{12} deficiency, blocking acid secretion by binding to H^+/K^+-ATPase, and enhancing β-amyloid have been suggested to be associated with PPI-related cognitive decline.[9] Nevertheless, because these studies have shown inconsistent results,[10,11] the relationship between PPIs and dementia remains unclear. A recent meta-analysis of 10 studies suggested that the use of PPIs may not increase the risk of dementia.[12,13] More recent studies, however, were not included in that meta-analysis,[14] and most studies did not fully adjust for various confounding factors such as medications and combined diseases. Furthermore, it is important to consider the length of PPI exposure. The current lack of consensus on the long-term complications of PPIs related to dementia warrants further investigation using different study populations, statistical approaches, and time-at-risk (TAR) window.

Therefore, we investigated the association between PPIs use and Alzheimer's disease (AD) or all-cause dementia in six observational Korean databases using a Common Data Model (CDM) and performed a distributed network analysis.

Methods

Data source

This study included patient-based retrospective cohort data from six medical centers including Ajou University Medical Center (AUMC, $n=3{,}109{,}677$), Kangdong Sacred Heart Hospital, Hallym University College of Medicine (KDH, $n=1{,}689{,}604$), Gangdong Kyung Hee University Hospital (KHNMC, $n=822{,}183$), Kangwon National University Hospital (KWMC, $n=542{,}934$), Pusan National University Hospital (PNUH, $n=1{,}753{,}001$), and Wonkwang University Hospital (WKUH, $n=1{,}001{,}794$) converted to the Observational Medical Outcomes Partnership (OMOP) CDM. OMOP-CDM contains standardized data with the same structure to generate network-wide results through distributed research networks using the same analysis program among collaborating organizations (Figure 1).

Observational Health Data Sciences and Informatics (OHDSI) is an international collaborative consortium aimed at facilitating the generation of high-quality evidence by generating and applying open-source data analysis solutions to a large network of health databases worldwide.[15] Most Korean hospitals use electronic health record (EHR) systems; however, numerous Korean codes for diagnosis, medications, and procedures are not compatible with international coding systems. Since 2016, data from Ajou University and the Korean nationwide cohort database were successfully transformed into the OMOP-CDM model and validated.[16,17] EHR data from each hospital were converted to the CDM version, which is potentially applicable for collaborating OHDSI networks worldwide. This study was approved by the Institutional Review Board of the study institution (Institutional Review Board number 2018-05-013) and conformed to the tenets of the Declaration of Helsinki.

Study design and cohort definitions

We conducted a retrospective, observational, comparative cohort study of all outpatient-based subjects aged over 18 years between 1 January 2004 and 31 December 2020. The study flowcharts of the included patients were shown in Figure 1 and Supplementary Figure 1, and diagram of study construction from six databases was depicted in Figure 2.

The index date of the target and comparative cohorts was defined as the first date of drug prescription. To avoid immortal time bias and duplication, both cohorts had continuous observation periods of 180 days before cohort entry as in our previous study.[18] Both cohorts were censored or end of database at the time of the identification of dementia. PPI exposure was defined as prescription for more than 90, 180, or 365 days. In this study, TAR start was defined as the period from 1 day after the index date. We used TAR start of 180 days or 365 days from the cohort start date. Because the TAR end was set to 99,999 days, it means that the subject is followed up until the end of the observation (Figure 2).

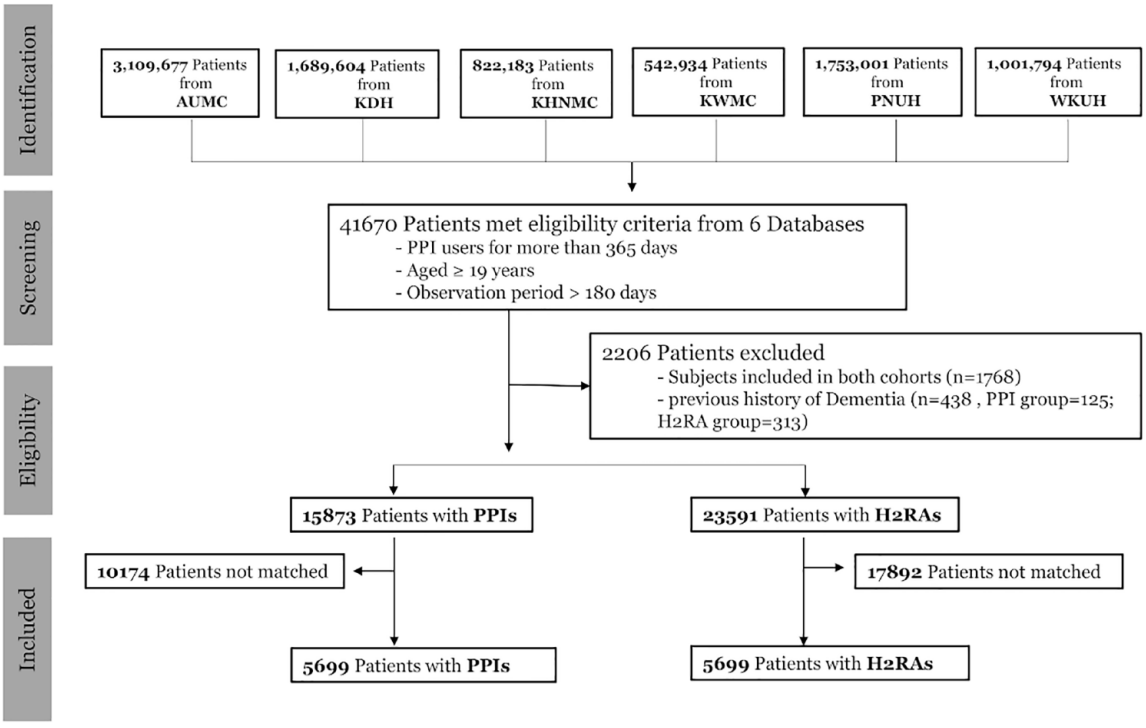

Figure 1. Study flowchart of included patient-based retrospective cohort data from six medical centers.

