EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2022;37:65-73
https://doi.org/10.3803/EnM.2021.1275
pISSN 2093-596X · eISSN 2093-5978

Drug Repositioning Using Temporal Trajectories of Accompanying Comorbidities in Diabetes Mellitus

Namgi Park[1,2,*], Ja Young Jeon[3,*], Eugene Jeong[4], Soyeon Kim[1], Dukyong Yoon[5,6]

[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon; [2]Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul; [3]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea; [4]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN, USA; [5]Department of Biomedical Systems Informatics, Yonsei University College of Medicine; [6]Center for Digital Health, Yongin Severance Hospital, Yonsei University Health System, Yongin, Korea

Background: Most studies of systematic drug repositioning have used drug-oriented data such as chemical structures, gene expression patterns, and adverse effect profiles. As it is often difficult to prove repositioning candidates' effectiveness in real-world clinical settings, we used patient-centered real-world data for screening repositioning candidate drugs for multiple diseases simultaneously, especially for diabetic complications.

Methods: Using the National Health Insurance Service-National Sample Cohort (2002 to 2013), we analyzed claims data of 43,048 patients with type 2 diabetes mellitus (age ≥40 years). To find repositioning candidate disease-drug pairs, a nested case-control study was used for 29 pairs of diabetic complications and the drugs that met our criteria. To validate this study design, we conducted an external validation for a selected candidate pair using electronic health records.

Results: We found 24 repositioning candidate disease-drug pairs. In the external validation study for the candidate pair cerebral infarction and glycopyrrolate, we found that glycopyrrolate was associated with decreased risk of cerebral infarction (hazard ratio, 0.10; 95% confidence interval, 0.02 to 0.44).

Conclusion: To reduce risks of diabetic complications, it would be possible to consider these candidate drugs instead of other drugs, given the same indications. Moreover, this methodology could be applied to diseases other than diabetes to discover their repositioning candidates, thereby offering a new approach to drug repositioning.

Keywords: Diabetes mellitus, type 2; Drug repositioning; Retrospective studies

INTRODUCTION

Drug repositioning is a drug development strategy that discovers new indications that differ from the original indication for approved or investigational drugs [1]. Drug repositioning research has increased in popularity in recent years, given its many advantages over traditional drug development strategies, such as lower investment requirements and a higher success rate [1-3].

Received: 21 September 2021, **Revised:** 18 December 2021,
Accepted: 22 December 2021

Corresponding author: Dukyong Yoon
Department of Biomedical Systems Informatics, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea
Tel: +82-31-5189-8450, **Fax:** +82-31-5189-8566
E-mail: dukyong.yoon@yonsei.ac.kr

*These authors contributed equally to this work.

In particular, systematic drug repositioning studies have received considerable attention. By screening multiple diseases or drugs simultaneously, this approach suggests multiple repositioning candidate drugs simultaneously. Cheng et al. [4] quantified the proximity between disease genes and drug targets based on a protein interaction network to discover new indications for 900 U.S. Food and Drug Administration-approved drugs. Xuan et al. [5] discovered new disease-drug associations by calculating the similarities between drugs using drug structure, target protein, and side effects, and integrating them with the similarities between diseases. As these systematic strategies make it possible to discover numerous repositioning candidates simultaneously, they can reduce time and costs for drug repositioning.

However, most studies of systematic drug repositioning have used drug-oriented data such as chemical structures, gene expression patterns, and adverse effect profiles. Thus, it is often difficult to demonstrate candidate drugs' effectiveness in real-world clinical settings [6].

Therefore, this study used claims data, which represent patient-centered real-world data (RWD), to screen repositioning candidate drugs for multiple diseases simultaneously. As a proof-of-concept study, we targeted type 2 diabetes mellitus (T2DM), which has many complications [7-9]. We sought candidate repositioning drugs that could prevent or treat diabetic complications, using temporal trajectories of T2DM constructed by Jeong et al. [10].

METHODS

Data source

We obtained data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), which is a representative population-based cohort database in South Korea [11]. As the National Health Insurance Service (NHIS) covers virtually the entire South Korean population [12], NHIS-NSC was constructed by stratified random sampling for an accurate representation of the population. It contains socioeconomic data, health examination data, and medical treatment data for 2.2% of the total eligible Korean population [11]. We used data collected from 2002 to 2013 (11 years).

