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Burden of diabetic macular oedema in patients receiving antivascular endothelial growth factor therapy in South Korea: a healthcare resource use and cost analysis

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ABSTRACT

Objective To examine healthcare resource utilisation (HRU) and direct medical costs for patients with diabetic macular oedema (DME) treated with antivascular endothelial growth factor (anti-VEGF) in Korea by comparing with those for (1) patients with diabetes mellitus (DM) without retinopathy and (2) patients with neovascular age-related macular degeneration (nAMD) treated with anti-VEGF.

Design Retrospective cohort study.

Setting The Korean National Health Insurance (NHI) database from 1 January 2014 to 31 December 2016.

Participants We identified 1398 patients older than 30 years of age who received anti-VEGF treatment for DME in 2015 after excluding patients who had a diagnosis of nAMD in 2015 and any cancer in the preceding year.

Main outcome measures One-year healthcare resource use and direct medical costs of patients with DME treated with anti-VEGF.

Results In total, 1398 patients with DME receiving anti-VEGF, 12 813 patients with DM without retinopathy and 12 222 patients with nAMD receiving anti-VEGF were identified. Hospital admissions and outpatient visits were highest in patients with DME, while the number of licensed anti-VEGF injections in those with DME was about half that of those with nAMD (2.1 vs 3.9 per patient per year). Mean 1-year medical costs were also higher in patients with DME (US$6723) than in those with DM without retinopathy (US$2687) and nAMD (US$4980). In a multivariable analysis with matched cohorts, DME was associated with 66% higher medical costs for comorbid diseases (adjusted OR (aOR), 1.66; 95% CI 1.45 to 1.90) and 50% lower anti-VEGF injections (aOR, 0.50; 95% CI 0.46 to 0.54) compared with nAMD.

Conclusions The overall HRU and economic burden for DME treated with anti-VEGF were higher than for DM without retinopathy or for nAMD treated with anti-VEGF. Meanwhile, the lower number of licensed anti-VEGF injections compared with nAMD may reflect a potential lack of ophthalmological treatment for DME supported by the NHI in Korea.

Strengths and limitations of this study

- This is the first study to examine healthcare resource utilisation and direct medical costs of patients with diabetic macular oedema (DME) treated with antivascular endothelial growth factor (anti-VEGF) in Korea by comparing them with two disease groups (patients with diabetes mellitus without retinopathy and patients with neovascular age-related macular degeneration (nAMD) treated with anti-VEGF).
- To reduce biases in estimating the effect of DME, we used a generalised linear model after applying exact matching and propensity score matching.
- As the clinical characteristics of patients with DME treated with anti-VEGF and those with nAMD treated with anti-VEGF are quite different, residual confounding can still exist despite application of various statistical approaches.
- Further studies considering the use of bevacizumab, an anti-VEGF agent used off-label, should be conducted to grasp healthcare resource utilisation and direct medical costs in patients with DME or nAMD more accurately.

INTRODUCTION

Diabetic macular oedema (DME) is an ocular complication of diabetes mellitus (DM) that may result in vision loss or blindness and thus significantly decrease patients' quality of life.[1–3] According to previous research, 13%–25% of patients with type 1 or 2 DM developed DME over a 10-year period.[4] Moreover, the 25-year cumulative incidence of DME was 29%, with an incidence of approximately 75 000 new patients annually in the USA.[5 6] Given the growing prevalence of DM,[7 8] the prevalence of DME is likewise expected to continue to increase.

A few studies have investigated the economic burden of DME. A cost-of-illness study using a cohort of US Medicare beneficiaries reported that 37.6% of patients with DME received laser photocoagulation 1.7 times over a 1-year period and that the 1-year direct medical cost was US$11 290.[2] In the study using US retrospective claims data based on a privately insured population, the

annual total cost of DME was US$28 606, which was 75% higher than those of diabetic retinopathy without DME.[9] A cross-sectional study in Germany showed that patients with DME visited ophthalmologists 7.3 times over 1 year and the total cost was €1433.[10] However, updated analyses are needed because these studies were conducted using data before the approval of ranibizumab and aflibercept and therefore do not reflect the use of these drugs.

Ranibizumab and aflibercept, which are licensed antivascular endothelial growth factor (anti-VEGF) drugs, were listed in the national drug formulary for treatment of DME by the Korean Ministry of Food and Drug Administration in 2015. Before the era of anti-VEGF antibody, macular laser treatment had been the gold standard of treatment for DME.[11 12] Although the dexamethasone intravitreal implant has been reimbursed for DME by the National Health Insurance (NHI) since 2016, intravitreal injection of anti-VEGF is the most commonly used therapy for DME in Korea.[11 13 14] Despite these dramatic changes, up-to-date information on healthcare resource utilisation (HRU) associated with and direct medical costs of DME is rare. Moreover, given that pro re nata (PRN) and treat-and-extend regimens are preferred for anti-VEGF treatment in routine practice over the fixed monthly or bimonthly injections used in clinical trials,[15–17] it is necessary to investigate the yearly mean number of anti-VEGF injections administered to patients with DME using real-world data.