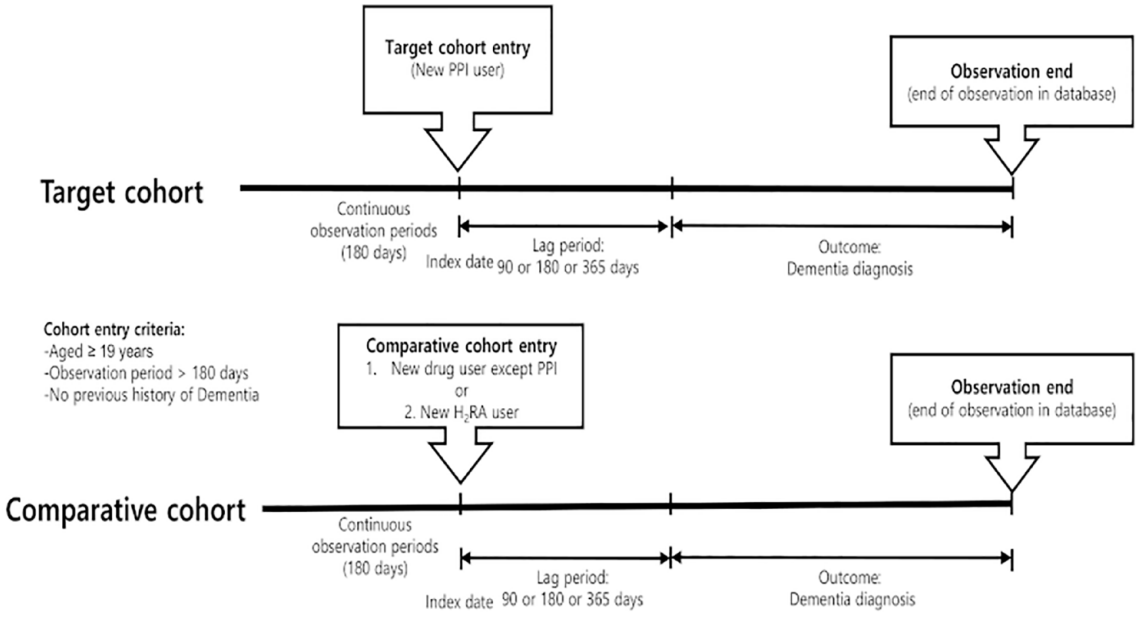

Figure 2. Diagram of cohort construction.
H2RA, histamine-2 receptor antagonist; PPI, proton-pump inhibitor.

Subjects who met at least one of the following criteria were excluded from the target and comparative cohorts: (1) history of dementia before cohort entry, (2) an observation period of less than 180 days before cohort entry, (3) history of drug use, and (4) aged <19 years. In the PPIs group, H_2RAs users of 180 days before PPI exposure and all H_2RAs users after PPI exposure were excluded,

and PPIs users of the same period were excluded from the H_2RAs group.

The target cohort was defined as new PPIs users who were prescribed PPIs for more than 90 consecutive days. In the subgroup analysis, the PPI group was further divided into subgroups by the duration of PPI exposure (⩾180 or ⩾365 days). All PPIs on the market in Korea were included in these analyses (esomeprazole, pantoprazole, lansoprazole, rabeprazole, omeprazole, ilaprazole, and dexlansoprazole). Continuous drug exposures were restricted by allowing less than 30-day gaps between the drug prescriptions. The comparative cohort was defined as subjects prescribed H_2RA for more than 90, 180, or 365 consecutive days. H_2RAs included ranitidine, nizatidine, cimetidine, famotidine, and lafutidine.

Outcomes

The primary analysis was performed to compare the risk of AD between PPIs and H_2RAs according to the duration of PPI exposure. The secondary analysis was performed to compare the risk of all-cause dementia including AD, Parkinson's disease dementia, Lewy body dementia, frontotemporal dementia, and vascular dementia between PPIs and H_2RAs. Furthermore, we conducted the same analyses using another comparative cohort of non-PPIs users.

The primary outcome was the incidence of AD at least 365 days after drug exposure. AD was defined by the diagnosis codes F000 to F002 in the 10th version of the *International Classification of Diseases* codes (ICD-10). To clarify the diagnosis, patients with AD were required to have at least one antidementia medication among donepezil, rivastigmine, memantine, and galantamine. The secondary outcome was the incidence of all-cause dementia at least 365 days after drug exposure. Dementia was defined when documented with one of the following ICD-10 codes: G30, F00, F01, F05.1, G31.1, G31.82, and G31.9. We did not differentiate between dementia subtypes.

Covariates

We performed large-scale propensity score matching using the OMOP-CDM tool. The following covariates were used between the target and comparative cohorts: age, sex, all recorded comorbidities, prescribed drugs 365 days before the index date, and Charlson's comorbidity index. The distribution of preference scores between groups receiving PPIs and those receiving H_2RAs before and after matching and covariate balance was summarized with mean values for all baseline covariates in the target and comparator cohorts, with the associated standardized mean difference computed for each covariate. Standardized mean differences were lower than 0.1 after propensity score matching (Supplementary Figure 2).

Statistical analysis

Most OHDSI analysis tools are embedded in the ATLAS platform and the OHDSI Methods Library R packages. The open-source software in OHDSI is publicly available at the GitHub repository (https://github.com/OHDSI/). ATLAS ver. 2.7.3 was used herein, and we analyzed the platform of FEEDER-NET, a health big-data platform based on OMOP-CDM supported by the Korean national project. We conducted the Cox regression analysis to examine the hazard ratio (HR) of two cohorts for AD and all-cause dementia. The Kaplan–Meier method was used to estimate the cumulative incidence rate (IR) of AD and all-cause dementia between the two groups. IRs were determined per 1000 person years by dividing the number of dementia events by the total number of person years at risk and multiplying the results by 1000. The cumulative incidence between the two groups was compared using the log-rank test. Two-sided p values <0.05 were considered statistically significant for all two-sided tests. We used 0.2 of the pooled standard deviation of the logit of the propensity score as caliper width for propensity score matching.

