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Effect of drug compliance on health care costs in newly-diagnosed dementia: Analysis of nationwide population-based data

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ABSTRACT

Background: The cost-effectiveness of both cholinesterase inhibitors and memantine by delaying nursing home placement has been supported by numerous studies. The importance of sustained pharmacological treatment in dementia has been relatively less recognized by public health policies compared to early diagnosis. We investigated the effect of the drug (donepezil, rivastigmine, galantamine, and memantine) compliance on the health care costs in newly-diagnosed dementia.
Methods: National Health Insurance Service (NHIS) database which covers the entire population of South Korea was used for analysis. Health care expenditure of patients newly-diagnosed with dementia in between 2012 and 2014 was investigated for 3–5 years. For drug compliance, we used Medication Possession Ratio (MPR) that indicates the percentage of time a patient has access to medication. Multivariate linear regression analysis including generalized estimated equation and gamma distribution was used for statistical analysis.
Results: We identified 252,594 patients who were both prescribed with cognitive enhancers and newly diagnosed with dementia. When initial MPR increased 20%, total health care costs decreased 8.4% (RR = 0.916, 95%; CI 0.914 to 0.916). Same relationship was shown with medical costs related to dementia, admission to a general hospital, and emergency room visits. When MPR increased 20% compared to the previous year, the total health care costs, admission to a general hospital, emergency room visits, and admission to a nursing hospital decreased.
Conclusions: This population-based retrospective cohort study provides evidence that patients newly-diagnosed with dementia who showed higher initial drug compliance or maintained antidementia drugs (Cholinesterase inhibitors and memantine) would benefit in total health-care costs.

1. Introduction

Dementia is a chronic neurodegenerative disorder that interferes with activities of daily living and its prevalence rate has continued to increase rapidly. According to the World Alzheimer Report 2018, 50 million people worldwide are living with dementia in 2018 and this number will more than triple to 152 million by 2050 (Patterson, 2018). One can easily be overwhelmed by this exponentially growing prevalence rate and then frustrated by fact that there still is no cure. In Alzheimer's disease (AD), cholinesterase inhibitors (ChEI) and memantine, so-called antidementia drugs are proved to delay the progression of the disease and alleviate symptoms allowing patients to remain independent in mild cases (Bond et al., 2012; Reisberg et al., 2003; Rountree et al., 2013; Schneider et al., 2014). Although there is insufficient evidence to support the widespread use, several studies have shown that the cholinesterase inhibitors and memantine produced small benefits in cognition in patients with mild to moderate vascular dementia (Kavirajan and Schneider, 2007).

The effect of both cholinesterase inhibitors and memantine in delaying nursing home placement has been supported by numerous studies (Geldmacher et al., 2003; Marin et al., 2003; Migliaccio-Walle et al., 2003; Rive et al., 2012). The benefits were higher when followed by early identification and treatment of the disease (Weimer and Sager, 2009). Without sustainability in pharmacological treatment, the effect of early diagnosis and treatment of dementia would be diminished. The importance of sustained pharmacological treatment in dementia has been relatively less recognized by public health policies compared to early diagnosis and very few studies exist regarding this subject. One study reported that treatment gaps do not compromise the outcome of patients treated with ChEIs in AD (Pariente et al., 2012). This may have resulted from the treatment interruption due to health deterioration that could have led to institutionalization or death and the analysis was done only in the persistence group (Pariente et al., 2012). Recent Taiwanese study found that sustained ChEI treatment in AD for more than 2 years is associated lower mortality risk after the first 3 years, as compared to those treated for less than 1 year (Ku et al., 2018).

The total estimated worldwide cost of dementia in 2030 reached US $2 trillion doubling from the cost in 2018 (Patterson, 2018). While the

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cost of antidementia drugs burdens both the patients (Campbell et al., 2017) and health care policies, it is questionable whether maintaining medication is still cost-effective. A previous comparison study of ChEI use and associated health care costs in AD showed a significant reduction in all-cause health care expenditure as adherence improved (Mucha et al., 2008). On the contrary, more recent population-based Taiwanese study reported no significant association between the adherence to ChEI and health care costs in AD (Ku et al., 2018). Both studies, however, did not subdivide the health care cost in detail as to better understand the medical use patterns. Since patients with dementia have high comorbidity (Chen et al., 2017), frequently use nursing facilities (Callahan et al., 2015) and are often hospitalized (Francois et al., 2018), understanding the expenditure patterns for hospital use among individuals with dementia is vital to the management of dementia-related healthcare policy budget. While previous studies about the efficacy of long-term ChEI therapy in dementia mostly had a follow-up period less than 3 years (Courtney et al., 2004; Howard et al., 2012; Rountree et al., 2009; Winblad et al., 2006), there was near unanimous agreement among dementia experts that these agents should not be discontinued after a year (Herrmann et al., 2011). Therefore, long-term data with the observation period more than 3 years can be very useful in antidementia drug use. In this retrospective population-based cohort study with the observation period longer than 3 years, we investigated the effect of the drug (donepezil, rivastigmine, galantamine, and memantine) compliance on the formal health care costs along with various types of hospital use in newly-diagnosed dementia.