Therefore, we aimed to estimate 1-year HRU and direct medical costs in total, including ophthalmology care and non-ophthalmology care, for patients with DME treated with anti-VEGF using nationwide claims data and compare them with those for patients with DM without retinopathy to better understand the HRU of patients with DME. In addition, we added one more comparison group, patients with neovascular age-related macular degeneration (nAMD) receiving anti-VEGF treatment. nAMD is the first approved indication of anti-VEGF treatment and, if untreated, may result in vision loss like DME. The clinical recommendations for using anti-VEGF in DME and nAMD are similar. According to the results from previous studies in other countries examining the number of anti-VEGF injections in patients with DME or nAMD using real-world data, the mean number of anti-VEGF injections per year for DME was similar to those for nAMD.[18–22] Generating data on HRU and medical costs of patients with DME in South Korea may be key to improve our understanding of the economic burden associated with DME and how anti-VEGFs are used to manage their disease. Also, comparison of total medical costs and HRU between patients with DME and nAMD could provide clinicians and policymakers meaningful insight into the economic burden as a whole in treating DME.

METHODS

Data source

We used 3-year data from the Korean NHI database (2014–2016). The NHI covers the entire South Korean population (97% by the NHI as compulsory social insurance and 3% by medical aid). The database includes demographic information such as sex, age and socioeconomic status of about 50 million inhabitants in Korea, as well as clinical information on prescribed drugs, procedures and disease diagnoses, which are coded according to the International Classification of Diseases, 10th revision (ICD-10), and treatment setting (inpatients or outpatients). Information on a prescribed drug includes the generic name, prescription date, duration of treatment and route of administration. It also includes information on the medical institution and medical costs incurred in hospitalisation or an outpatient visit. For administrative purposes, registration codes for the specific diseases are also recorded. The South Korean government implemented a policy to decrease the copayment for patients with rare and intractable diseases. A government agency, Health Insurance Review and Assessment Service, reviews patient eligibility and reliability of disease diagnosis; thus, using the registration code can be more accurate to select patients with the specific diseases than the ICD-10-based diagnosis code.[23] A previous study showed the overall agreement between the diagnoses derived from the claims database and the actual diagnoses of inpatients' medical records from hospital or clinic to be 82.0%.[24]

Study design and population

We conducted a retrospective cohort study to generate 1-year HRU and cost estimates of DME. Patients older than 30 years of age who received anti-VEGF treatment for DME in 2015 were included in the study since anti-VEGFs have been approved for the treatment of DME in South Korea as of February 2015. Currently, a specific diagnosis code for DME does not exist in the South Korean healthcare system, and the diabetic retinopathy (H36.0) code has been used for reimbursement of medical service for DME. We defined patients treated with licensed anti-VEGF, steroid or laser therapy with the diagnosis code for diabetic retinopathy as patients with advanced diabetic retinopathy including DME. We excluded patients who had a diagnosis of any cancer during the preceding year from the cohort because these patients may contribute to the overestimation of HRU and medical costs. After excluding patients who had nAMD in 2015, patients treated with anti-VEGFs were included in the final analysis. Patients were followed up for 1 year from the earliest date of anti-VEGF treatment for DME in 2015 (index date) (figure 1A). Eligible patients were required to have a diagnosis of DM (E10–E14) during the year before the index date.

Patients with DM without retinopathy were selected as the first comparison group. This group consisted of patients older than 30 years of age and who had a diagnosis code of DM (E10–E14) in 2015. Patients who had nAMD and any cancer during the preceding year were excluded. We selected patients using propensity score matching (1:10 matching) with patients with DME treated with anti-VEGF based on age and sex, due to the overly

