Patient-Centered Economic Burden of Diabetic Macular Edema: Retrospective Cohort Study

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Table of Contents

Original Manuscript **5**
Supplementary Files **28**
..... **28**
Figures **29**
Figure 1 ..... **30**
Figure 2 ..... **31**
Figure 3 ..... **32**
Multimedia Appendixes **33**
Multimedia Appendix 1 ..... **34**
Multimedia Appendix 2 ..... **34**
Multimedia Appendix 3 ..... **34**
CONSORT (or other) checklists **35**
CONSORT (or other) checklist 0 ..... **35**

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Abstract

Background: Diabetic macular edema (DME), a leading cause of blindness, necessitates costly treatments like anti-vascular endothelial growth factor (VEGF) agents. The long-term regular use of effective but expensive drugs causes an incremental economic burden for DME patients compared to diabetes mellitus (DM) patients. However, there is no study on the long-term patient-centered economic burden of DME after reimbursement of anti-VEGF.

Objective: This retrospective cohort study aims to estimate the long-term patient-centered economic burden of DME compared to DM without DME, using the observational medical outcomes partnership-common data model (OMOP-CDM).

Methods: A retrospective cohort study utilized 1,903,603 patients' medical data transformed and validated with the Observational Medical Outcome Partnership Common Data Model from Seoul National University Bundang Hospital (2003-2020). We defined the DME group as patients aged >18 years with a non-proliferative diabetic retinopathy (NPDR) diagnosis and intravitreal anti-VEGF or steroids prescriptions. As control group, we defined DM group as patients aged >18 years with a DM or diabetic retinopathy diagnosis without prescription of intravitreal anti-VEGF or steroids. Propensity score matching using a regularized logistic regression with a Laplace prior addressed selection bias. We estimated the direct medical costs categorized into total, reimbursement, non-reimbursement, out-of-pocket costs, and costs covered by insurance for three-years, and health resource utilization. The exponential conditional model and count model with generalized linear model estimated unbiased incremental patient-centered economic burden using generalized linear models.

Results: In a cohort of 454 patients with DME matched with 1,640 patients with DM, the economic burden of DME was significantly higher than that of DM (P<.001 in all cases), with a 2.09 times higher total cost for three years (95% confidential interval (CI): 1.78–2.47). Reimbursement costs were 1.89 times higher for the DME group compared to the DM group (95% CI: 1.57–2.28), while non-reimbursement costs were 2.54 times higher (95% CI: 2.12–3.06). Out-of-pocket costs and costs covered by insurance were also higher by a factor of 2.11 (95% CI: 1.58–2.59) and 2.01 (95% CI: 1.85–2.42), respectively. DME patients had a significantly higher number of outpatient (1.87-fold) and inpatient (1.99-fold) visits compared to DM (P<.001 in all cases).

Conclusions: Patients with DME exhibit a heightened economic burden compared to those with DM. The substantial and enduring economic impact from real-world underscores the imperative to alleviate patients' burden through preventive measures, effective management, appropriate reimbursement policies, and the advancement of innovative treatments. Strategies

to mitigate the economic impact on DME should include proactive approaches such as expanding anti-VEGF reimbursement criteria, approving and reimbursing cost-effective drugs like bevacizumab, advocating for proactive eye examinations, and embracing early diagnosis facilitated by cutting-edge methodologies such as artificial intelligence and machine learning techniques for patients with DM by ophthalmologists.

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Original Manuscript

Original Paper

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Abstract

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Objective: This retrospective cohort study aims to estimate the 3-year patient-centered economic burden of DME compared to DM without DME, using the observational medical outcomes partnership-common data model (OMOP-CDM).

Methods: A retrospective cohort study utilized 1,903,603 patients' medical data transformed and validated with the OMOP-CDM from Seoul National University Bundang Hospital (2003-2020). We defined the DME group as patients aged >18 years with a non-proliferative diabetic retinopathy (NPDR) diagnosis and intravitreal anti-VEGF or steroids prescriptions. As control group, we defined DM group as patients aged >18 years with a DM or diabetic retinopathy diagnosis without prescription of intravitreal anti-VEGF or steroids. Propensity score matching using a regularized logistic regression with a Laplace prior addressed selection bias. We estimated the direct medical costs categorized into total, reimbursement, non-reimbursement, out-of-pocket costs, costs covered by insurance, and health resource utilization for 3-years. The exponential conditional model and count model estimated unbiased incremental patient-centered economic burden using generalized linear models and zero-inflation model.