The assessment for statistical heterogeneity was calculated using the Chi-square and I^2 statistics. If heterogeneity ($p>0.05$; $I^2<50\%$) did not exist, a fixed-effect model was used. Otherwise, a random-effect model was used.

Sensitivity analysis

To assess the robustness of the results, several sets of sensitivity analyses were performed using different definitions of TAR, propensity score matching, comparatives, and outcomes. First, in addition to 1:1 propensity score matching, 1:4 propensity score adjustments were performed. Second, two TAR periods (180 or 365 days) were applied. Third, we conducted this study using two control groups (H_2RA users or non-PPIs users). Fourth, we added logistic regression analyses.

Results

Among 7,293,565 subjects from 6 cohorts, 41,670 patients met the eligibility criteria. Because 2206 patients were included in both cohorts or had a history of dementia were excluded, 15,873 subjects who were PPIs users and 23,592 subjects who were H_2RAs users were left. After propensity matching, 5699 propensity-matched pairs between the PPIs and H2RAs users were included in this study (Figure 1). The baseline characteristics are shown in Table 1.

The mean follow-up time was different from the six cohorts (AUMC = 1457 days, KDH = 1630 days, KHNMC = 1564 days, KWMC = 1758 days, PNUH = 1207 days, and WKUH = 1930 days). The number of subjects, follow-up time, number of outcome events, and event IR per 1000 patient years are presented in Table 2.

Association of PPIs and risk of AD and dementia compared with H_2RA

We conducted the Kaplan–Meier analyses for the risk of AD and all-cause dementia between PPIs and H_2RAs after propensity score matching.

In the 1:1 propensity score matching, the risk of AD was not significantly different between the PPIs and H_2RAs groups in all six databases [AUMC = 0.89 (95% confidence interval (CI) = 0.46–1.73), KDH = 0.80 (95% CI = 0.31–2.06), KHNMC = 1.00 (95% CI = 0.53–1.90), KWMC = 1.00 (95% CI = 0.54–1.84), PNUH = 0.67 (95% CI = 0.27–1.66), and WKUH = 1.00 (95% CI = 0.46–2.18)] (Figure 3).

In the 1:1 propensity score matching, the risk of all-cause dementia was not significantly different between the PPIs and H_2RAs groups in all six databases [AUMC = 1.20 [95% CI = 0.60–2.40], KDH = 1.00 (95% CI = 0.47–2.12); KHNMC = 0.6 (95% CI = 0.31–1.14), KWMC = 1.18 (95% CI = 0.79–1.75), PNUH = 1.00 (95% CI = 0.43–2.34), and WKUH = 1.13 (95% CI = 0.69–1.84)] (Figure 4).

In the distributed network analysis with 1:1 propensity score matching, the long-term PPIs users (⩾365 days) were unassociated with AD [HR = 0.92, 95% CI = 0.68–1.23; I^2 = 0%; Figure 5(a)] and all-cause dementia [HR = 1.04, 95% CI = 0.82–1.31; I^2 = 0%; Figure 5(b)] compared with H_2RAs users.

To assess the robustness of the results, in addition to 1:1 propensity score matching, 1:4 propensity score adjustment and 1:1 propensity score matching with an additional TAR period (365 days) were applied. No differences, however, were observed between PPIs and H_2RAs in all analyses (Table 3).

Association of PPIs and risk of AD and all-cause dementia compared with non-PPIs

In addition, to clarify the effect of long-term PPI use on cognitive decline, we compared PPI users and non-PPI users.

In the distributed network analysis with 1:1 propensity score matching, the long-term PPI users (⩾365 days) were unassociated with AD [HR = 1.08, 95% CI = 0.59–1.99; I^2 = 38.9%; Figure 6(a)] and all-cause dementia [HR = 1.16, 95% CI = 0.81–1.67; I^2 = 0%; Figure 6(b)] compared with non-PPIs users. To assess the robustness of the results, in addition to 1:1 propensity score matching, 1:4 propensity score adjustment and 1:1 propensity score matching with an additional TAR period (365 days) were applied. No differences, however, were observed between PPI and non-PPIs users in all analyses (Table 3).

Sensitivity analysis

To support the robustness of the results, we also conducted the logistic regression analyses. In the distributed network analysis with 1:1 propensity score matching, the long-term PPIs users (⩾365 days) were unassociated with AD [odds ratio (OR) = 0.87, 95% CI = 0.72–1.06; I^2 = 0%], but were marginally associated with all-cause dementia (OR = 0.84, 95% CI = 0.71–0.99; I^2 = 0%) compared with H_2RAs users (see the Supplementary Table). In the distributed network analysis with 1:1 propensity score matching, the long-term PPIs users (⩾365 days) were unassociated with AD (OR = 1.14, 95% CI = 0.76–1.71; I^2 = 0%) and all-cause dementia (OR = 0.79, 95% CI = 0.62–1.02; I^2 = 0%) compared with non-PPIs users (see the Supplementary Table).

In addition, we performed sensitivity analysis to identify the influence of PPI duration on subjects with PPI use exceeding 90 and 180 days. Similar to the long-term PPI users (⩾365 days), the risks of AD or all-cause dementia in these subgroups (PPI user ⩾90 or ⩾180 days) were unassociated with PPI use (Table 3).

Table 1. Distribution of baseline characteristics across six databases between the PPI ⩾365 days group and the comparative group (H_2RA) in the overall population before and after propensity score matching.