2. Methods

2.1. NHIS database

In South Korea, there are three mandatory healthcare programs: National Health Insurance (NHI), Medical Aid (MA), and Long-Term Care Insurance (LTCI) (Song et al., 2014; Song, 2009). The whole South Korean population is covered by this program. The individuals insured by NHI are classified as either employee or self-employed. MA program is a public assistance scheme managed by the Korean government that helps the minimum livelihood and provides medical services to the low-income households. The LTCI additionally provides long-term care benefits (e.g. home care service, paid domestic service, non-hospital long-term care facility service) to the elderly who have difficulty taking care of themselves for a period of at least 6 months due to old age or geriatric disease. Medical care providers in Korea must submit claims data to the National Health Insurance Service (NHIS), a nonprofit organization that manages the NHI and MA program in order to acquire reimbursement for all medical costs (e.g. inpatient and outpatient care, laboratory and radiology services, prescribed drug fees, and emergency room services). The National Health Insurance Service (NHIS) database used in this study covers all the formal medical cost consumed by the entire population of South Korea, except the cost processed through LTCI and other informal care costs such as caregiver's help. Claims data are categorized in the form of International Classification of Diseases, 10th revision (ICD-10) codes and also include personal information such as age, gender, household income, type of insurance, and residential area. Additional data retrieved for baseline covariates included the following information: types of insurance, type of pharmacological treatment, prescribed antidementia drugs (donepezil, rivastigmine, galantamine, or memantine), year of initial dementia diagnosis, duration of illness, Charlson Comorbidity Index (CCI), disability, and mortality. Dependent variables were total health care costs, medical costs related to dementia, admission to a general hospital, emergency room visit, admission to a nursing hospital, and hospital stay in a nursing hospital. The total health care costs included any type of formal cost incurred by the patient in hospital. Medical costs related to dementia refer to formal cost incurred by the patients under principal diagnosis of dementia.

2.2. Study population and case selection

In this retrospective population-based study using NHIS database, we identified 2,000,479 patients with ICD-10 (International Classification of Disease, 10th Revision) diagnosis, either principal or additional, of several dementia types from 2010 to 2016: dementia in Alzheimer disease (F00), vascular dementia (F01), dementia in other disease classified elsewhere (F02), and unspecified dementia (F03). To establish study population with newly-diagnosed dementia, we excluded patients who received diagnostic codes of dementia in 2010 and 2011, thereby setting-up a washout period of 2 years. Patients with the diagnostic codes of dementia may include suspected cases or definite cases but not indicated for pharmacological treatment and drug compliance could be underestimated in these cases. So patients without prescription of any antidementia drug (donepezil, rivastigmine, galantamine, or memantine) were also excluded. For thorough evaluation, patients with the observation period less than 3 years after initial diagnosis of dementia were excluded. Overall process of study population selection is shown in Fig. 1.

2.3. Medication Possession Ratio (MPR)

For drug compliance, we used Medication Possession Ratio (MPR) that indicates the percentage of time a patient has access to medication. It is calculated as the sum of the days' supply of medication divided by the number of days for observation period in each patient. MPR is one of the most common measures for medication adherence used in the analysis of administrative claims databases for the ease of calculation and interpretability (Andrade et al., 2006; El-Saifi et al., 2018). Target medications were donepezil, rivastigmine, galantamine, and memantine. Each year's MPR is calculated as sum of days supplied divided by the number of days observed regarding all target medications at once. As previous studies reported that drug compliance in dementia usually decrease over time even within the first year (Brewer et al., 2013; Gardette et al., 2014), we determined two target variables for MPR: MPR in the first year of initial dementia diagnosis (initial MPR) and change in MPR from the previous year. We used MPR as a continuous measure and did not distinguish adherent from non-adherent patients based on the empirical threshold such as MPR $\geq$ 80% (Benner et al., 2002; Doro et al., 2005; Hansen et al., 2010; Haynes et al., 1980). For interpretation, we set the 20% increase from each target variable as a reference point.

2.4. Statistical analysis

Descriptive statistics were used to show the study population's demographic data and clinical characteristics at the first year of each patient's initial diagnosis with dementia. Multivariate linear regression analysis including generalized estimated equation model, and gamma distribution, estimated the relatives risk (RR) of total health care cost and dementia related medical cost by drug compliance in dementia controlling for age, sex, diagnostic code, year of initial diagnosis of dementia, duration of illness, type of pharmacological treatment, household income, type of insurance, residential area, Charlson Comorbidity Index (CCI), disability, mortality, admission to a general hospital, emergency room visit, admission to a nursing hospital, and hospital stay in a nursing hospital). Other medical uses (admission to a general hospital, emergency room visit, admission to a nursing hospital, and hospital stay in a nursing hospital) in association with the drug compliance were also analyzed using the same model. We used SAS 9.3 (SAS Institute Inc., Cary, North Carolina) to conduct statistical analyses.