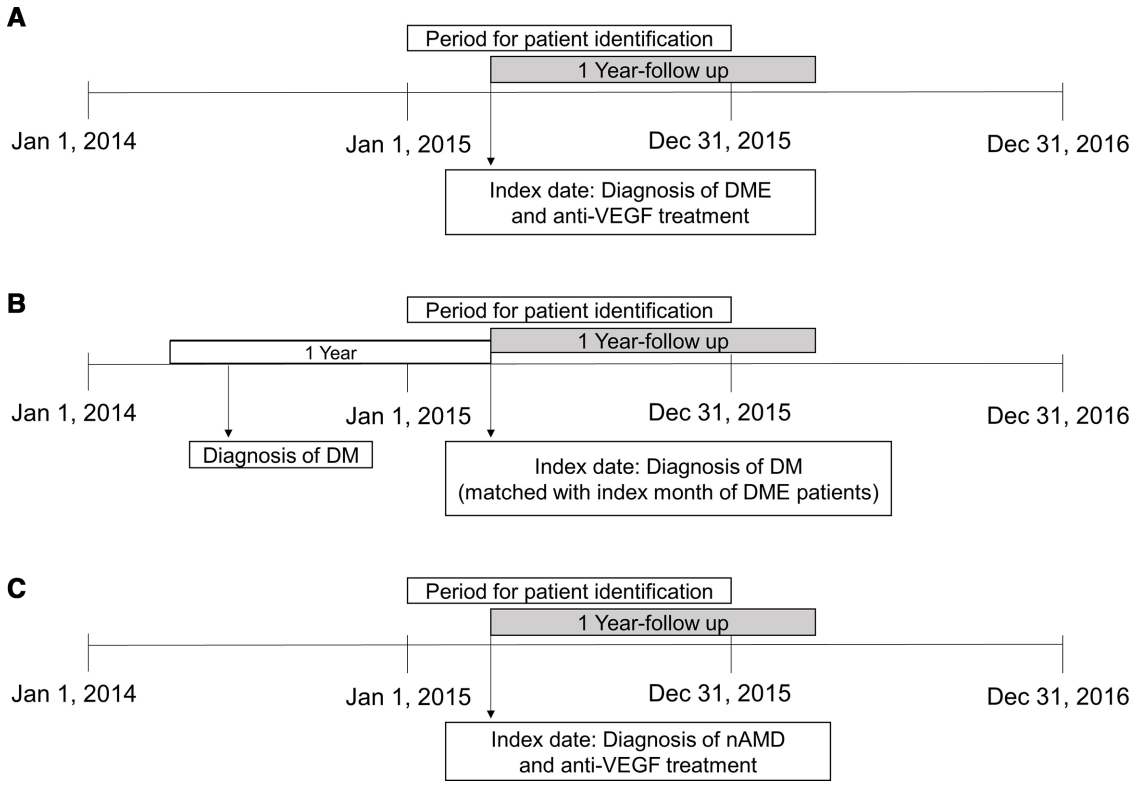

Figure 1 Study scheme and selection of patients with DME treated with anti-VEGF (A), DM without retinopathy (B), and nAMD treated with anti-VEGF (C). Anti-VEGF, antivascular endothelial growth factor; DM, diabetes mellitus; DME, diabetic macular oedema; nAMD, neovascular age-related macular degeneration.

large number of patients with DM without retinopathy in our database. We designated the index date as the date of DM record in 2015, of which the month was matched with that of the index date for patients with DME (figure 1B). Patients were eligible for inclusion in the study if they had no history of retinopathy (H30–H36) during the year before the index date. Patients older than 30 years of age and who had nAMD treated with anti-VEGF were selected as the second comparison group. Because nAMD is covered by the copayment decreasing policy as an extra-benefit scheme for rare and intractable diseases, its registration code (V201) was used for patient selection. The index date for patients with nAMD was the earliest date when nAMD and anti-VEGF treatment were recorded at the same time in 2015 (figure 1C). Patients who had any cancer in 2015 and diabetic retinopathy during the preceding year were excluded.

HRU and direct medical costs

Regarding HRU, the total number of outpatient and ophthalmologist visits, the number of hospitalisations, the length of stay per hospitalisation and the number of anti-VEGF injections were computed during 1 year from the index date. We also calculated 1-year total medical costs using a gross-costing method, by summing all medical costs incurred in clinics or hospitals at the patient level. Since the extent of medical costs incurred in inpatients and outpatients can be different by disease groups, we examined the total costs in each setting. The costs in ophthalmology, the costs per outpatient/ophthalmologist visits and the costs for each disease of interest were also computed. The costs for each disease of interest indicate the medical costs for the treatment of DME in the DME group, the treatment of DM in the DM without retinopathy group and the treatment of nAMD in the nAMD group. We also calculated the medical costs for other diseases by subtracting the medical costs for each disease of interest from the 1-year total medical cost in the matched cohorts to examine the economic burden due to other diseases in each patient group. All costs were converted from Korean won to US dollars based on the average exchange rate in 2015 (US$1=1179.1 Korean won).[25]

Statistical analysis

As the primary analysis, baseline characteristics were investigated to identify differences among the three groups. Age, sex, income-based insurance contribution levels (11 levels) as a proxy for socioeconomic status, residential district, and location and type of medical institution were assessed on the index date. Charlson Comorbidity Index (CCI) scores and comorbidity conditions (cataract, cerebrovascular disease, coronary heart disease, glaucoma, hypertension, peripheral vascular disease and renal disease) were identified for the year before the index date. In addition, duration of DM (<5 years, 5–9 years and ≥10 years) was identified using the 10-year medical record

before the index date for the DME treated with anti-VEGF group and for the DM without retinopathy group.

In the secondary analysis, we compared 1-year HRU and medical costs of patients with DME treated with anti-VEGF with those of patients with DM without retinopathy or of patients with nAMD using exact matching, propensity score matching and adjustment with a generalised linear model (GLM). Comparison of resource consumption and costs between different disease groups in observational studies is prone to bias due to the fundamental differences in the characteristics of each group.[26] Therefore, a three-step approach was applied to minimise bias and to estimate the disease-specific costs attributable to DME. First, for the comparison between DME and DM without retinopathy groups, patients were exact-matched based on age, sex, duration of DM and the index month. In the comparison between DME and nAMD groups, patients were matched based on age, sex, CCI score and the index month. Second, subsequent matching with propensity score was applied to the exact-matched cohorts. A propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates.[27] In this study, we calculated the propensity score for the possibility of a diagnosis of DME through multiple logistic regression analysis using demographic and clinical baseline characteristics, such as age, sex, income level, CCI score and comorbidities. Variables related to HRU and costs for the year before the index date (1-year medical cost, number of outpatient visits, hospitalisations and mean length of stay per hospitalisation) were also included in the calculation of propensity score. A greedy matching method was used to match patients with DME treated with anti-VEGF with patients with DM without retinopathy or patients with nAMD treated with anti-VEGF. Standardised difference was calculated to examine the balance of covariate distribution between groups (absolute value greater than 0.1 considered as imbalance). Third, to estimate the effect of DME on HRU and medical costs relative to DM without retinopathy and nAMD treated with anti-VEGF, we calculated the OR for HRU and cost ratios with 95% CI using a GLM with Poisson and gamma distribution, respectively. In these regression analyses, baseline characteristics including age, sex, income level, CCI score and all comorbidities were adjusted in model 1, and variables related to HRU and costs for the year before the index date were added in model 2. These ratios refer to the relative increase or decrease in HRU and medical costs of patients with DME treated with anti-VEGF compared with patients with DM without retinopathy and patients with nAMD treated with anti-VEGF. All statistical analyses were performed in SAS V.9.4.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research since we used de-identified participant data.