Dementia	Before PS adjustment			After PS adjustment		
	PPIs	H_2RA	SMD	PPIs	H_2RA	SMD
Age group (years)						
30–34	1.0	1.3	−0.02	0.7	0.9	−0.02
35–39	1.9	2.3	−0.02	1.6	2.2	−0.04
45–49	5.5	5.6	0.00	5.6	6.0	−0.02
50–54	8.3	8.6	−0.01	7.8	8.4	−0.02
55–59	12.2	11.2	0.03	12.2	11.5	0.02
60–64	13.7	14.0	−0.01	13.7	13.8	0.00
65–69	13.8	14.1	−0.01	14.2	13.4	0.02
70–74	14.0	15.1	−0.03	14.7	14.7	0.00
75–79	12.8	13.0	−0.01	13.2	13.0	0.01
80–84	8.0	6.8	0.05	7.6	7.6	0.00
85–89	3.0	2.5	0.03	3.0	3.0	0.00
Gender: female	54.9	51.9	0.06	53.3	53.0	0.01
Medical history: general						
Acute respiratory disease	2.1	2.2	−0.01	1.9	2.1	−0.01
Chronic obstructive lung disease	3.4	4.5	−0.05	3.5	3.0	0.03
Depressive disorder	3.3	3.5	−0.01	3.2	3.3	0.00
Diabetes mellitus	11.9	12.0	0.00	11.7	12.1	−0.01
Gastroesophageal reflux disease	13.4	3.2	0.38	5.4	6.6	−0.05
Hypertensive disorder	28.8	30.2	−0.03	29.4	30.0	−0.01
Lesion of liver	3.9	3.2	0.04	3.4	3.6	−0.01
Osteoarthritis	4.1	2.2	0.11	2.7	2.7	0.00
Renal impairment	5.5	4.1	0.07	5.1	5.2	0.00
Urinary tract infectious disease	1.2	1.0	0.02	1.1	1.0	0.01
Visual system disorder	9.3	8.8	0.02	8.6	9.0	−0.02
Medical history: cardiovascular disease						
Cerebrovascular disease	6.3	9.9	−0.13	7.6	7.1	0.02
Heart disease	26.1	24.6	0.04	27.8	28.8	−0.02
Ischemic heart disease	15.6	13.8	0.05	16.8	17.5	−0.02

(Continued)

Table 1. (Continued)

Dementia	Before PS adjustment			After PS adjustment		
	PPIs	H_2RA	SMD	PPIs	H_2RA	SMD
Peripheral vascular disease	2.4	1.9	0.04	1.9	2.0	0.00
Pulmonary embolism	0.5	0.3	0.03	<0.1	0.0	NaN
Medication use						
Agents acting on the renin–angiotensin system	31.7	34.1	−0.05	34.7	35.2	−0.01
Antibacterials for systemic use	27.9	30.9	−0.07	25.3	25.7	−0.01
Antidepressants	23.5	21.5	0.05	19.7	20.4	−0.02
Antiepileptics	17.7	20.8	−0.08	16.6	16.5	0.00
Anti-inflammatory and antirheumatic products	60.3	58.7	0.03	56.5	57.8	−0.03
Antineoplastic agents	20.7	12.5	0.22	13.1	14.7	−0.05
Antipsoriatics	1.5	1.6	−0.02	1.0	1.1	−0.01
Antithrombotic agents	47.7	53.4	−0.11	52.5	52.5	0.00
Beta blocking agents	23.0	23.3	−0.01	24.1	24.4	−0.01
Calcium channel blockers	28.6	31.7	−0.07	29.9	30.8	−0.02
Diuretics	23.1	24.1	−0.02	23.3	23.6	−0.01
Drugs for acid-related disorders	36.4	47.4	−0.22	33.9	33.8	0.00
Drugs for obstructive airway diseases	21.0	22.3	−0.03	17.1	17.1	0.00
Drugs used in diabetes	17.6	17.6	0.00	17.2	17.7	−0.01
Immunosuppressants	12.2	7.7	0.15	8.5	8.8	−0.01
Lipid-modifying agents	38.6	38.0	0.01	40.2	42.3	−0.04
Opioids	39.2	35.6	0.07	32.2	33.2	−0.02
Psycholeptics	31.6	34.0	−0.05	28.6	28.6	0.00

H_2RA, histamine-2 receptor antagonists; PPIs, proton-pump inhibitors; PS, propensity score; SMD, standardized mean difference; NaN, not a number.

Two propensity score adjustments (1:1 *versus* 1:4) and two different TAR factors (180 days and 365 days) were evaluated. These subgroup analyses results confirm the primary study outcomes.

Discussion

In the distributed network analysis of six Korean hospital databases using OMOP-CDM data, the long-term use of PPIs, compared with H_2RA or non-PPIs, was not associated with an increased risk of AD or all-cause dementia. There was no significant difference in the risk for AD or all-cause dementia according to the duration of PPI use. These results are consistent with other analyses using different propensity score matching and time windows. The findings are consistent with those of a recent meta-analysis of 10 studies involving 642,305 patients.[13]

To confirm a causal relationship, but not association, of the long-term complication of drugs, we should conduct well-designed randomized controlled trials (RCTs). This type of RCT, however,

Table 2. Incidence rates and risk of Alzheimer's disease between long-term PPI users (⩾365 days) and comparatives (H_2RA) in the six medical centers.

Alzheimer's disease	Number of subjects		Mean follow-up time (days)		Number of outcome events		Event incidence rate (IR) per 1000 patient years	
1:1 PS, time at risk 180 days	PPI users	H_2RA users	PPI users	H_2RA users	PPI users	H_2RA users	PPI users	H_2RA users
AUMC	1507	1507	1457	1975	23	36	4.36	4.86
KDH	486	486	1630	1891	15	18	7.77	7.90
KHNMC	669	669	1564	1845	23	29	9.07	9.50
KWMC	772	772	1758	2126	28	32	8.39	7.78
PNUH	1180	1180	1207	1373	13	15	3.91	3.89
WKUH	874	874	1930	2458	22	18	5.25	3.30

AUMC, Ajou University Medical Center; H_2RA, histamine-2 receptor antagonists; KDH, Kangdong Sacred Heart Hospital, Hallym University College of Medicine; KHNMC, Gangdong Kyung Hee University Hospital; KWMC, Kangwon National University Hospital; PNUH, Pusan National University Hospital; PPIs, proton-pump inhibitors; WKUH, Wonkwang University Hospital.