Results: In a cohort of 454 patients with DME matched with 1,640 patients with DM, the economic burden of DME was significantly higher than that of DM, with a 2.09 times higher total cost for 3 years (95% confidential interval (CI): 1.78–2.47). Reimbursement costs were 1.89 times higher for the DME group compared to the DM group (95% CI: 1.57–2.28), while non-reimbursement costs were 2.54 times higher (95% CI: 2.12–3.06). Out-of-pocket costs and costs covered by insurance were also higher by a factor of 2.11 (95% CI: 1.58–2.59) and 2.01 (95% CI: 1.85–2.42), respectively. DME patients had a significantly higher number of outpatient (1.87-fold) and inpatient (1.99-fold) visits compared to DM (P<.001 in all cases).

Conclusions: Patients with DME exhibit a heightened economic burden compared to those with DM. The substantial and enduring economic impact from real-world underscores the imperative to alleviate patients' burden through preventive measures, effective management, appropriate reimbursement policies, and the advancement of innovative treatments. Strategies to mitigate the economic impact on DME should include proactive approaches such as expanding anti-VEGF reimbursement criteria, approving and reimbursing cost-effective drugs like bevacizumab, advocating for proactive eye examinations, and embracing early diagnosis facilitated by cutting-edge methodologies such as artificial intelligence and machine learning techniques for patients with DM by ophthalmologists.

Keywords: diabetic macular edema; economic burden; cost of illness; retrospective cohort study; patient-centered care; common data model

Introduction

Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM) that affects the eyes and can lead to vision loss or blindness [1-3]. Non-proliferative diabetic retinopathy (NPDR) is an early stage of diabetic retinopathy that causes small leaks in blood vessels and changes in the retina. As NPDR progresses to proliferative diabetic retinopathy (PDR), new abnormal blood vessels grow, causing severe vision loss or blindness. Patients with DR can develop diabetic macular edema (DME) at any stage, even in the early stage of NPDR. DME is a macular thickening disease resulting from fluid accumulation in the macula due to diabetic retinopathy. DME is the most common cause of vision loss in patients with diabetic retinopathy [4-6]. Since DME management is crucial to preventing severe vision loss, active treatment options for DME include the use of intravitreal anti-vascular endothelial growth factors (VEGFs), intra/periocular steroids, focal laser photocoagulation, and vitrectomy. Based on a network meta-analysis of clinical trials, anti-VEGF agents are recommended as the primary treatment for DME [7], but they can be costly. While certain anti-VEGF drugs, including aflibercept, ranibizumab, faricimab, and brolucizumab, are eligible for reimbursement, the high cost of these medications, coupled with co-payment rates at tertiary hospitals and stringent reimbursement criteria, imposes a substantial economic burden on patients. Another anti-VEGF drug, Bevacizumab, is also recommended in clinical guidelines [8, 9], and is cost-effective for treating DME [10]. However, it is neither approved nor reimbursed in the UK, Korea, and other countries.

Patients with PDR are treated with anti-VEGF agents regardless of the presence of DME and have a high disease burden. No treatment is necessary for NPDR without DME, and patients with NPDR without DME may not have a significant economic burden. However, in NPDR with DME, treatment is typically prioritized for DME, and compared with patients with DM, patients with NPDR and DME may face a considerable economic burden owing to the high cost of treatment and frequent visits to tertiary hospitals, resulting in high co-payment rates and costly non-reimbursable items.

Understanding the direct medical healthcare costs and health resource utilization (HRU) associated with managing these conditions, including non-reimbursement and out-of-pocket costs, is crucial for developing cost-effective strategies for DR prevention and management. Specifically, estimating the economic burden and HRU forms a crucial basis for allocating public health resources and making informed decisions on new drug reimbursement, including economic evaluations and budget impact analyses in health policy. Numerous economic burden of disease studies have been published in various forms such as policy reports and academic papers [11-14], providing essential political evidence. However, despite studies detailing the direct costs of DME patients over 1 year (€4516 (€1128-€8257) in France [15], there remains a significant gap in well-designed research examining the long-term economic burden of DME from the patients' perspective.