RESULTS

In total, 1398 patients with DME treated with anti-VEGF, 12 813 patients with DM without retinopathy and 12 222 patients with nAMD treated with anti-VEGF were included in the final analysis. The mean (SD) age of patients with DME treated with anti-VEGF and patients with DM without retinopathy was 58 (10.9) years, and approximately 60% of the patients in these two groups were male (table 1). The mean (SD) age of patients with nAMD treated with anti-VEGF was 71.9 (8.9) years. The proportion of patients with a DM duration of ≥10 years was considerably higher in the DME group than in the DM without retinopathy group (49.5% vs 7.7%). In the DME and DM without retinopathy groups, 22.2% and 25.6% were recipients of medical aid, respectively, compared with 5.7% in the nAMD group. The mean (SD) CCI score in the DME group was 3.9 (0.3), which was the highest CCI score among the groups. The overall proportion of patients with comorbidities was higher in the DME group than in the other groups.

One-year HRU and direct medical costs for each disease group are described in table 2. The mean (SD) number of hospitalisations per patient among patients with DME with anti-VEGFs was 1.4 (2.9), and the mean (SD) length of stay per hospitalisation was 7.6 (7.5) days. The mean (SD) number of outpatient visits was 49.2 (35.8). The mean (SD) number of ophthalmologist visits was 9.1 (5.5) and that of anti-VEGF injections was 2.1 (1.5). The overall HRU of patients with DM without retinopathy and of patients with nAMD was lower than that of patients with DME, except in the case of the mean length of stay per hospitalisation among patients in the DM group (10.3; SD 9.0) and the mean number of anti-VEGF injections in the nAMD group (3.9; SD 2.0). In the subgroup analysis with patients with nAMD who did not receive intravitreal anti-VEGF injections during the year before the index date (anti-VEGF treatment-naive patients), the mean (SD) number of anti-VEGF injections was 4.1 (2.0) (data not shown).

The mean 1-year total medical cost (US$6913; SD US$8266) was higher in the DME group than in the other groups. The medical costs for the DM without retinopathy group were substantially lower than for the other groups. In the nAMD group, the mean (SD) ophthalmological care costs per patient and costs for each disease of interest were US$3777 (US$1814) and US$3720 (US$1877), which were higher than in the DME group.

After exact and propensity score matching of the DME and DM without retinopathy groups, 535 pairs of patients were generated. In the matching of patients with DME with patients with nAMD, 470 patients from each group were included. We observed that the distributions of covariates were balanced in the matched cohort (online supplemental tables S1 and S2). The HRU and direct medical costs of the matched sample of patients with DME, patients with DM without retinopathy and patients with nAMD are described in online supplemental tables S3-S6.

Table 1 Sociodemographic and clinical characteristics of patients with DME treated with anti-VEGF, patients with DM without retinopathy and patients with nAMD treated with anti-VEGF

	DME patients treated with anti-VEGF (n=1398)	DM patients without retinopathy (n=12813)		nAMD patients treated with anti-VEGF (n=12222)	
	n(%)	n(%)	aSD	n(%)	aSD
Age (years), mean±SD	58.8±10.9	58.5±10.9	0.028	71.9±8.9	1.317
Male	844 (60.4)	7768 (60.6)	0.004	7525 (61.6)	0.025
Disease duration of DM			1.116		
<5 years	264 (18.9)	6801 (53.1)		–	
5–9 years	442 (31.6)	5020 (39.2)		–	
≥10 years	692 (49.5)	992 (7.7)		–	
Income level*			0.203		0.610
Medical aid	310 (22.2)	3283 (25.6)		694 (5.7)	
first quantile	173 (12.4)	2112 (16.5)		1552 (12.7)	
second quantile	185 (13.2)	1847 (14.4)		1192 (9.8)	
third quantile	202 (14.4)	1818 (14.2)		1470 (12.0)	
fourth quantile	238 (17.0)	1831 (14.3)		2367 (19.4)	
fifth quantile	290 (20.7)	1922 (15.0)		4947 (40.5)	
Residential district†			0.191		0.070
Metropolitan	756 (54.1)	7896 (61.6)		6319 (51.7)	
Urban	249 (17.8)	2336 (18.2)		2504 (20.5)	
Rural	393 (28.1)	2581 (20.1)		3399 (27.8)	
Location of institution†			0.074		0.268
Metropolitan	821 (58.7)	7903 (61.7)		7105 (58.1)	
Urban	305 (21.8)	2429 (19.0)		3724 (30.5)	
Rural	272 (19.5)	2481 (19.4)		1393 (11.4)	
Type of institution‡			0.853		0.616
Tertiary hospital	409 (29.3)	1163 (9.1)		5481 (44.8)	
General hospital	460 (32.9)	2309 (18.0)		2009 (16.4)	
Hospital	168 (12.0)	1259 (9.8)		3081 (25.2)	
Clinic	361 (25.8)	8082 (63.1)		1651 (13.5)	
CCI, mean±SD	3.9±1.8	2.8±10.9	0.141	1.7±1.6	1.292
0–1	127 (9.1)	2822 (22.0)		6707 (54.9)	
2	182 (13.0)	3633 (28.4)		2483 (20.3)	
≥3	1089 (77.9)	6358 (49.6)		3032 (24.8)	
Comorbidities					
Cataract§	263 (18.8)	224 (1.7)	0.585	1016 (8.3)	0.310
Glaucoma¶	133 (9.5)	104 (0.8)	0.053	547 (4.5)	0.197
Hypertension	957 (68.5)	7797 (60.9)	0.160	7170 (58.7)	0.205
Coronary heart disease	227 (16.2)	1739 (13.6)	0.073	1955 (16.0)	0.005
Cerebrovascular disease	224 (16.0)	1608 (12.5)	0.100	1761 (14.4)	0.045
Peripheral vascular disease	224 (16.0)	1559 (12.2)	0.109	1518 (12.4)	0.103
Renal disease	53 (3.8)	513 (4.0)	0.010	321 (2.6)	0.068