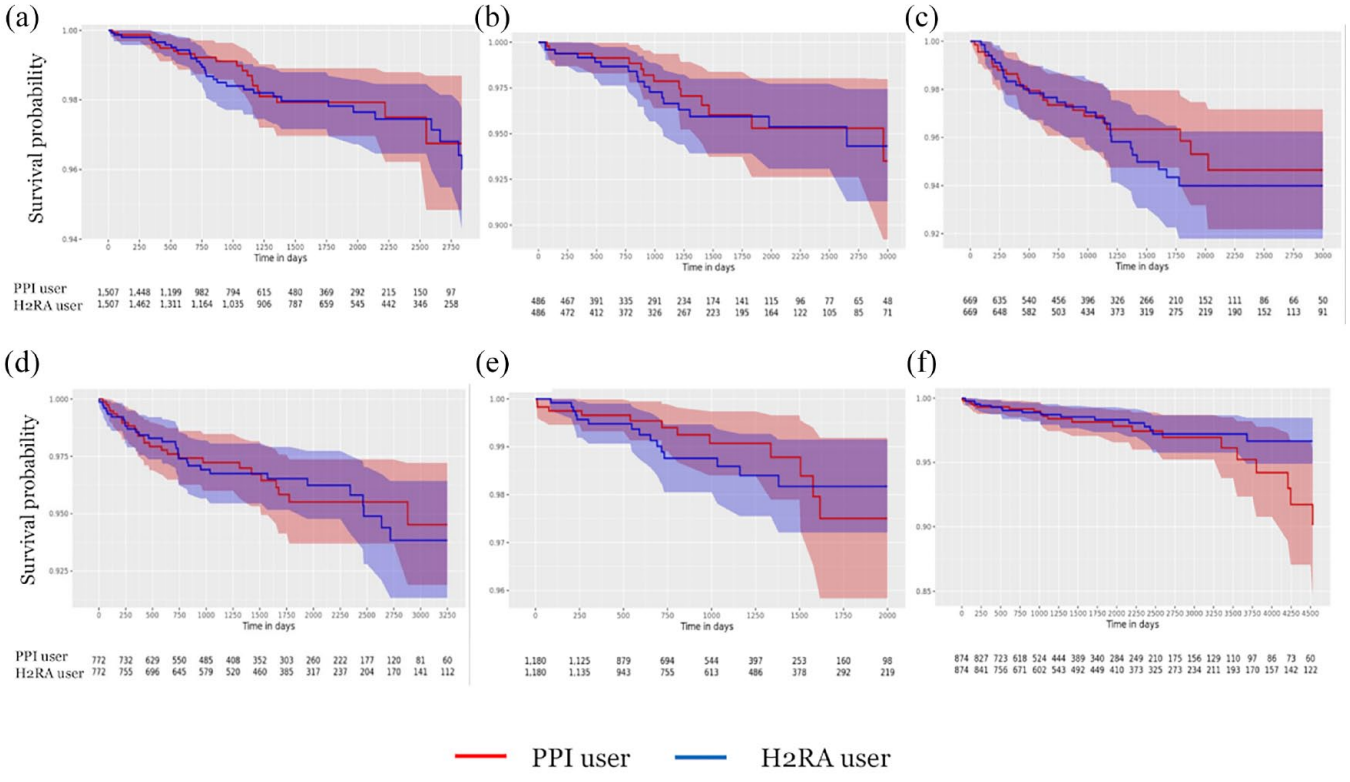

Figure 3. Kaplan–Meier plots for the risks of Alzheimer's disease on-treatment comparisons of proton-pump inhibitors *versus* histamine-2 receptor antagonists. (a) Ajou University Medical Center (AUMC), (b) Kangdong Sacred Heart Hospital, Hallym University College of Medicine (KDH), (c) Gangdong Kyung Hee University Hospital (KHNMC), (d) Kangwon National University Hospital (KWMC), (e) Pusan National University Hospital (PNUH), and (f) Wonkwang University Hospital (WKUH).