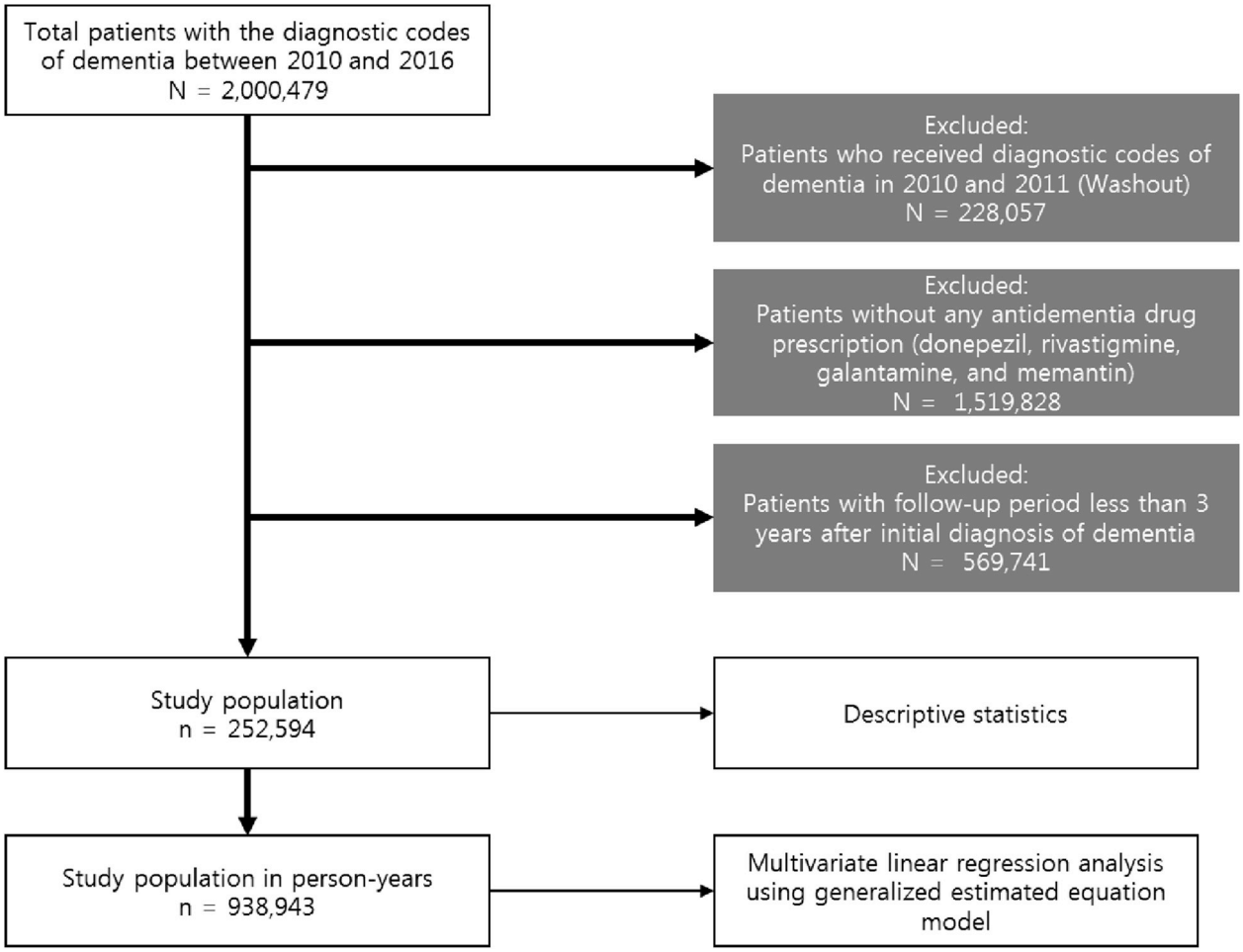

Fig. 1. The flow chart of the study population. Data from National Health Insurance Service database of South Korea.

3. Results

3.1. Baseline characteristics of study population

252,594 patients were identified as final study population who were both prescribed with at least one of 4 cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) and newly diagnosed with dementia. The average of total observation period was 2.44 years which was shorter than 3 years because of mortality. Table 1 shows the characteristics of the study population. The characteristics were based on the year when each participant was initially diagnosed with dementia. Dementia in Alzheimer disease was most common among the study population reaching 77.0% (n = 194,409), followed by vascular dementia (12.1%), unspecified dementia (10.3%), and dementia in other diseases classified elsewhere (0.6%). Female patients (n = 180,922 (71.6%)) were more than twice as many as male patients (n = 71,672 (28.4%)). The average age at the participant's initial diagnosis of dementia was 78.5 (study p.