Any patient could be included as a duplicate patient in >1 group of treatment history for DME.
*Income levels were classified into six groups according to type of health insurance and health insurance premium. The higher the number, the higher the income.
†Metropolitan included Seoul, Incheon and Gyeonggi-do Province. Urban included the rest of the cities, and rural included the rest of the provinces.
‡Type of institution was classified as number of beds. Clinic, hospital, general hospital and tertiary hospital each has <30, 30–100, 100–500 and over 500 beds, respectively.
§Cataract was defined as patients who had both diagnosis (H25–28, Q120) and surgery procedure (S5110–5111, S5117, S5119) code for cataract.
¶Glaucoma was defined as patients who received prescription medications (Anatomical Therapeutic Chemical (ATC) code: S01E) for glaucoma.
anti-VEGF, antivascular endothelial growth factor; aSD, absolute standardised difference; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; DME, diabetic macular oedema; nAMD, neovascular age-related macular degeneration.

Table 2 Healthcare resource utilisation and direct medical costs for patients with DME treated with anti-VEGF, patients with DM without retinopathy and patients with nAMD treated with anti-VEGF during the 1-year follow-up period

	Patients with DME treated with anti-VEGF (n=1398)	Patients with DM without retinopathy (n=12 813)	Patients with nAMD treated with anti-VEGF (n=12 222)
Healthcare resource utilisation			
Number of hospitalisations*, mean±SD	1.4±2.9	1.1±3.4	0.5±1.6
0	729 (52.1)	9223 (72.0)	9135 (74.7)
1–2	416 (29.8)	2327 (18.2)	2496 (20.4)
≥3	253 (18.1)	1263 (9.9)	591 (4.8)
Length of stay per hospitalisation*			
Mean±SD	7.6±7.5	10.3±9.0	6.5±7.3
Median (Q1–Q3)	5.0 (2.4–10.5)	7.5 (3.0–15.0)	4.0 (1.7–8.8)
Number of outpatient visits†			
Mean±SD	49.2±35.8	29.8±32.0	42.2±30.9
Median (Q1–Q3)	40.0 (28.0–58.0)	20.0 (12.0–35.0)	35.0 (23.0–51.0)
Number of ophthalmologist visits‡			
Mean±SD	9.1±5.5	0.3±1.2	8.4±5.0
Median (Q1–Q3)	8.0 (5.0–12.0)	0.0 (0.0–0.0)	8.0 (5.0–11.0)
Number of anti-VEGF injections§			
Mean±SD	2.1±1.5	–	3.9±2.0
Median (Q1–Q3)	2.0 (1.0–3.0)	–	3.0 (3.0–5.0)
Direct medical costs¶ (US$)			
Total medical costs per patient			
Mean±SD	6913±8266	2763±6816	5121±4028
Median (Q1–Q3)	4151 (2597–7012)	552 (260–1672)	4355 (3136–6031)
Medical costs in inpatient setting			
Mean±SD	2326±5234	1738±5810	778±3371
Median (Q1–Q3)	0 (0–2370)	0 (0–248)	0 (0–0)
Medical costs in outpatient setting			
Mean±SD	4587±5620	1025±3370	4343±2181
Median (Q1–Q3)	3059 (2105–4695)	426 (224–835)	4020 (2989–5458)
Medical costs in ophthalmology per patient‡			
Mean±SD	2973±1918	35±145	3777±1814
Median (Q1–Q3)	2442 (1529–3900)	0 (0–248)	3514 (2645–4881)
Medical costs per outpatient visit†			
Mean±SD	95±69	27±53	133±87
Median (Q1–Q3)	78 (53–116)	2 (14–27)	112 (74–166)
Medical costs per ophthalmology visit‡			
Mean±SD	76±57	1±4	121±90
Median (Q1–Q3)	64 (37–101)	0 (0–1)	99 (60–157)
Medical costs for each disease of interest per patient**			
Mean±SD	2285±1700	1201±4234	3720±1877
Median (Q1–Q3)	1804 (1018–2867)	169 (84–348)	3452 (2590–4792)

*Hospitalisations were identified by claims issued from inpatient visits through medical institute, public health institute and neuropsychiatric department. In the categories (0, 1–2, ≥3) the number refers to the number of patients and percentage in parentheses.
†Outpatient visits were identified by claims issued from outpatient visits through medical institute, public health institute, neuropsychiatric department including day ward and haemodialysis.
‡Ophthalmologist visits were identified by claims with fundus examination issued from ophthalmology department.
§Calculated with the licensed anti-VEGFs (ranibizumab and aflibercept).
¶Direct medical costs were converted from Korean won to US dollars based on the average exchange rate in 2015 (US$1=1179.1 Korean won).
**The total medical costs for each disease of interest were defined as follows: DME, costs from all prescriptions for patients with DME (H360) and treated with licensed anti-VEGF, steroid or laser therapy; DM, costs from all prescriptions for patients with DM (E10–E14); nAMD, costs from all claims with a registration code for nAMD (V201).
anti-VEGF, antivascular endothelial growth factor; DM, diabetes mellitus; DME, diabetic macular oedema; nAMD, neovascular age-related macular degeneration; Q1, first quartile; Q3, third quartile.