This retrospective cohort study aimed to estimate the economic burden of DME patients compared with that of DM without DME patients using an observational medical

outcome partnership-common data model (OMOP-CDM). Real-world data on DME are challenging to define using claims data as diagnosis codes do not exist and treatment overlaps with that of PDR or other ophthalmic diseases. By analyzing standardized data from electronic health records (EMRs) of patients diagnosed with DME, we estimated the direct medical healthcare costs associated with managing DME, particularly from a patient-centered perspective including non-reimbursement and out-of-pocket costs.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using the EMRs of Seoul National University Bundang Hospital (SNUBH), standardized to Observational Health Data Sciences and Informatics (OHDSI) OMOP-CDM by SNUBH Healthcare ICT Research Center. SNUBH is the first Stage 7 hospital outside of North America, and the first full digital hospital with electronic medical records system in South Korea. The electronic medical data were extracted, transformed, and loaded, including laboratory results, non-reimbursement items, and cost data, into OMOP-CDM version 5.3, following OHDSI's guidelines [16]. The dataset included 1,903,603 patients from April 2003 to December 2020, verified using Automated Characterization of Health Information at Large-Scale Longitudinal Evidence Systems [17] and checked by data analysts and clinicians.

Study Population

We defined the eligibility criteria for patients with DME (DME group) and the DM without DME (DM group) by ophthalmologists. For a 3-year follow-up period and a one-year wash-out period, we set the intake period from July 1, 2004, to July 31, 2017. We defined the index date for the DME group as the first prescription date of intraocular anti-VEGF, triamcinolone, or dexamethasone from an ophthalmologist in the intake period. To ensure patients with DME, we defined DME as patients who had at least one occurrence of NPDR prior to the index date or one year after the index date and excluded those with other ophthalmic diseases using intraocular anti-VEGFs or steroids (choroidal neovascularization, central serous chorioretinopathy, exudative age-related macular degeneration, PDR, retinal vein occlusion, variceal hemorrhage, neovascular glaucoma, endophthalmitis, uveitis, thrombosis of the retinal vein, and retinal dystrophy). For the DM group, the index date was defined as the date of diagnosis of DM or DR. Patients who had any prescription of intraocular anti-VEGF, triamcinolone, or dexamethasone, any occurrence of NPDR, or other ophthalmic diseases using intraocular anti-VEGFs or steroids were excluded. To prevent overfitting of the model by outliers, we excluded patients with cancer, renal replacement, or severe cardiovascular disease (cerebrovascular accident, ischemic heart disease, and acute heart disease) in both groups (Figure 1).

Outcomes

To assess the economic burden of patients with DME, our primary outcomes focused on direct medical costs incurred in the hospital for 3 years following the index date. We categorized the direct medical and incremental costs of the DME group into five segments: total medical costs, reimbursement costs, non-reimbursement costs, out-of-

pocket costs, and costs covered by insurance (Textbox 1). Total medical costs were calculated as the sum of reimbursement and non-reimbursement costs, or the sum of costs covered by insurance and out-of-pocket costs. We further analyzed total medical costs based on reimbursement categorization and payment entities. For reimbursement categorization, we calculated reimbursement and non-reimbursement costs for each relevant item, irrespective of the payer. To estimate medical costs by payment entities, costs covered by insurance included all costs from National Health Insurance Services, insurance contractors, and employers. Out-of-pocket costs encompassed all expenses directly incurred by the patients. All costs were measured in Korean won and subsequently converted to U.S. dollars, with a fixed exchange rate of US $1 = 1,200 Korean won.

Textbox 1. Definitions of cost categories for patient-centered economic burden outcome

- Total medical cost: All expenses associated with each patient in the hospital, encompassing both reimbursed and non-reimbursed expenditures for 3 years (sum of the reimbursement cost and non-reimbursement cost or sum of costs covered by insurance and out-of-pocket costs).
- Reimbursement cost: All expenses incurred by patients restricted to items eligible for reimbursement for 3 years.
- Non-reimbursement cost: All expenses incurred by patients restricted to items eligible for non-reimbursement for 3 years.
- Costs covered by insurance: All expenses from National Health Insurance Services, insurance contractors, and employers for 3 years.
- Out-of-pocket cost: All expenses borne directly by the patient, irrespective of any reimbursement for 3 years.

As secondary outcomes, we analyzed medical costs by follow-up date and HRU. The medical costs by follow-up date were calculated as the average costs per group by follow-up day and the accumulated costs by follow-up day. HRUs were estimated by 3 categories regardless of specialty for 3 years: count of outpatient visits, inpatient visits, and length of stay (LOS) for inpatients.
Estimating the medical costs by follow-up date:

$$Medical\,cost_{group \vee T} = \sum_{t=1}^{T} \left(\frac{1}{N} \sum_{i=1}^{N} \cos t_{i \vee group} \right) \vee t$$

where medical cost is the accumulated cost by group at T (day), cost is the medical costs at t (day) in group, i indexes the individual in the treatment group (i.e., DME or DM group) and t indexes the time as day.
To assess bias after propensity score matching, negative control outcomes were utilized. A total of 598 covariates, such as vedolizumab, zolpidem, zinc bromide, zafirlukast, wrist drop, and tramadol, were included as negative control outcomes.