3.2. Drug compliance estimated by MPR

The average MPR of the study population throughout the whole observation period was 54.17%. On annual basis, MPR was highest (77.22%) in the first year of initial dementia diagnosis and decreased continuously in the following years: 2nd year (53.63%) > 3rd year (43.04%) > 4th year (38.97%) > 5th year (36.65%). This tendency of decreasing MPR was same in each subgroup of dementia diagnostic code groups. Table 2 shows the average MPR of the study population by various characteristics.

3.3. Health care costs and other medical uses in association with drug compliance

The average of total annual health care costs in study population was approximately US$ 5007.31 at the exchange rate of 1100 Korean won for 1 US dollar. Of this, the average medical cost related to dementia was about US$ 1399.81. In the annual basis, the total health care costs as well as the medical costs related to dementia were lowest in the first year of initial diagnosis of dementia and highest in the second year. After second year, the total health care costs and the medical costs related to dementia continued to decrease.

Multivariate linear regression analysis showed that when MPR in the first year of initial dementia diagnosis increased 20%, total health care cost decreased 8.4% (RR = 0.916, 95%; CI 0.914 to 0.916). In the same condition, medical cost related to dementia decreased 5.3% (RR = 0.947; CI 0.944 to 0.951), risk of admission to a general hospital decreased 12.4% (RR = 0.876; CI 0.873 to 0.88), and risk of emergency room visit decreased 9.9% (RR = 0.901; CI 0.899 to 0.905). On the contrary, the risk of admission to a nursing hospital increased 5.3% (RR = 1.053; CI 1.047 to 1.058) and hospital stay in a nursing hospital increased 0.6% (RR = 1.006; CI 1.006 to 1.008) when initial MPR increased 20%. Fig. 2 shows the overview of the effect of 20% increase in initial MPR on each variable regarding health care use as mentioned above.

When MPR increased 20% compared to the previous year, the total health care costs decreased 1.8% (RR = 0.982; CI 0.98 to 0.984), but

Table 1
Characteristics of study population (n = 252,594).

Variable	n	Percent
Diagnostic code (ICD-10[a])		
F00 dementia in Alzheimer disease	194,409	77.0%
F01 vascular dementia	30,560	12.1%
F02 dementia in other diseases classified elswhere	1,503	0.6%
F03 unspecified dementia	26,122	10.3%
Year of initial diagnosis of dementia		
2012	72,509	28.7%
2013	83,788	33.2%
2014	96,297	38.1%
Sex		
Male	71,672	28.4%
Female	180,922	71.6%
Age		
≤74	74,230	29.4%
75–79	65,993	26.1%
80–84	60,041	23.8%
85≤	52,330	20.7%
Household income		
1st quintile	69,955	27.7%
2nd quintile	21,625	8.6%
3rd quintile	28,248	11.2%
4th quintile	43,425	17.2%
5th quintile	89,341	35.4%
Type of insurance		
Medical Aid beneficiary	37,511	14.9%
Self-employed insured	66,754	26.4%
Employee insured	148,329	58.7%
Residential area		
Urban	79,365	31.4%
Suburban	60,819	24.1%
Rural	112,410	44.5%
Charlson Comorbidity Index		
≤2	169,819	67.2%
3–4	54,845	21.7%
5≤	27,930	11.1%
Disability		
No	190,832	75.5%
Yes	61,762	24.5%
Average of total observation period (years)	2.44	(s.d. = 1.18)

[a] ICD-10: International Classification of Diseases, 10th revision.

the medical costs related to dementia increased 3.5% (RR = 1.035; CI 1.033 to 1.039). In the same condition, risk of admission to a general hospital decreased 9.3% (RR = 0.907; CI 0.903 to 0.91), risk of emergency room visit decreased 7.3% (RR = 0.927; CI 0.923 to 0.932), risk of admission to a nursing hospital decreased 4.9% (RR = 0.951; CI 0.947 to 0.955), and hospital stay in a nursing hospital increased 0.6% (RR = 1.006; CI 1.004 to 1.008). Fig. 3 shows the overview of these associations. Detailed results on each independent variable are shown in the supplementary table.

4. Discussion

In this population-based retrospective cohort study from year 2010–2016, increase in drug compliance in newly-diagnosed dementia was associated with the decrease in all-cause total health care formal costs. To rephrase this conclusion since the results showed that MPR tends to decrease by time, the all-cause total health care costs decreased as the patient's MPR was maintained rather than decreasing for 20%. This association was shown both in the MPR of the first year of initial dementia diagnosis and the change in MPR from the previous year. From the pharmacoeconomic perspective, it would be cost-effective to maintain antidementia drug treatment in newly-diagnosed dementia.

Earlier study in the United States based on the claims data showed that each additional month of ChEI treatment in AD was associated with a 1% reduction in total health care costs, but our study included memantine with broader inclusion of dementia diagnosis and was based on the nation-wide data with longer follow-up period (versus 12 months) and longer medication wash-out period (versus 6 months) (Mucha et al., 2008). The diagnosis of dementia subject to variability through time (de Moraes and Bertolucci, 2017), and the patients with dementia usually maintain their medication for years. Therefore, our study confirmed the previous study's result in the long-term real-world setting based on the nation-wide data. In contrast, the recent population-based Taiwanese study reported that there was no significant effect of ChEI adherence on health care costs in AD (Ku et al., 2018). In the

Table 2
Average Medication Possession Ratio (MPR) of the study population by various characteristics.