Table 3 OR for healthcare resource utilisation and cost ratios for direct medical costs of patients with DME treated with anti-VEGF, relative to patients with DM without retinopathy

	OR/cost ratio (95% CI)		
	Crude	Model 1*	Model 2†
Healthcare resource utilisation			
Number of hospitalisations‡	2.18 (1.84 to 2.58)	2.17 (1.83 to 2.57)	2.17 (1.83 to 2.58)
Number of outpatient visits§	1.25 (1.22 to 1.27)	1.24 (1.21 to 1.26)	1.27 (1.24 to 1.29)
Number of ophthalmologist visits¶	12.29 (11.38 to 13.27)	12.33 (11.42 to 13.32)	12.35 (11.44 to 13.34)
Direct medical costs			
1-year medical costs per patient	2.44 (2.13 to 2.79)	4.05 (3.60 to 4.55)	4.66 (4.17 to 5.20)
Medical costs in inpatient setting	1.00 (0.76 to 1.31)	1.03 (0.78 to 1.38)	1.05 (0.79 to 1.40)
Medical costs in outpatient setting	2.51 (2.21 to 2.85)	4.78 (4.33 to 5.27)	5.70 (5.23 to 6.22)
Medical costs in ophthalmology per patient¶	25.26 (22.11 to 28.87)	29.66 (25.73 to 34.18)	30.32 (26.30 to 34.97)
Medical costs per outpatient visit§	3.39 (3.13 to 3.67)	3.79 (3.53 to 4.08)	4.06 (3.81 to 4.32)
Medical costs per ophthalmology visit¶	30.16 (26.49 to 34.33)	29.66 (25.96 to 33.90)	27.58 (24.18 to 31.46)
Medical costs for other diseases per patient**	3.21 (2.75 to 3.74)	3.81 (3.30 to 4.40)	4.30 (3.73 to 4.95)

*Adjusted for age, sex, income level, DM duration, CCI and all comorbidities.
†Adjusted for 1-year medical costs per patient, number of outpatient visits, number of hospitalisations and mean length of stay per hospitalisation in the prior year, in addition to all covariates in model 1.
‡Hospitalisations were identified by claims issued from inpatient visits through medical institute, public health institute and neuropsychiatric department.
§Outpatient visits were identified by claims issued from outpatient visits through medical institute, public health institute, neuropsychiatric department including day ward and haemodialysis.
¶Ophthalmologist visits were identified by claims with fundus examination issued from ophthalmology department.
**1-year total medical costs per patient: the total medical costs per patient excluding the costs relevant to each disease.
anti-VEGF, antivascular endothelial growth factor; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; DME, diabetic macular oedema.

DME was associated with 2.17 (95% CI 1.83 to 2.58) and 1.27 (95% CI 1.24 to 1.29) times more hospitalisations and outpatient visits than DM without retinopathy in model 2 (table 3). One-year medical costs of patients with DME were 4.66 times higher than those of patients with DM without retinopathy (95% CI 4.17 to 5.20). Compared with the nAMD group, the number of hospitalisations in the DME group was 60% higher (OR 1.65; 95% CI 1.39 to 1.85) and the number of anti-VEGF injections was 50% lower (OR 0.50; 95% CI 0.46 to 0.54) in model 2 (table 4). The DME group had 16% lower 1-year medical costs than the nAMD group (95% CI 0.78 to 0.90). Other medical costs were 29%–33% lower in general, but medical costs excluding the costs for each disease of interest for patients with DME were 66% higher than those for patients with nAMD (cost ratio 1.66; 95% CI 1.45 to 1.90).

DISCUSSION

Using real-world data, we examined the HRU and direct medical costs of patients with DME treated with anti-VEGF and compared them with those of patients with DM without retinopathy and patients with nAMD treated with anti-VEGF. The mean number of hospital admissions and outpatient visits in the DME group was 1.4 and 49.2, and the mean number of anti-VEGF injections was 2.1. The mean medical costs were US$6913 in the DME group. In the multivariate analysis with GLM after matching, patients with DME were likely to have had 1.3 times more outpatient visits and to have been hospitalised 2.2 times more often than patients with DM without retinopathy. One-year direct medical costs were 4.7 times higher in patients with DME. Compared with nAMD, DME was associated with 1.6 times more hospitalisations and 50% fewer licensed anti-VEGF injections.

Regarding the comparison between the DME group and the DM without retinopathy group, our results were consistent with those of previous studies.[28 29] Shea *et al*[2] showed that the 1-year cost in the DME group was 31% higher than in the DM without retinopathy group.[2] In addition, approximately three times as many patients with DME visited an ophthalmologist during a 1-year period after diagnosis compared with controls. The authors concluded that DME was a significant independent predictor of 1-year and 3-year total medical costs. In another retrospective cohort study, working-age patients with DME exhibited a significantly higher mean number of total healthcare visit days than patients with DM without DME (28.6 vs 16.9 days; p<0.001).[29] Even when compared with DM with diabetic retinopathy without DME, DME was associated with higher rates of HRU and medical costs.[9 10]

The overall HRU of patients with nAMD was lower in general than that of patients with DME, with the exception of an approximately twofold higher number of licensed anti-VEGF injections (3.9 vs 2.1). After adjusting the various factors in GLM, the OR regarding the anti-VEGF injections was significantly lower in the DME group. When restricting patients to first-ever users, the difference in the number of anti-VEGF injections remained (nAMD vs DME: 4.1 vs 2.1).