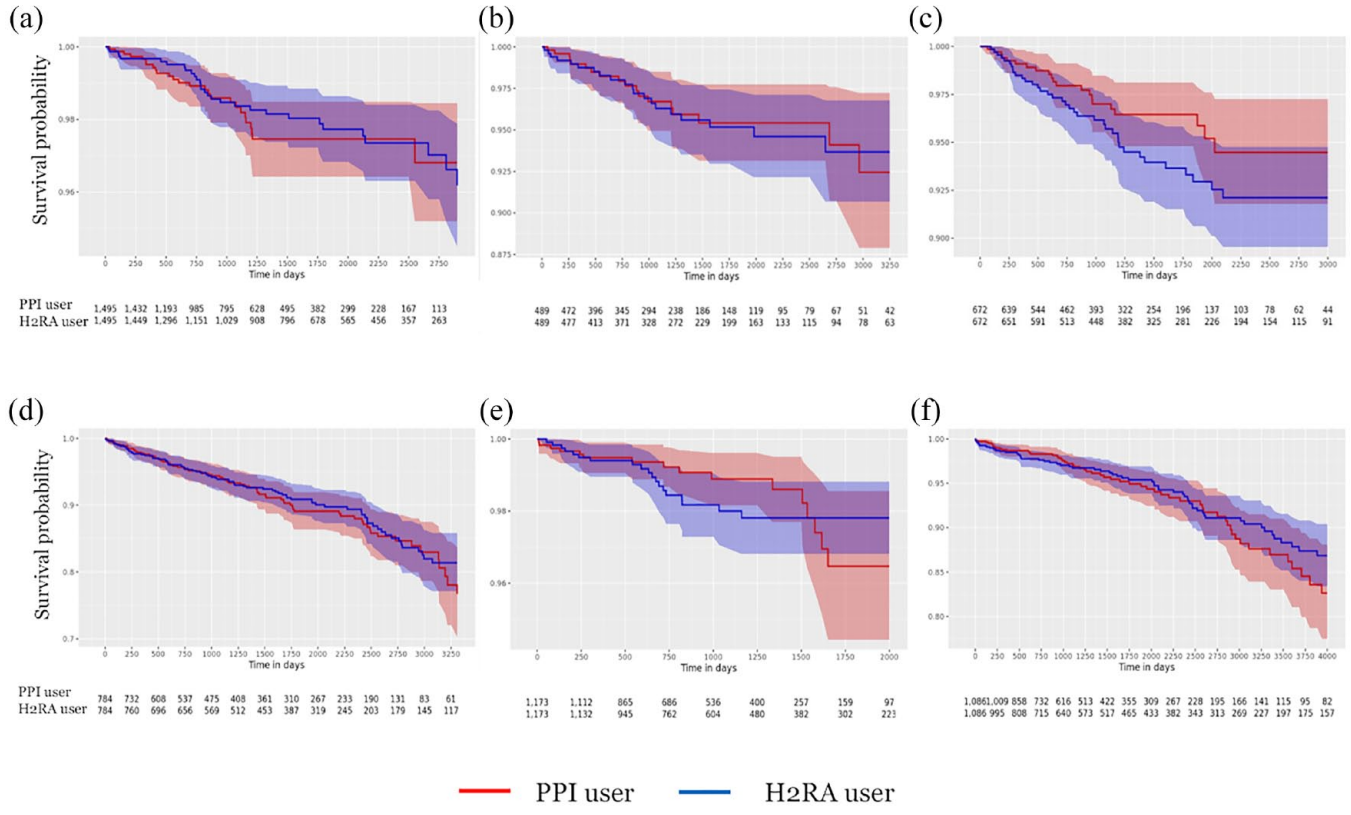

Figure 4. Kaplan–Meier plots for the risks of all-cause dementia on-treatment comparisons of proton-pump inhibitors *versus* histamine-2 receptor antagonists. (a) Ajou University Medical Center (AUMC), (b) Kangdong Sacred Heart Hospital, Hallym University College of Medicine (KDH), (c) Gangdong Kyung Hee University Hospital (KHNMC), (d) Kangwon National University Hospital (KWMC), (e) Pusan National University Hospital (PNUH), and (f) Wonkwang University Hospital (WKUH).

is very difficult to perform because of the long observation periods, huge cost, and ethical problems. Instead, causal inference from observational databases can be evaluated as a try to emulate a particular target trial.[19,20] Thus, we can evaluate the causality of drug complications indirectly by satisfying the Hill criteria including strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment, and analogy.[21,22]

These study results should be reliable as the design of our research was based on a review of previous studies. First, regarding the strength of the association, the dementia risk of PPIs in previous reports had an HR of <2. This means that more clinical trials are needed to examine this connection because an HR <3 has a likelihood of potential bias, although it can also suggest biological plausibility. Second, this study showed consistent results in the extensive sensitivity and subgroup analyses. We conducted several sensitivity analyses using different drug exposure periods (⩾90, ⩾180, and ⩾365 days), TAR windows (⩾180 and ⩾365 days), and propensity score matching (1:1 and 1:4). Third, regarding the specificity, because patients with dementia may have multiple comorbidities, there may be many drug–drug interactions. This study, however, was conducted using OMOP-CDM, which allowed large-scale propensity score matching including multiple drugs. Fourth, regarding the temporality, it is unknown how long dementia takes to develop. Dementia may be diagnosed at late stages or be undiagnosed. Therefore, to overcome this limitation, we used continuous observation periods of 180 days before cohort entry. After drug exposure, we used two different TAR windows (⩾180 and ⩾365 days) to clarify the drug effect on dementia occurrence. Fifth, regarding the biological gradient, although we conducted three different drug exposures (⩾90, ⩾ 180, and ⩾365 days), we did not find a dose–response relationship in this study. Sixth, regarding analogy, a systematic review