This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB-MED-EXP-20-427), which waived the requirement for informed consent.

The overall scheme of this study

We conducted the study in three steps: selection of target diseases, selection of cases and controls for each disease, and statistical analysis. Fig. 1 demonstrates these steps and the overall scheme of this study.

In the first step, we selected target diseases. Complications of T2DM were selected as target diseases based on the temporal trajectories of accompanying comorbidities of T2DM constructed by Jeong et al. [10]. We describe the details of these trajectories in the "Temporal trajectories of accompanying comorbidities" sub-section. Second, we extracted the cases and controls for each target disease from patients with T2DM to conduct a nested case-control study for each disease-drug pair. Finally, conditional logistic regressions were conducted for each pair, which comprised all target diseases and prescribed drugs, except for topical drugs, fluids, and drugs prescribed for less than 30 days in patients. A candidate repositioning drug was selected when the $P<0.05$ and the upper limit of the 95% confidence interval (CI) for the odds ratio (OR) was less than 0.99.

Study population

We extracted the patients with T2DM aged over 40 years, who had first developed the condition after 2003 (Fig. 2). Type T2DM was defined as any T2DM-related diagnostic codes (E11–E14) with any prescription of anti-diabetic medications within 1 year of diagnosis. The anti-diabetic medications included metformin, insulin, glimepiride, glibenclamide, gliclazide, glipizide, chlorpropamide, gliquidone, acarbose, voglibose, miglitol, rosiglitazone, pioglitazone, nateglinide, repaglinide, mitiglinide, vildagliptin, gemigliptin, sitagliptin, saxagliptin, linagliptin, alogliptin, and exenatide. To determine the exact diagnosis date for T2DM among the extracted patients, we excluded patients who were diagnosed with T2DM before 2003, who entered the cohort after 2003, or who were initially diagnosed with T2DM coded E14.9. Of those who were initially diagnosed as E14.9, we observed a tendency toward the E14.9 code being assigned to patients whose diagnosis of T2DM mellitus was not confirmed at the first visit. In addition, those who were less than 40 years of age or who had died during the cohort period were also excluded.

Temporal trajectories of accompanying comorbidities

To select target diseases, we used the temporal trajectories of accompanying comorbidities constructed by Jeong et al. [10]. These trajectories were constructed using NHIS-NSC, which was also used in this study, to determine diabetic complications, the pattern of their development, and differences in the pattern by gender and age group. These trajectories provided progres-