Table 4 OR for healthcare resource utilisation and cost ratios for direct medical costs of patients with DME treated with anti-VEGF, relative to patients with nAMD treated with anti-VEGF

	OR/cost ratio (95% CI)		
	Crude	Model 1*	Model 2†
Healthcare resource utilisation			
Number of hospitalisations‡	1.65 (1.43 to 1.90)	1.67 (1.45 to 1.92)	1.60 (1.39 to 1.85)
Number of outpatient visits§	1.01 (1.00 to 1.03)	1.02 (1.00 to 1.04)	1.00 (0.99 to 1.02)
Number of ophthalmologist visits¶	0.97 (0.93 to 1.01)	0.97 (0.93 to 1.01)	0.97 (0.93 to 1.01)
Number of anti-VEGF injections**	0.50 (0.46 to 0.53)	0.50 (0.46 to 0.54)	0.50 (0.46 to 0.54)
Direct medical costs			
1-year medical costs per patient	0.88 (0.81 to 0.96)	0.85 (0.79 to 0.92)	0.84 (0.78 to 0.90)
Medical costs in inpatient setting	1.09 (0.83 to 1.43)	1.06 (0.80 to 1.40)	1.06 (0.80 to 1.40)
Medical costs in outpatient setting	0.73 (0.68 to 0.78)	0.72 (0.67 to 0.77)	0.71 (0.67 to 0.76)
Medical costs in ophthalmology visits per patient¶	0.70 (0.65 to 0.75)	0.69 (0.65 to 0.75)	0.70 (0.65 to 0.75)
Medical costs per outpatient visit§	0.65 (0.61 to 0.70)	0.68 (0.63 to 0.72)	0.68 (0.64 to 0.72)
Medical costs per ophthalmology visit¶	0.64 (0.59 to 0.70)	0.66 (0.61 to 0.71)	0.67 (0.62 to 0.72)
Medical costs for other diseases per patient††	1.57 (1.35 to 1.82)	1.63 (1.42 to 1.87)	1.66 (1.45 to 1.90)

*Adjusted for age, sex, income level, DM duration, CCI and all comorbidities.
†Adjusted for 1-year medical costs per patient, number of outpatient visits, number of hospitalisations and mean length of stay per hospitalisation in the prior year, in addition to all covariates in model 1.
‡Hospitalisations were identified by claims issued from inpatient visits through medical institute, public health institute and neuropsychiatric department.
§Outpatient visits were identified by claims issued from outpatient visits through medical institute, public health institute, neuropsychiatric department including day ward and haemodialysis.
¶Ophthalmologist visits were identified by claims with fundus examination issued from ophthalmology department.
**Calculated with the licensed anti-VEGFs (ranibizumab and aflibercept).
††1-year total medical costs per patient: the total medical costs per patient excluding the costs relevant to each disease.
anti-VEGF, antivascular endothelial growth factor; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; DME, diabetic macular oedema; nAMD, neovascular age-related macular degeneration.

There are a few studies examining treatment patterns with anti-VEGF injections among patients with age-related macular degeneration (AMD) or DME in routine clinical practice. A study investigating the number of anti-VEGF injections administered with PRN treatment regimens for AMD and DME in a German hospital found that the median number of injections during the first year was 6 in patients with AMD and those with DME and the distribution of patients by number of injections was similar.[30] In a study using the Danish National Patient Registry, the mean number of anti-VEGF injections in the first half of 2014 was 5.71 in patients with nAMD and 5.93 in patients with DME.[18] When analysing US Medicare standard analytic claim files (2006–2010), patients with AMD received an average of 4.3 injections in the first year.[19] Another study using the same database (2008–2010) showed that the mean number of anti-VEGF injection claims for DME per patient was 4.2.[20] Studies conducted in Turkey reported the annual mean number of injections to be 4.1±1.9 in patients with nAMD[21] and 3.1–4.6 in patients with DME.[22] The literature review indicates that the mean number of injections administered in a year in DME and nAMD should be comparable, although the number of loading doses of aflibercept for each disease is different in year 1 (3 in nAMD vs 5 in DME). However, our results showed that the mean number of injections in patients with nAMD was twofold higher than in patients with DME, indicating potential lack of treatment supported by the NHI among patients with DME.

This particular pattern was also shown in another Korean study. Jee *et al*[31] found that the mean (SD) number of licensed anti-VEGF injections in patients with nAMD was 4.87 (3.37), while that in patients with DME was 3.1 (1.98). Considering that the number of loading dose of aflibercept in the first year of treatment is higher in DME than nAMD (5 times vs 3 times), the very low number of anti-VEGF injection in DME amplifies the possibility of lack of treatment. The different copayment rate of patients with DME and nAMD may be one reason that explains this difference in the number of injections. In South Korea, nAMD has been designated as a rare and intractable disease since 2009, and patients with this disease receive benefit from a copayment decreasing policy (ie, extra benefit in national health insurance) in HRU. Because the copayment rate for patients with DME, which falls in the standard benefit scheme, is three to six times higher than for patients with nAMD (30%–60% vs 10%), it could be burdensome for patients with DME to receive anti-VEGF treatment. In addition, the relatively low income level of patients with DME might contribute to the low number of anti-VEGF injection. While the proportion of medical aid and patients in the fifth quantile of income level (the highest level) in patients with nAMD were 5.7% and 40.5%, those in patients with DME were 22.2% and 20.7%, respectively. Despite the low economic status, patients with DME were also likely to have more complicated comorbidity and thus might not afford to receive sufficient therapy. We could not

disregard the possibility of switching from the licensed anti-VEGF to an off-label treatment, bevacizumab, which could not be captured in our database. For patients with DME, the price of bevacizumab per one injection is cheaper than that of ranibizumab or aflibercept even if reimbursed. However, it surely indicated that ophthalmological treatment supported by the NHI may be insufficient for patients with DME compared with patients with nAMD.