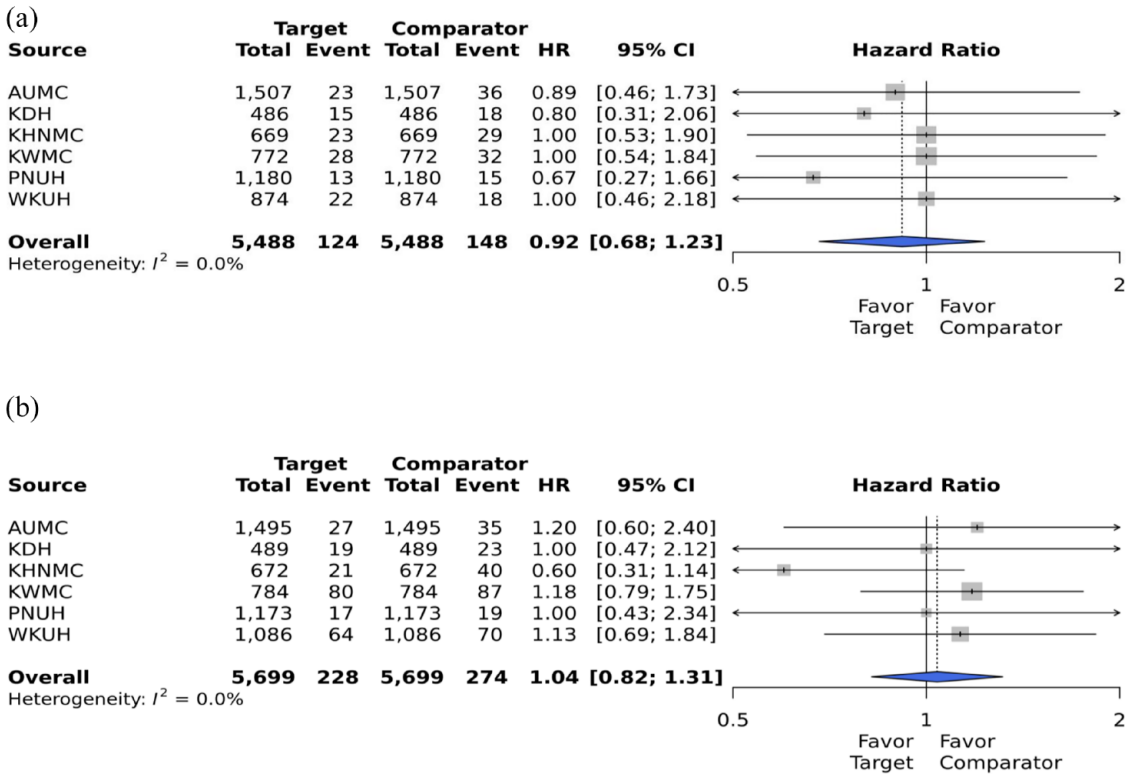

Figure 5. Meta-analysis of risk of PPIs on Alzheimer's disease and all-cause dementia compared with histamine-2 receptor antagonists. In the distributed network analysis with 1:1 propensity score matching, the long-term PPI users (⩾365 days) were unassociated with AD [HR = 0.92, 95% CI = 0.68–1.23; I^2 = 0%; (a)] and all-cause dementia [HR = 1.04, 95% CI = 0.82–1.31; I^2 = 0%; (b)].

reported that cognitive function was improved after bariatric surgery, which is a situation similar to vitamin B_{12} deficiency.[23]

The association between PPI use and dementia, however, is still vague. Regarding plausibility and experiments, some plausible mechanisms such as the increased production of β-amyloid (Aβ),[24] vitamin B_{12} deficiency,[10] and blocking acid secretion by binding to H^+/K^+-ATPase[10] might be related. We cannot explain the exact mechanisms for the discrepancy between our findings and those of the prior studies. Given the widespread use of PPIs, however, these findings will be a significant step in better understanding the safety of long-term use of PPIs.

This study had some strengths. First, to define outcomes, other health claims data should depend on the medical code of diagnosis, and this always has a limitation of uncertainty. In Korea, however, physicians are required to demonstrate a clinical diagnosis of dementia from the medical history, as well as medical scores using the Mini-Mental State Examination, Clinical Dementia Ratings, or Global Deterioration Scale in order to prescribe the antidementia medications.[24] To improve the diagnostic accuracy of AD, we classified patients with AD when they had been prescribed antidementia medications with documented dementia codes. Second, this study was designed to focus on robustness and we performed various sensitivity analyses, which were consistent with our main analysis. Third, to clarify the impact of PPIs on AD or all-cause dementia, we compared PPI users and non-PPIs users, as well as PPI uses and H_2RA users.

Despite these strengths, there were some limitations in this study. First, we could not determine the dementia status of patients or those with undiagnosed dementia. Physicians in South Korea, however, are required to provide strict diagnostic criteria before prescribing antidementia

Table 3. Risk of Alzheimer's disease or all-cause dementia in the overall population between PPI users and comparatives (H_2RA or non-PPIs).

Primary outcome: Alzheimer's disease	PPIs		H_2RA			PPIs		Non-PPIs		
	Subjects	Event	Subjects	Event	HR	Subjects	Event	Subjects	Event	HR
PPI ⩾90 days										
1:1 PS, time at risk 180	15,638	279	15,638	344	1.00 (0.81–1.24)	7553	97	7553	98	1.23 (0.83–1.82)
1:1 PS, time at risk 365	13,585	257	13,585	271	1.15 (0.91–1.46)	6477	87	6477	89	1.37 (0.88–2.13)
1:4 PS, time at risk 180	15,638	279	28,840	629	1.07 (0.90–1.29)	7553	97	21,076	291	1.29 (0.96–1.73)
PPI ⩾180 days										
1:1 PS, time at risk 180	10,120	231	10,120	233	0.99 (0.78–1.26)	5877	87	5877	105	1.02 (0.68–1.52)
1:1 PS, time at risk 365	8812	176	8812	172	1.09 (0.75–1.58)	4972	76	4972	79	0.92 (0.54–1.56)
1:4 PS, time at risk 180	10,120	231	18,561	431	1.04 (0.84–1.28)	5877	87	16,747	285	1.10 (0.82–1.48)
PPI ⩾365 days										
1:1 PS, time at risk 180	5488	124	5488	148	0.92 (0.68–1.23)	3461	55	3461	70	1.08 (0.59–1.99)
1:1 PS, time at risk 365	5488	97	5448	123	1.03 (0.72–1.47)	3442	46	3442	67	1.18 (0.55–2.50)
1:4 PS, time at risk 180	5488	124	10,225	300	0.93 (0.72–1.21)	3461	55	10,249	232	1.07 (0.64–1.78)
Secondary outcome: all-cause dementia	**Subjects**	**Event**	**Subjects**	**Event**	**HR**	**Subjects**	**Event**	**Subjects**	**Event**	**HR**
PPI ⩾90 days										
1:1 PS, time at risk 180	16,008	513	16,008	607	0.97 (0.74–1.28)	6846	153	6846	151	1.16 (0.84–1.61)
1:1 PS, time at risk 365	13,937	440	13,037	483	1.12 (0.94–1.33)	5839	130	5839	142	0.95 (0.68–1.32)
1:4 PS, time at risk 180	16,008	513	29,529	1111	1.06 (0.86–1.32)	6846	153	19,267	461	1.15 (0.91–1.46)
PPI ⩾180 days										
1:1 PS, time at risk 180	10,456	373	10,456	395	1.12 (0.77–1.62)	5387	144	5387	143	1.40 (0.84–2.35)
1:1 PS, time at risk 365	9073	343	9073	336	1.25 (1.02–1.53)	4542	113	4542	130	1.08 (0.76–1.54)
1:4 PS, time at risk 180	10,456	373	19,169	787	1.13 (0.84–1.51)	5387	144	15,545	424	1.28 (0.96–1.71)
PPI ⩾365 days										
1:1 PS, time at risk 180	5699	228	5699	274	1.04 (0.82–1.31)	3194	101	3194	113	1.16 (0.81–1.67)
1:1 PS, time at risk 365	5667	210	5667	237	1.19 (0.89–1.58)	3179	76	3179	100	0.72 (0.47–1.11)
1:4 PS, time at risk 180	5699	228	10,618	525	1.08 (0.86–1.35)	3194	101	9473	337	1.27 (0.97–1.66)

H_2RA, histamine-2 receptor antagonists; HR, hazard ratio; PPIs, proton-pump inhibitors; PS, propensity score.