	MPR	
	average	s.d.
Type of pharmacological treatment		
Monotherapy	52.44	44.06
Polytherapy	79.8	25.64
Diagnostic code (ICD-10[a])		
F00 dementia in Alzheimer disease	55.13	43.51
F01 vascular dementia	53.28	43.79
F02 dementia in other diseases classified elswhere	56.49	43.2
F03 unspecified dementia	48.11	43.88
Year of initial diagnosis of dementia		
2012	49.49	44.07
2013	53.71	43.66
2014	60.02	42.42
Duration of illness		
< 1 year	77.22	35.3
1–2 years	53.63	42.16
2–3 years	43.04	43.3
3–4 years	38.97	43.33
5–5 years	36.65	43.15
Sex		
Male	53.88	43.56
Female	54.29	43.67
Age		
≤74	52.02	44.1
75–79	54.99	43.68
80–84	56.21	43.25
85≤	53.43	43.43
Household income		
1st quintile	53.38	43.75
2nd quintile	52.93	43.67
3rd quintile	53.29	43.64
4th quintile	54.37	43.59
5th quintile	55.28	43.54
Type of insurance		
Medical Aid beneficiary	53.76	43.81
Self-employed insured	53.32	43.67
Employee insured	54.65	43.57
Residential area		
Urban	55.43	43.39
Suburban	55.98	43.54
Rural	52.27	43.8
Charlson Comorbidity Index		
≤2	54.74	45.17
3–4	55.06	42.55
5≤	51.79	41.11
Disability		
No	54.38	43.57
Yes	53.6	43.82
Mortality		
Yes	22.22	28.19
No	56.32	43.65
Admission to a general hospital		
Yes	44.07	40.87
No	56.45	43.92
Admission to a nursing hospital		
Yes	56.17	41.83
No	53.61	44.11
Visit to emergency room		
Yes	44.21	40.92
No	56.18	43.89

[a] ICD-10: International Classification of Diseases, 10th revision.

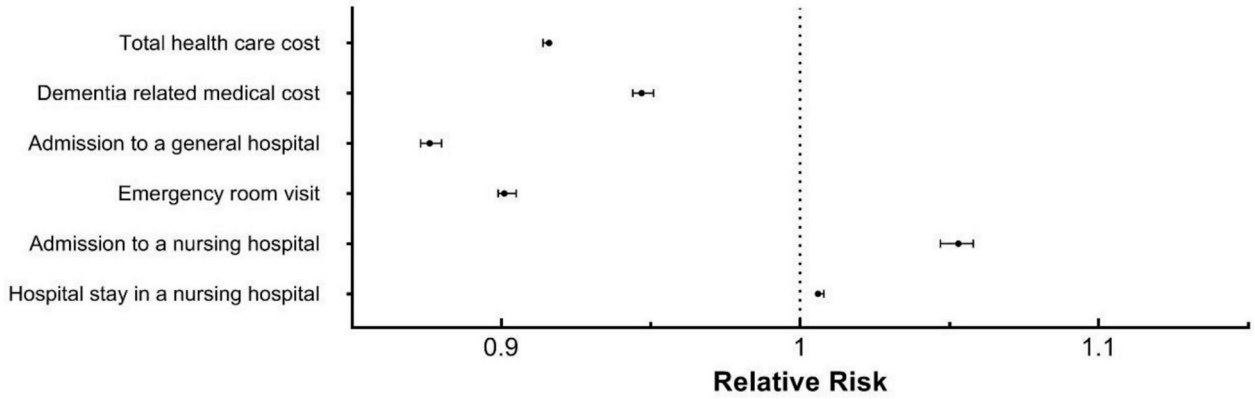

Fig. 2. Effect of 20% increase in initial Medication Possession Ratio (MPR) of antidementia drugs (cholinesterase inhibitors and memantine) on each variable regarding health care use in patients newly-diagnosed with dementia.