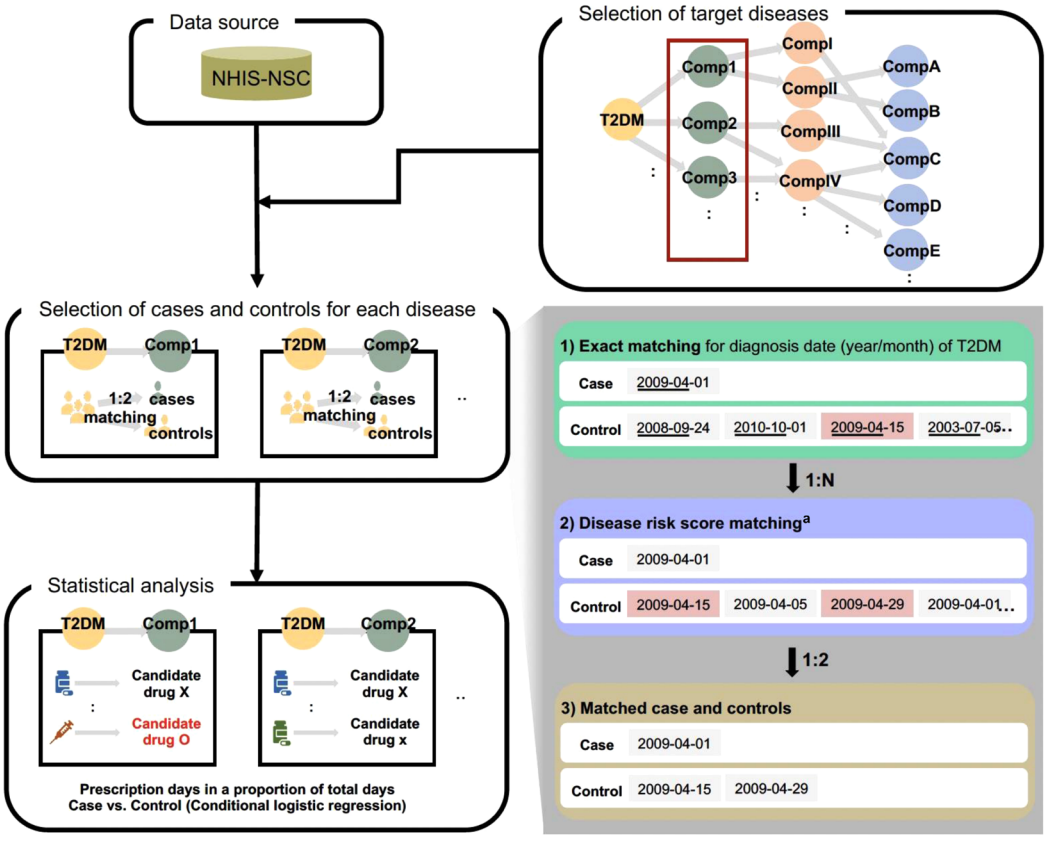

Fig. 1. The overall scheme of the methodology. It consisted of three steps: selection of target diseases; selection of cases and controls for each disease; and statistical analysis. NHIS-NSC, National Health Insurance Service-National Sample Cohort; T2DM, type 2 diabetes mellitus; Comp, complication. [a]Matching variables: gender, age group, days classes of anti-diabetic medications were prescribed as a proportion of the assessment period (from the day first diagnosed with T2DM to a year thereafter), comorbidities, and Charlson comorbidity index (CCI).

sion patterns (temporal trajectories) and relative risk for comorbidities of T2DM, which helped us delineate candidate diabetic complications according to their relative risk. Several diseases were determined to be significant but commonly not considered diabetic complications, such as epilepsy and mental and behavioral disorders due to use of alcohol. Therefore, the term "comorbidities" was adopted rather than "complications" in our previous study [10], but these could be candidate complications. In this context, we used the term "complications" generally.

Among three temporal trajectories, namely (Type 2 diabetes → First complication), (First complication → Second complication), and (Second complication → Third complication), we only considered the (Type 2 diabetes → First complication) stage. For this stage, we selected the top 30 diabetic complications (trajectories) with the highest relative risk. Among those, we excluded the (Type 2 diabetes → Type 1 diabetes) trajectory, as it was not a diabetic complication. In this case, patients might have had latent autoimmune diabetes in adults, which is often initially misdiagnosed as T2DM [13], and then correctly diagnosed as type 1 diabetes mellitus. Therefore, we selected 29 diabetic complications as the target diseases. Diagnoses are listed in descending order by their relative risks in Supplemental Table S1.

Matching cases and controls in each trajectory

To conduct a nested case-control study for each disease-drug pair, cases who had developed a complication at least a year after T2DM were obtained. Next, controls who did not develop a complication throughout the observational period (2002 to 2013) were matched in a ratio of 1:2 to the cases in each trajectory. Matching was conducted in two steps (Fig. 1). First, to reduce the error related to the duration of diabetes, controls with the same diagnosis date of T2DM (year and month) were selected. Then, a disease risk score was used to finally match the most similar controls to cases in a ratio of 1:2 [14]. Disease risk