Statistical Analysis

Data analyses were conducted using ATLAS (version 2.10.1; OHDSI) Health Resources Econometric Analysis Tool (HERMES (version 0.1.0)) R packages, and the Health Analytic Data-to-Evidence Suite, formally known as the OHDSI Methods Library and

HADES (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). To compare the two groups, we evaluated the baseline characteristics of the patients and performed up to 1:4 propensity score matching using regularized logistic regression with a Laplace prior (LASSO). Baseline patient characteristics such as biological sex, age groups, index year, condition, and Charlson comorbidity index (CCI), were used as covariates for the propensity score matching model, while highly correlated covariates such as anti-VEGF and NPDR were excluded. After propensity score matching, we considered covariates with a standardized difference of over 0.10 between the two groups as unmatched covariates and included them in the exponential conditional model (ECM). If the hazard ratio for negative control outcomes included 1 at the 75% confidence interval (CI), we considered that there was no selection bias. To prevent distortion and overfitting of the model, we defined groups without outliers, including zero-cost patients who did not incur any cost due to their participation in clinical trials. For the primary outcome, HERMES was used for the ECM to estimate the precise cost, with adjustments for confounders and positive skewness [18]. In the ECM, the gamma distribution and log link function were determined by modified Park tests, Box-Cox tests, and goodness of fit using the Akaike information criterion and Bayesian information criterion [19]. We performed descriptive analyses as a sensitivity analysis (Multimedia Appendix 1, 2, 3). Among the secondary outcomes, count outcomes such as HRU for 3 years were analyzed using HERMES with Poisson or negative binomial models. Age, sex, pre-index cost, and unmatched covariates from propensity score matching were considered covariates in the ECM and count model, including the group variable. If the observed median was zero, a zero-inflation model was considered, and the covariates were selected by backward elimination for addressing the convergence issue. We assumed that there were no missing data for covariates before matching, and that any missing data for outcomes and follow-up loss due to other diseases were similar between groups as a result of propensity matching. The medical costs by follow-up date were suggested as a cumulative average daily increase for each group after propensity score matching and outlier removal.

Ethical Considerations

This study was approved by the institute review board of SNUBH (X-2012-657-902). The data was de-identified and anonymized; therefore, informed consent was not required. Since our study involved secondary data analysis, there was no direct interaction with participants, nor was any compensation provided. Also, we followed STROBE reporting guidelines.

Results

Patient characteristics

Of the 1,903,603 patients who visited SNUBH, we identified a total of 33,044 patients who met the eligibility criteria, with 486 patients with NPDR and DME and 32,558 patients with DM. After propensity score matching, we matched 454 patients in the DME

group with 1,646 in the DM group with outliers. After excluding outliers, the number of patients in the DM group was 1,460 (Figure 2).

In the propensity score model, we matched 140 covariates, and most of them had a standardized mean difference of 0.10 or less between the DME group and the DM group (Table 1). However, 11 variables, including the Charlson comorbidity index, had a standardized mean difference greater than 0.10, indicating unmatched covariates, and were included in the ECM. Of the 598 negative control outcomes, events could be identified for only four outcomes: impingement syndrome of shoulder region, falls, hyperosmolality, and difficulty sleeping, with a hazard ratio of 1 within the 75% confidence interval.

Table 1. Baseline demographic and clinical characteristics for the diabetic macular edema (DME) group and diabetes mellitus (DM) group in the index period from July 2004 to July 2017 before and after propensity score (PS) matching