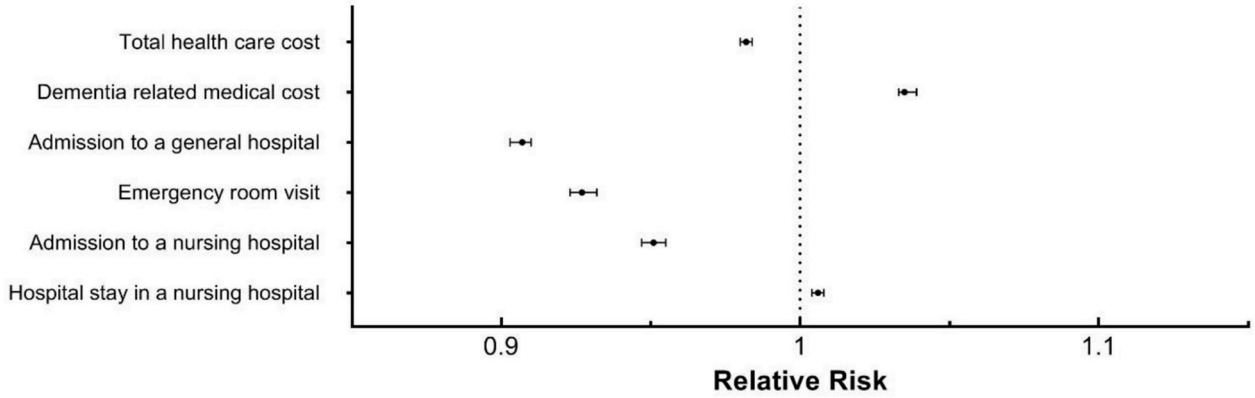

Fig. 3. Effect of 20% increase in Medication Possession Ratio (MPR) change from the previous year of antidementia drugs (cholinesterase inhibitors and memantine) on each variable regarding health care use in patients newly-diagnosed with dementia.

Taiwanese study, the ChEI adherence group was divided into two groups (high and low) based on MPR of 0.9 which was higher than the empirical threshold and this dichotomy of adherence group predisposes the result to depend on the threshold. Compared with the Taiwanese study, our study used MPR as a continuous measure and had much larger study population (n = 252,594) with broader inclusion of adjusted variables (e.g. admission to a general hospital, emergency room visit, admission to a nursing hospital, and hospital stay in a nursing hospital). To comprehensively consider the variability in the effect of sustained medication adherence on health care cost due to one nation's healthcare policy or cultural difference, multi-national study embracing diverse ethnic group should be conducted.

Medical cost related to dementia was more likely to decrease when initial MPR increased 20%, but was more likely to increase when MPR change from the previous year increased 20%. As the average of MPR decreased over time in this study, these contradicting results may have resulted from the additional costs related to medication. Patients who showed 20% higher MPR than the previous year would have spent more money on medication when compared with the patients with lower MPR. This difference in medication cost, however, did not seem to affect total health care cost further highlighting the cost-effectiveness of pharmacological treatment of dementia. Since 2008, the first objective of the healthcare policy for dementia in Korea was to lower the lead time to the treatment through early diagnosis (Lee, 2010). In accordance with this study's results, as recent systematic review has also emphasized (El-Saifi et al., 2018), it is time for health care policies to focus also on promoting antidementia drug compliance.

The risk of admission to a nursing hospital and hospital stay in a nursing hospital were likely to increase when initial MPR was maintained rather than decreasing 20%. This was not consistent with the results of the previous study that the use of antidementia drugs was associated with the delayed institutionalization (Geldmacher et al., 2003; Marin et al., 2003; Migliaccio-Walle et al., 2003; Rive et al., 2012). However, our study only analyzed nursing hospitals, not including nursing care facilities and non-hospital long-term care institutions, and this result should not be mistaken for generalized conclusion. It would rather imply the blind spot of the healthcare system where some patients were already too severe by the time of dementia diagnosis that they need to be institutionalized soon. To clarify the meaning of this result, we need further study that includes the evaluation of dementia severity.

The strength of this study is the large sample size of patients with dementia among the whole population in South Korea. This presumably the largest cost-effective cohort study so far regarding drug compliance in dementia reflects best the realistic health care system of dementia. Inclusion of variables such as admission to a general hospital, emergency room visit, admission to a nursing hospital, and hospital stay in a nursing hospital gives us better insight into the overall status of dementia management than just calculating the total health care costs. Also, patients with dementia were not only identified by ICD-10 diagnostic codes, but also by their antidementia medication (donepezil, rivastigmine, galantamine, or memantine) prescription records. This increased the accuracy of diagnoses among our claims data in which miscoding problems are common.

There are, however, some limitations to this study. First, we could not retrieve information regarding dementia severity, such as Mini-Mental State Examination (MMSE) or Clinical Dementia Rating (CDR) scores. Differences in the severity of dementia could have affected the

drug compliance since cognitive impairment is a predictor of poor adherence to medications in older patients (Chapman et al., 2008; Jacobs et al., 2011). As previous studies showed that the increase in disease severity is associated with higher mortality in dementia (Todd et al., 2013), controlling for the severity factor could have further strengthened the power of this study. Another limitation was that we could not identify the reasons for non-compliance. If the cessation of medication was due to the clinical decision, implication of this study's results would be different because policies that promotes drug compliance won't have any effect on this matter. We were also unable to gather information about the caregivers including any costs incurred regarding them. Recent systematic review study revealed that dementia showed highest annual value of informal care costs with the average annual cost of €21,065 among the six selected diseases: arthritis or osteoarthritis, cancer, dementia, mental diseases, multiple sclerosis and stroke (Oliva-Moreno et al., 2017). More comprehensive study that includes both formal and informal care costs is needed for true cost-effective evaluation. Additionally, as other methods in evaluating medication adherence and persistence such as discontinuation, switching, and medication gaps are being considered in recent studies for additional information of timeliness and consistence of medication (Andrade et al., 2006; El-Saifi et al., 2018), comparative research of these measures would help us understand more deeply of medication-taking pattern in patients with dementia.