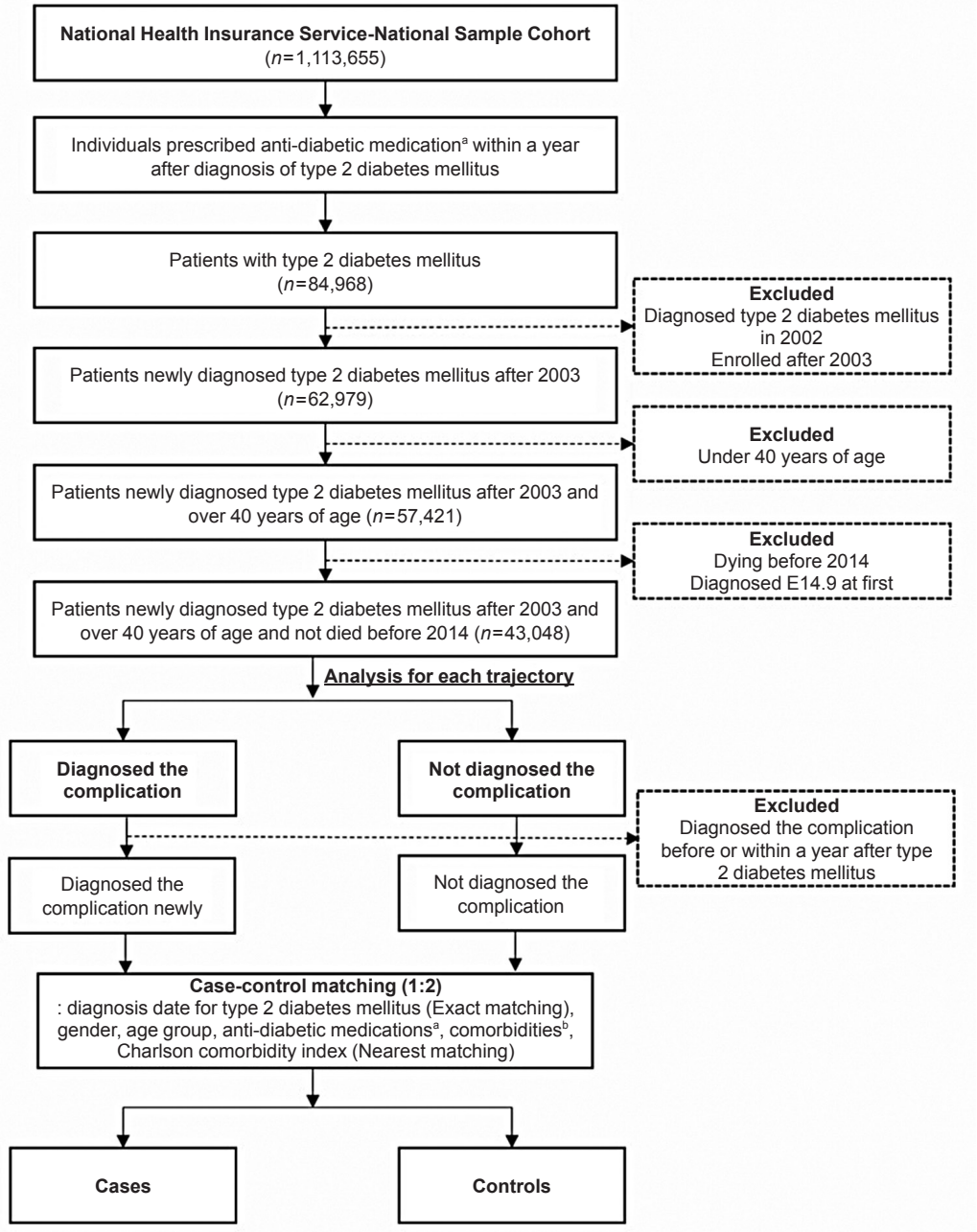

Fig. 2. The flowchart of selecting the study population and cases/controls. [a]Anti-diabetic medications: insulin, metformin, others (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonist), and combinations; [b]Comorbidities: hypertension, diabetes with complications, arrhythmia, acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, and renal disease.

score showed statistically better values than exact matching for multiple factors in a nested case-control study [15].