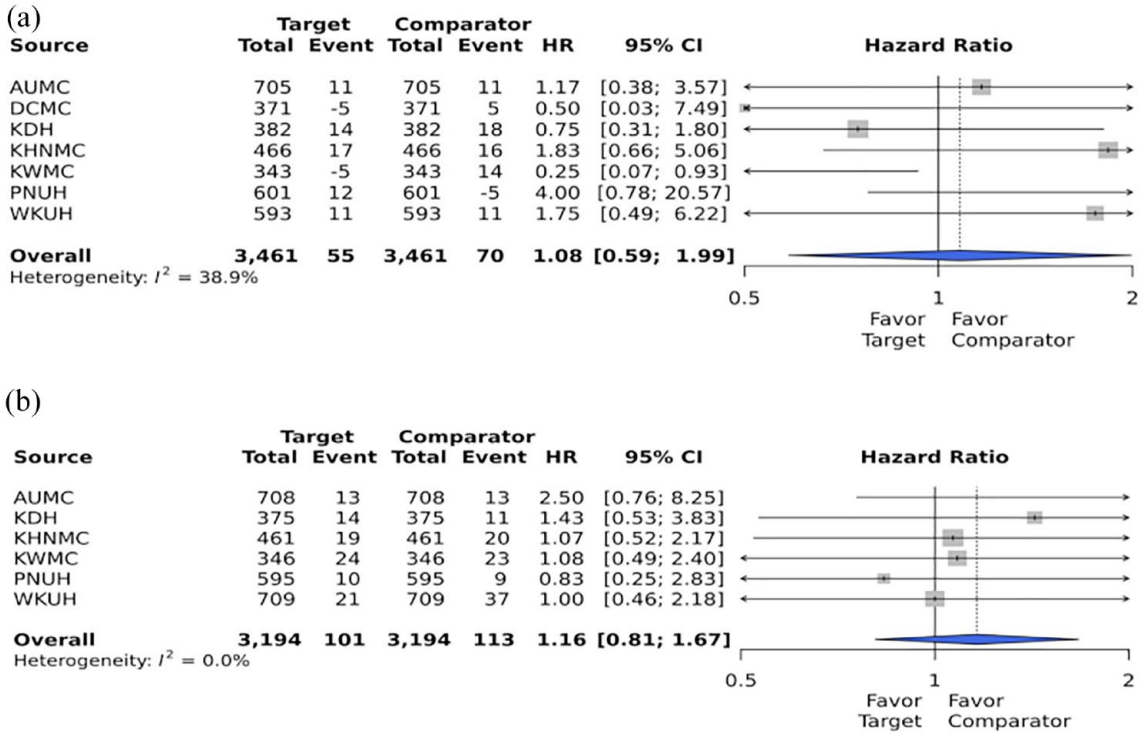

Figure 6. Meta-analysis of Risk of PPIs on Alzheimer's disease and all-cause dementia compared with non-PPIs. In the distributed network analysis with 1:1 propensity score matching, the long-term PPI users (⩾365 days) were unassociated with AD [HR = 1.08, 95% CI = 0.59–1.99; I^2 = 38.9%; (a)] and all-cause dementia [HR = 1.16, 95% CI = 0.81–1.67; I^2 = 0%; (b)] compared with non-PPI users.

medications. Therefore, among all the diagnoses in the health claims data, the diagnosis of dementia is established relatively accurately. Second, we could not determine whether the prescribed dose was the actual dose taken. This, however, is a fundamental *limitation of health claims data. Third, in the logistic regression analysis to evaluate the associations between PPI and all-cause dementia, some analyses showed marginal association differently from the main results. We suggest that because secondary outcome is all cause dementia including* AD, Parkinson's disease dementia, Lewy body dementia, frontotemporal dementia, and vascular dementia, many confounding factors might affect this result. *Despite that, our aim is to investigate the impact of PPI on AD and primary outcome analyses showed similar patterns consistent with the main analyses.* Finally, the results of this study should not be generalized because this study included only six retrospective observational cohort databases from South Korea. However, we suggest that this study, which was well matched and showed consistent results through various statistical and multiple comparative analyses, is critical for the interpretation of the impact of PPIs on dementia.

Conclusion

In conclusion, long-term PPI use was not significantly associated with an increased risk of AD or all-cause dementia. These results are consistent with other analyses using different propensity score matching and time windows. Given some of the conflicting results, further researches will be needed. However, we suggest that physicians should not avoid these medications because of concern about dementia risk.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Kangdong Sacred Heart Hospital, Seoul, Korea (IRB no. 2018-05-013).

Consent for publication

Not required.

Author contributions

Yerim Kim: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation;

Methodology; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

Seung In Seo: Methodology; Writing – review & editing.

Kyung Joo Lee: Data curation; Formal analysis; Methodology; Writing – review & editing.

Jinseob Kim: Data curation; Formal analysis; Methodology; Visualization; Writing – review & editing.

Jong Jin Yoo: Investigation; Writing – review & editing.

Won-Woo Seo: Investigation; Writing – review & editing.

Hyung Seok Lee: Investigation; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data are available upon reasonable request. The analytic R code is available from the corresponding author W.G.S. (e-mail: sgun9139@gmail.com).

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Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Supplemental material

Supplemental material for this article is available online.

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