In conclusion, our population-based retrospective cohort study provides evidence that patients newly-diagnosed with dementia who show higher initial drug compliance or maintain antidementia drugs (ChEIs and memantine) would benefit in total health care costs. Despite the variability of clinical practice guidelines on pharmacological treatment (Ngo and Holroyd-Leduc, 2014), using cholinesterase inhibitor or memantine is still a viable and cost-effective option in the management of dementia. Our study also implies that community-based care for dementia, recently being strongly supported by health care policy in Korea (National Institue of Dementia, 2018), needs to promote medication adherence. Further studies that examine the cause of non-adherence to medication and the effect of dementia severity on health care cost are required to establish appropriate health care policies.

Conflicts of interest

The authors have declared no conflicts of interest with respect to the research, authorship, and/or publication of this article. This research was supported by a grant of the clinic-based big data research project (No. 2018-20-012) of National Health Insurance Service Ilsan Hospital Research Center (administrative number: NHIS-2017-1-159).

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.08.010.

References

Andrade, S.E., Kahler, K.H., Frech, F., Chan, K.A., 2006. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol. Drug Saf. 15, 565–574 discussion 575-567.
Benner, J.S., Glynn, R.J., Mogun, H., Neumann, P.J., Weinstein, M.C., Avorn, J., 2002. Long-term persistence in use of statin therapy in elderly patients. Jama 288, 455–461.
Bond, M., Rogers, G., Peters, J., Anderson, R., Hoyle, M., Miners, A., et al., 2012. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. Health Technol. Assess. 16, 1–470.
Brewer, L., Bennett, K., McGreevy, C., Williams, D., 2013. A population-based study of dosing and persistence with anti-dementia medications. Eur. J. Clin. Pharmacol. 69, 1467–1475.
Callahan, C.M., Tu, W., Unroe, K.T., LaMantia, M.A., Stump, T.E., Clark, D.O., 2015. Transitions in care in a nationally representative sample of older Americans with dementia. J. Am. Geriatr. Soc. 63, 1495–1502.
Campbell, N.L., Perkins, A.J., Gao, S., Skaar, T.C., Li, L., Hendrie, H.C., et al., 2017. Adherence and tolerability of alzheimer's disease medications: a pragmatic randomized trial. J. Am. Geriatr. Soc. 65, 1497–1504.
Chapman, R.H., Petrilla, A.A., Benner, J.S., Schwartz, J.S., Tang, S.S., 2008. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. Drugs Aging 25, 885–892.
Chen, T.B., Yiao, S.Y., Sun, Y., Lee, H.J., Yang, S.C., Chiu, M.J., et al., 2017. Comorbidity and dementia: a nationwide survey in Taiwan. PLoS One 12 e0175475.
Courtney, C., Farrell, D., Gray, R., Hills, R., Lynch, L., Sellwood, E., et al., 2004. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 363, 2105–2115.
de Moraes, F.M., Bertolucci, P.H.F., 2017. Clinical variables related to the diagnostic stability of demential syndromes. Int. Psychogeriatr. 29, 1735–1741.
Doro, P., Benko, R., Kosik, E., Matuz, M., Toth, K., Soos, G., 2005. Utilization of oral antihyperglycemic drugs over a 7-year period (1998-2004) in a Hungarian population and adherence to drug therapy. Eur. J. Clin. Pharmacol. 61, 893–897.
El-Saifi, N., Moyle, W., Jones, C., Tuffaha, H., 2018. Medication adherence in older patients with dementia: a systematic literature review. J. Pharm. Pract. 31, 322–334.
Francois, M., Sicsic, J., Pelletier Fleury, N., 2018. Drugs for dementia and excess of hospitalization: a longitudinal French study. J. Alzheimer's Dis. 61, 1627–1637.
Gardette, V., Lapeyre-Mestre, M., Piau, A., Gallini, A., Cantet, C., Montastruc, J.L., et al., 2014. A 2-year prospective cohort study of antidementia drug non-persistency in mild-to-moderate Alzheimer's disease in Europe : predictors of discontinuation and switch in the ICTUS study. CNS Drugs 28, 157–170.
Geldmacher, D.S., Provenzano, G., McRae, T., Mastey, V., Ieni, J.R., 2003. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J. Am. Geriatr. Soc. 51, 937–944.
Hansen, R.A., Farley, J.F., Droege, M., Maciejewski, M.L., 2010. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. Clin. Ther. 32, 1308–1319.