To match variables by disease risk score, we considered gender, age group, the number of days each class of anti-diabetic medications were prescribed as a proportion of the assessment period (from the day first diagnosed with T2DM to a year thereafter), comorbidities, and Charlson comorbidity index (CCI) [16]. The classes of anti-diabetic medications were defined as insulin, biguanides, others (sulfonylureas, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists), and a combination of two or more of the classes (insulin,

biguanides, sulfonylureas, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists). For the comorbidities, we selected macrovascular and microvascular-associated diseases, as the development of diabetic complications is strongly associated with macrovascular and microvascular disorders [17]. Therefore, we selected hypertension, diabetes with complications, arrhythmia, acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, and renal disease as covariates. After the matching, the index dates of controls were assigned as the index dates of the matched cases. We tried to exclude trajectories for which the number of the cases and controls matched was fewer than 100, to ensure statistical power. However, no trajectory was excluded as the number of cases and controls matched was greater than 100 in all 29 trajectories.

Statistical analysis

To discover candidate drugs for drug repositioning that could prevent a complication in each trajectory, the number of days each drug was prescribed was calculated from the diagnosis date of T2DM to the index date as a proportion of that period. We excluded topical drugs, fluids, and drugs prescribed for fewer than 30 days for the patients.

We conducted a conditional logistic regression using the calculated proportion of the prescription days for each drug as an independent variable. As covariates, we used the prescription days for classes of anti-diabetic medications as a proportion of the assessment period (from the first day of T2DM diagnosis to a year thereafter), comorbidities, and CCI. The classes of anti-diabetic medications and the comorbidities were defined as above (see "Matching the cases and controls in each trajectory" sub-section). Finally, a disease-drug pair with $P<0.05$ and upper limit of the 95% CI for the OR <0.99 was selected as a repositioning candidate.

External validation

To validate this methodology, an external validation study was conducted using an electronic health record (EHR) dataset from Ajou University Hospital. Among the disease-drug pairs, a candidate pair was selected with two criteria: (1) a drug that could be taken in the relatively long term and (2) among those, a drug that was prescribed most in the EHR dataset. In accordance with these two criteria, we selected the (cerebral infarction–glycopyrrolate [Anatomical Therapeutic Chemical (ATC) Classification System code "A03AB02" or "R03BB06"]) candidate pair. Next, we chose comparable drugs to glycopyrrolate, which were used for the same indications as glycopyrrolate. The other anticholinergics for peptic ulcer or obstructive airway diseases (drugs with an ATC code that started with "A03AB" or "R03BB") were selected as comparator drugs.

As the study population, we selected the patients with T2DM who had first developed the condition after 1999. Then, we extracted the patients who had taken glycopyrrolate and one of the comparator drugs from the patients with T2DM. Next, three exclusion criteria were applied: (1) patients who had taken both glycopyrrolate and one of the comparator drugs; (2) patients whose index date, which was the first prescription date of the drug (glycopyrrolate or one of the comparator drugs), was within 180 days of the diagnosis date of T2DM; and (3) patients whose index date was after the date cerebral infarction was diagnosed. After applying exclusion criteria, extracted patients who had taken glycopyrrolate or one of the comparator drugs were considered as treated or non-treated, respectively. To adjust for confounding factors, treated and non-treated cases were then matched in a ratio of 1:1 using propensity score matching. Matching variables used were gender, age group, and comorbidities.

A Cox proportional hazards model was used to test whether the treated and non-treated groups differed in the development of cerebral infarction. Covariates consisted of hypertension, diabetes with complications, acute myocardial infarction, cardiac arrhythmia, peripheral vascular disease, cerebrovascular disease, and renal disease.

RESULTS

Candidate disease-drug pairs for drug repositioning drawn from RWD

From the NHIS-NSC dataset, 43,048 patients were extracted as the study population. After excluding topical drugs, fluids, and drugs prescribed for fewer than 30 days in the study population, 29,270 disease-drug pairs with 29 trajectories were analyzed.

Of these, 24 pairs with 13 trajectories were identified as candidates for drug repositioning (Table 1). Among these, the top five pairs with the lowest ORs were: mental and behavioral disorders due to use of alcohol–pyridostigmine (OR, 0.51; 95% CI, 0.31 to 0.85); hypertensive renal disease–ondansetron (OR, 0.61; 95% CI, 0.37 to 0.99); sequelae of cerebrovascular disease–lysozyme (OR, 0.66; 95% CI, 0.46 to 0.95); heart failure–pyridostigmine (OR, 0.69; 95% CI, 0.57 to 0.84); and sequelae of cerebrovascular disease–kanamycin (OR, 0.81; 95% CI, 0.69 to 0.95).