The mean 1-year total medical costs were higher in the DME group than in the nAMD group (US$6913 vs US$5121). A previous study in South Korea reported that 1-year medical costs were US$2995 and US$1834 in patients with DME treated with anti-VEGF and patients with nAMD treated with anti-VEGF, respectively.[31] The costs of that study were considerably different from those in the present study owing to differences in details of patient definition, but the trend of higher medical costs for the DME group compared with the nAMD group was similar. However, the costs relevant to ophthalmological care (the total medical costs for ophthalmological care per patient, the total medical costs per ophthalmologist visit and the total medical costs for each disease of interest per patient) in the DME group were lower than those of the nAMD group. In the GLM analysis with the matched cohort, we identified that DME was associated with 1-year medical costs that were 16% lower but with costs for comorbid diseases that were 1.66 times higher compared with nAMD. This indicates that patients with nAMD spent substantial money on treatment for nAMD, including anti-VEGF injections, whereas patients with DME spent more money on treatments for diseases other than DME due to complicated comorbidity.

We used the nationwide administrative claims database to identify patients with DME, patients with DM without retinopathy and patients with nAMD. Use of administrative data is relatively free of the recall bias and non-response that may occur with the survey method. Furthermore, use of the administrative claims database allowed retrospective examination of the duration of DM in patients with DME and those with DM using 10-year data before the index date. Thus, claims data seem suitable to analyse the prevalence of disease and medical use and costs. In addition, to our knowledge, this is the first study to compare HRU and direct medical costs between a group of patients with DME treated with anti-VEGF and two comparison groups (patients with DM without retinopathy and patients with nAMD treated with anti-VEGF). To enhance comparability, we established a propensity score-matched cohort. In particular, the results from the comparison of the DME and nAMD groups show that healthcare use by patients can be affected by a pharmaceutical policy and may suggest the direction of future policy to decision makers. Moreover, GLM analyses were applied to the propensity score-matched cohort to identify the adjusted effect of DME relative to other disease statuses. These various statistical methods would contribute to reducing biases in estimating the effect of DME on HRU and medical costs.

This study had several limitations. First, because the clinical characteristics of patients with DME and those with nAMD are very different, propensity score matching does not completely control the confounders. Although we matched the groups by specific variables and adjusted for various confounders, residual confounding can still remain. Second, HRU and medical costs of patients with DME would have been underestimated. The NHI database does not include information on non-reimbursed drugs. Since information on the injection of bevacizumab, which has the same mechanism of action as ranibizumab and off-label treatment for DME and nAMD, is absent in the NHI database, the actual HRU and medical costs of patients would be higher than our results. However, it does not change the fact that patients with DME had higher HRU and medical costs overall and fewer licensed anti-VEGF injections. Third, there is a possibility of misclassification of patients with DME because there is no specific diagnosis code for DME in South Korea. Although we attempted to set the selection criteria reflecting clinical practice to distinguish patients with DME with accuracy, the misclassification may have remained and may have thus affected our results. Fourth, our findings may not be consistent if we look into the longer term, since we calculated the HRU and medical costs during a 1-year period. Intravitreal anti-VEGF treatment for DME versus nAMD can be different in the long term and thus the results should be interpreted with caution. Lastly, contrary to our interpretation, potential lack of anti-VEGF treatment in patients with DME might have contributed to their higher HRU and direct medical costs. Without timely treatment for DME, patients could have blurry vision, which might incur accidents such as falls, and subsequently result in ambulatory healthcare visit or hospital admission.

CONCLUSION

Compared with patients with DM without retinopathy, higher HRU and direct medical costs were incurred in patients with DME treated with anti-VEGF. The overall HRU of patients with DME was higher than that of patients with nAMD, while the use of licensed anti-VEGFs in patients with DME was half that in those with nAMD. The mean 1-year total medical costs of DME were higher than those of nAMD, but the mean medical costs for treatment of DME were lower than those for treatment of nAMD, which may reflect that patients with DME bear a heavy economic burden and that there is a potential lack of ophthalmological treatment supported by the NHI.

Contributors H-LJ, HL, DY and YL designed the study. HL and DY played a key role in data analysis. H-LJ, HL, YL, JHK, DJ and J-YS participated in the interpretation of the results. YL administered the project. H-LJ and J-YS wrote the draft manuscript. All authors contributed to the final manuscript writing. J-YS is the guarantor of the study.

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Bayer Korea. JHK is a consultant for Bayer Korea in this study. DJ has no conflicts of interest to declare.

Patient consent for publication Not required.

Ethics approval This retrospective study was approved by the Institutional Review Board (IRB) of Sungkyunkwan University in Korea (IRB no. SKKU-2018-04-018). The IRB official waiver of ethical approval was granted by the IRB of Sungkyunkwan University.

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Data availability statement Data may be obtained from a third party and are not publicly available. We used the National Health Insurance (NHI) database established by the National Health Insurance Service (NHIS) in South Korea. NHIS forbids transfer, rent or sale of the database to any other third party except the researchers who obtained approval for access to database (official website of NHIS: https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).

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