Haynes, R.B., Taylor, D.W., Sackett, D.L., Gibson, E.S., Bernholz, C.D., Mukherjee, J., 1980. Can simple clinical measurements detect patient noncompliance? Hypertension 2, 757–764.
Herrmann, N., Black, S.E., Li, A., Lanctot, K.L., 2011. Discontinuing cholinesterase inhibitors: results of a survey of Canadian dementia experts. Int. Psychogeriatr. 23, 539–545.
Howard, R., McShane, R., Lindesay, J., Ritchie, C., Baldwin, A., Barber, R., et al., 2012. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N. Engl. J. Med. 366, 893–903.
Jacobs, U., De Castro, M.S., Fuchs, F.D., Ferreira, M.B., 2011. The influence of cognition, anxiety and psychiatric disorders over treatment adherence in uncontrolled hypertensive patients. PLoS One 6, e22925.
Kavirajan, H., Schneider, L.S., 2007. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. The Lancet. Neurology 6, 782–792.
Ku, L.E., Li, C.Y., Sun, Y., 2018. Can persistence with cholinesterase inhibitor treatment lower mortality and health-care costs among patients with alzheimer's disease? A population-based study in taiwan. Am. J. Alzheimer's Dis. Other Dementias 33, 86–92.
Lee, S., 2010. Dementia strategy Korea. Int. J. Geriatr. Psychiatry 25, 931–932.
Marin, D., Amaya, K., Casciano, R., Puder, K.L., Casciano, J., Chang, S., et al., 2003. Impact of rivastigmine on costs and on time spent in caregiving for families of patients with Alzheimer's disease. Int. Psychogeriatr. 15, 385–398.
Migliaccio-Walle, K., Getsios, D., Caro, J.J., Ishak, K.J., O'Brien, J.A., Papadopoulos, G., 2003. Economic evaluation of galantamine in the treatment of mild to moderate Alzheimer's disease in the United States. Clin. Ther. 25, 1806–1825.
Mucha, L., Shaohung, S., Cuffel, B., McRae, T., Mark, T.L., Del Valle, M., 2008. Comparison of cholinesterase inhibitor utilization patterns and associated health care costs in Alzheimer's disease. Journal of managed care pharmacy. JMCP 14, 451–461.
National Institute of Dementia, 2018. Annual Report 2018. https://www.nid.or.kr/info/dataroom_view.aspx?bid=183.
Ngo, J., Holroyd-Leduc, J.M., 2014. Systematic review of recent dementia practice guidelines. Age Ageing 44, 25–33.
Oliva-Moreno, J., Trapero-Bertran, M., Pena-Longobardo, L.M., Del Pozo-Rubio, R., 2017. The valuation of informal care in cost-of-illness studies: a systematic review. PharmacoEconomics 35, 331–345.
Pariente, A., Fourrier-Reglat, A., Bazin, F., Ducruet, T., Dartigues, J.F., Dragomir, A., et al., 2012. Effect of treatment gaps in elderly patients with dementia treated with cholinesterase inhibitors. Neurology 78, 957–963.
Patterson, C., 2018. World Alzheimer Report 2018—The State of the Art of Dementia Research: New Frontiers. Alzheimer's Disease International (ADI): London, UK.
Reisberg, B., Doody, R., Stoffler, A., Schmitt, F., Ferris, S., Mobius, H.J., 2003. Memantine in moderate-to-severe Alzheimer's disease. N. Engl. J. Med. 348, 1333–1341.
Rive, B., Aarsland, D., Grishchenko, M., Cochran, J., Lamure, M., Toumi, M., 2012. Cost-effectiveness of memantine in moderate and severe Alzheimer's disease in Norway. Int. J. Geriatr. Psychiatry 27, 573–582.
Rountree, S.D., Atri, A., Lopez, O.L., Doody, R.S., 2013. Effectiveness of antidementia drugs in delaying Alzheimer's disease progression. Alzheimer's & dementia. J. Alzheimers .Assoc. 9, 338–345.
Rountree, S.D., Chan, W., Pavlik, V.N., Darby, E.J., Siddiqui, S., Doody, R.S., 2009.

Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimer's Res. Ther. 1, 7.
Schneider, L.S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., et al., 2014. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J. Intern. Med. 275, 251–283.
Song, S.O., Jung, C.H., Song, Y.D., Park, C.-Y., Kwon, H.-S., Cha, B.S., et al., 2014. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. Diabetes Metabol. J. 38, 395–403.
Song, Y.J., 2009. The South Korean health care system. JMAJ 52, 206–209.
Todd, S., Barr, S., Roberts, M., Passmore, A.P., 2013. Survival in dementia and predictors of mortality: a review. Int. J. Geriatr. Psychiatry 28, 1109–1124.
Weimer, D.L., Sager, M.A., 2009. Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. Alzheimer's & dementia. J. Alzheimers .Assoc. 5, 215–226.
Winblad, B., Wimo, A., Engedal, K., Soininen, H., Verhey, F., Waldemar, G., et al., 2006. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement. Geriatr. Cognit. Disord. 21, 353–363.