Table 1. Twenty-Four Candidate Disease-Drug Pairs for Drug Repositioning

Diabetic complication (ICD-10 code)	Drug	OR (95% CI)	*P* value[a]
Atherosclerosis (I70)	Methylprednisolone	0.93 (0.88–0.99)	0.017
Atherosclerosis (I70)	Bisacodyl	0.94 (0.89–0.99)	0.016
Atherosclerosis (I70)	Hemocoagulase	0.95 (0.90–0.99)	0.014
Atrial fibrillation and flutter (I48)	Melilotus extract+proxyphylline	0.89 (0.80–0.99)	0.032
Cerebral infarction (I63)	Ondansetron	0.82 (0.70–0.97)	0.018
Cerebral infarction (I63)	Glycopyrrolate	0.86 (0.78–0.95)	0.004
Glomerular disorders in diseases classified elsewhere (N08)	Methylphenidate	0.94 (0.89–0.99)	0.011
Heart failure (I50)	Pyridostigmine	0.69 (0.57–0.84)	<0.001
Hemiplegia (G81)	Aluminum hydroxide gel+magnesium silicate	0.92 (0.87–0.98)	0.014
Hemiplegia (G81)	Chlorpheniramine+phenylephrine	0.95 (0.91–0.99)	0.010
Hypertensive heart disease (I11)	Guaifenesin	0.89 (0.80–0.98)	0.018
Hypertensive renal disease (I12)	Ondansetron	0.61 (0.37–0.99)	0.044
Hypertensive renal disease (I12)	Haloperidol	0.83 (0.70–0.99)	0.037
Hypertensive renal disease (I12)	Mirtazapine	0.84 (0.72–0.98)	0.023
Hypertensive renal disease (I12)	Aluminum magnesium silicate 40 mg and etc.[b]	0.87 (0.78–0.97)	0.013
Mental and behavioral disorders due to use of alcohol (F10)	Pyridostigmine	0.51 (0.31–0.85)	0.010
Mental and behavioral disorders due to use of alcohol (F10)	Amoxicillin+clavulanate	0.90 (0.83–0.98)	0.015
Nephrotic syndrome (N04)	Cefazedone	0.89 (0.82–0.97)	0.009
Polyneuropathy in diseases classified elsewhere (G63)	Iopromide	0.88 (0.84–0.93)	<0.001
Polyneuropathy in diseases classified elsewhere (G63)	Midazolam	0.95 (0.91–0.99)	0.011
Retinal disorders in diseases classified elsewhere (H36)	Nadroparin	0.89 (0.80–0.99)	0.029
Retinal disorders in diseases classified elsewhere (H36)	Flavin adenine dinucleotide+liver extract	0.95 (0.91–0.99)	0.009
Sequelae of cerebrovascular disease (I69)	Lysozyme	0.66 (0.46–0.95)	0.026
Sequelae of cerebrovascular disease (I69)	Kanamycin	0.81 (0.69–0.95)	0.012

ICD-10, International Classification of Diseases, 10th Revision; OR, odds ratio; CI, confidence interval.
[a]*P* value of conditional logistic regression; [b]Aluminum magnesium silicate 40 mg and etc. a combination drug of biodiastase-2000+lipase AP6+magnesium metasilicate aluminum+powdered glycyrrhiza+precipitated calcium carbonate+scopolia extract+sodium carbonate hydroxide+trimebutine.

External validation using electronic health records from a tertiary hospital

To validate this methodology, we selected a candidate pair using two criteria described in the Methods section. By applying them, we selected the (cerebral infarction–glycopyrrolate [ATC code "A03AB02" or "R03BB06," which is anticholinergics for peptic ulcer or obstructive airway diseases]) candidate pair with 10,428 prescription records in the EHR dataset.

After the matching, the number of treated and non-treated patients was 596 in each case. Comparison of their baseline characteristics (Table 2) revealed that the treated group was younger and had a higher proportion of females. In terms of comorbidities, the treated group had a higher proportion of hypertension and diabetes with complications. However, the former had a lower proportion of acute myocardial infarction, cardiac arrhythmia, peripheral vascular disease, cerebrovascular disease, and renal disease.

The Kaplan-Meier curve showed a significant difference between the glycopyrrolate-treated and comparator drugs-treated group (Fig. 3). In the Cox proportional hazards model, glycopyrrolate was associated with decreased risk of cerebral infarction compared to the comparator drugs (hazard ratio, 0.10; 95% CI, 0.02 to 0.44), consistent with our study results.

DISCUSSION

In this study, we presented a methodology to identify candidate disease-drug pairs for drug repositioning. To do this, we used

Table 2. Baseline Characteristics of Treated and Non-Treated Patients

Characteristic	Non-treated	Treated	*P* value	Standardized mean difference
Gender				
Male	340 (57.1)	263 (44.1)	<0.001	0.261
Female	256 (43.0)	333 (55.9)		
Age, yr	67.51±11.38	46.86±9.43	<0.001	–1.975
Hypertension	182 (30.5)	236 (39.6)	0.001	0.191
Diabetes with complication	195 (32.7)	254 (42.6)	0.001	0.205
Acute myocardial infarction	31 (5.2)	7 (1.2)	<0.001	–0.231
Cardiac arrhythmia	26 (4.4)	6 (1.0)	<0.001	–0.209
Peripheral vascular disease	20 (3.4)	8 (1.3)	0.034	–0.133
Cerebrovascular disease	31 (5.2)	9 (1.5)	0.001	–0.206
Renal disease	92 (15.4)	59 (9.9)	0.005	–0.167
Cerebral infarction	13 (2.2)	2 (0.3)	0.007	–0.166

Values are expressed as number (%) or mean±standard deviation.

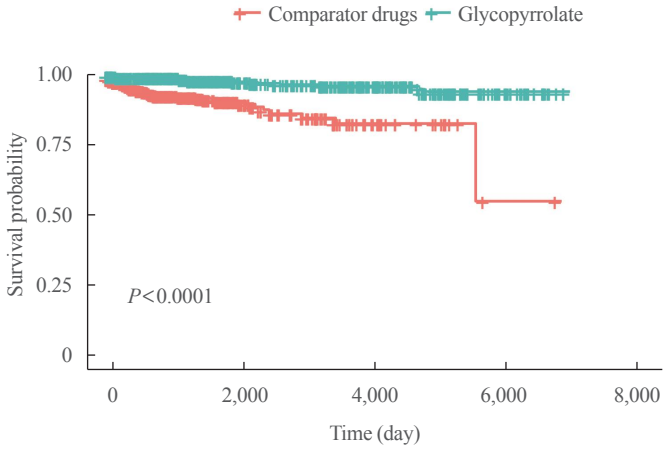

Fig. 3. Kaplan-Meier curves of the time to the first event (cerebral infarction) in the external validation study. The glycopyrrolate group (blue line) and the comparator drugs group (red line) showed different patterns; the *P* value of the log-rank test (*P* in the graph) was less than 0.0001. This indicates that the incidence of cerebral infarction was significantly different between the groups.

temporal trajectories of accompanying comorbidities in patients with T2DM established in a previous study [10], based on a claims dataset.

Using a nested case-control study for each disease-drug pair, we analyzed 29,270 disease-drug pairs with 29 trajectories. As a result, we identified 24 candidate pairs with 13 trajectories. Most candidate drugs had original indications that were completely different from the predicted indications. For example, pyridostigmine is currently used for myasthenia gravis; however, our results revealed its effectiveness at reducing alcohol-use-related heart failure incidence and mental and behavioral disorders. Amoxicillin and clavulanic acid, which is a combination of antibiotics, was associated with decreased incidence of mental and behavioral disorders due to alcohol use. In contrast, mirtazapine, an antidepressant, was associated with decreased incidence of hypertensive kidney disease.

To validate a candidate pair using an external dataset, we performed a retrospective cohort study on the (cerebral infarction–glycopyrrolate) pair using the EHR dataset from a tertiary hospital in South Korea. The Cox proportional hazards model found a hazard ratio of 0.10 (95% CI, 0.02 to 0.44), which enabled us to support the association of this candidate pair.

Moreover, to determine whether our results were consistent with other studies, we conducted a literature review for the candidate pairs. Several studies corresponded with our results. Regarding the (heart failure–pyridostigmine [used for myasthenia gravis]) pair, which had the lowest OR in this study, it was shown to be effective in double-blind randomized clinical trials, which is a highly reliable study design. It was effective at reducing the incidence of ventricular arrhythmia and improving heart rate variability in patients with heart failure [18]. Further, it was equally effective at reducing heart rate when compared to ivabradine, which was proven effective at reducing hospitalization and mortality due to chronic heart failure [19]. In a study related to the (atherosclerosis–methylprednisolone [a steroid])

pair, the group exposed to the inhaled steroid had a lower incidence of atherosclerosis compared with the non-exposed group, suggesting its effectiveness in preventing atherosclerosis [20]. Studies of the (hypertensive kidney disease–mirtazapine [an antidepressant]) pair confirmed that rats treated with mirtazapine were protected against kidney damage caused by ischemia-reperfusion [21,22].

Contrary to our study, most studies of systematic drug repositioning have utilized drug-oriented data such as chemical structures, gene expression patterns, and adverse effect profiles. Moreover, to the best of our knowledge, most repositioning studies using RWD targeted either a drug or a disease instead of targeting multiple drugs and diseases simultaneously [3,23]. Therefore, there was a need for systematic drug repositioning studies using RWD to analyze multiple disease-drug pairs.

Several systematic drug repositioning studies have used RWD. Using the EHR dataset, Wu et al. [24] screened non-antineoplastic drugs effective at increasing the survival rate for cancers. Retrospective cohort studies conducted of 146 non-antineoplastic drugs using the EHR dataset of 43,310 cancer patients at a university medical center found 22 candidate drugs [24]. However, as this study used an EHR dataset of a single hospital, there was a limitation that it is unknown whether the patients had taken target drugs in other hospitals. Further, as this study analyzed overall survival rate for cancers, the association between a specific cancer type and a drug could not be identified. In contrast, our study had the advantage of having available relatively accurate prescription records by using claims data and identifying the association between a specific disease and a drug.

Our study has several limitations. First, given the nature of retrospective studies, it was difficult to determine whether other confounding factors were present in this study. Second, in the external validation study, we could not determine whether patients had been diagnosed with T2DM or prescribed glycopyrrolate (or comparator drugs) from other hospitals. Using additional datasets for validation would improve reliability.

In summary, we suggested a new methodology for systematic drug repositioning using RWD. We found 24 repositioning candidate disease-drug pairs and validated the (cerebral infarction–glycopyrrolate) pair using EHR. The study results suggest the possibility of using the candidate drugs to lower risks of diabetic complications, instead of other drugs, given the same indications. Moreover, this methodology could be applied to other diseases beyond diabetic complications, to discover their repositioning candidates, thereby offering a new approach to drug repositioning.

CONFLICTS OF INTEREST

Dukyong Yoon is an employee of BUD.on Inc. BUD.on Inc. did not have any role in the study design, analysis, decision to publish, or the preparation of the manuscript. There are no patents, products in development, or marketed products to declare. The other authors declare that they have no competing interests.

ACKNOWLEDGMENTS

This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT; Ministry of Trade, Industry and Energy; Ministry of Health & Welfare; and Ministry of Food and Drug Safety) (Project Number: 1711138152, KMDF_PR_20200901_0095). This work was also supported by a Government-wide R&D Fund project for infectious disease research (GFID), Republic of Korea (grant number: HG18C0067).

AUTHOR CONTRIBUTIONS

Conception or design: N.P., E.J., D.Y. Acquisition, analysis, or interpretation of data: N.P., J.Y.J., S.K. Drafting the work or revising: N.P., J.Y.J., D.Y. Final approval of the manuscript: J.Y.J., D.Y.

ORCID

Namgi Park *https://orcid.org/0000-0002-2161-5093*
Ja Young Jeon *https://orcid.org/0000-0002-3877-0479*
Dukyong Yoon *https://orcid.org/0000-0003-1635-8376*

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