Characteristic[a]	Before PS matching			After PS matching		
	DME group (n=486)	DM group (n=32,358)	SMD[b]	DME group (n=454)	DM group (n=1646)	SMD[b]
Age (years), mean (SD)	64.97 (11.15)	58.21 (13.79)	0.54	64.57 (11.27)	64.99 (11.99)	−0.01
Sex, n (%)						
Female	242 (49.79)	16,191 (50.00)	0.00	224 (49.34)	819 (51.12)	−0.04
Charlson index: Romano adaptation, mean (SD)[c]	2.39 (1.18)	1.48 (0.88)	0.87	2.30 (1.12)	2.45 (1.27)	−0.19
Medical history: general, n (%)[d]						
Acute respiratory disease	1 (0.21)	145 (0.45)	−0.04	1 (0.22)	2 (0.28)	−0.01
Chronic liver disease	3 (0.62)	563 (1.74)	−0.10	3 (0.66)	14 (0.81)	−0.02
Chronic obstructive lung disease	1 (0.21)	118 (0.36)	−0.03	1 (0.22)	9 (0.66)	−0.07
Dementia	6 (1.23)	469 (1.45)	−0.02	5 (1.10)	19 (1.23)	−0.01
Depressive disorder	6 (1.23)	323 (1.00)	0.02	6 (1.32)	22 (1.38)	0.00
Gastroesophageal reflux disease	5 (1.03)	543 (1.68)	−0.06	5 (1.10)	20 (1.17)	−0.01
Gastrointestinal hemorrhage	1 (0.21)	267 (0.83)	−0.09	1 (0.22)	8 (0.46)	−0.04
Hyperlipidemia	18 (3.70)	2982 (9.22)	−0.23	17 (3.74)	43 (3.10)	0.04
Hypertensive disorder	78 (16.05)	7998 (24.72)	−0.22	71 (15.64)	234 (14.87)	0.02
Lesion of liver	2 (0.41)	579 (1.79)	−0.13	2 (0.44)	9 (0.53)	−0.01
Osteoarthritis	13 (2.67)	1478 (4.57)	−0.10	12 (2.64)	42 (2.37)	0.02
Pneumonia	3 (0.62)	495 (1.53)	−0.09	3 (0.66)	12 (0.83)	−0.02
Renal impairment	16 (3.29)	663 (2.05)	0.08	16 (3.52)	80 (4.88)	−0.07
Rheumatoid arthritis	4 (0.82)	304 (0.94)	−0.01	4 (0.88)	8 (0.44)	0.05
Viral hepatitis C	3 (0.62)	91 (0.28)	0.05	1 (0.22)	1 (0.06)	0.04
Medical history: cardiovascular disease, n (%)[d]						
Atrial fibrillation	5 (1.03)	536 (1.66)	−0.05	5 (1.10)	12 (0.66)	0.05
Cerebrovascular disease	17 (3.50)	2389 (7.38)	−0.17	16 (3.52)	60 (3.69)	−0.01

Coronary arteriosclerosis	8 (1.65)	761 (2.35)	−0.05	8 (1.76)	19 (1.05)	0.06
Heart disease	15 (3.09)	2347 (7.25)	−0.19	14 (3.08)	49 (2.86)	0.01
Heart failure	1 (0.21)	310 (0.96)	−0.10	1 (0.22)	10 (0.55)	−0.05
Peripheral vascular disease	5 (1.03)	111 (0.34)	0.08	2 (0.44)	15 (0.84)	−0.05
Unmatched covariates, n (%)[c, d]						
Rhegmatogenous retinal detachment	5 (1.03)	4 (0.01)	0.14	5 (1.10)	1 (0.06)	0.14
Degeneration of macular and posterior pole	5 (1.03)	7 (0.02)	0.14	5 (1.10)	3 (0.17)	0.12
Degeneration of posterior pole of eye	5 (1.03)	7 (0.02)	0.14	5 (1.10)	3 (0.17)	0.12
Discharge from eye	5 (1.03)	10 (0.03)	0.14	5 (1.10)	3 (0.17)	0.12
Obstruction of nasolacrimal duct	5 (1.03)	20 (0.06)	0.13	5 (1.10)	1 (0.06)	0.14
Lesion of eyelid	4 (0.82)	17 (0.05)	0.12	4 (0.88)	1 (0.06)	0.12
Hypertensive retinopathy	4 (0.82)	20 (0.06)	0.11	3 (0.66)	1 (0.06)	0.10
Secondary glaucoma	3 (0.62)	7 (0.02)	0.11	3 (0.66)	1 (0.06)	0.10
Labyrinthine disorder	3 (0.62)	297 (0.92)	−0.03	3 (0.66)	1 (0.06)	0.10
Diabetic foot	3 (0.62)	144 (0.45)	0.02	3 (0.66)	34 (1.87)	−0.11

[a]These covariates are a subset of the 140 covariates used for propensity score matching.

[b]SMD: standardized mean difference

[c]The covariates were considered as unmatched covariates based on standardized difference, which were adjusted in following exponential conditional model and count model.

[d]Medical history and medication use were identified by diagnosis and prescription within 1 year before the index date.

The Incremental Patient-centered Economic Burden for Diabetic Macular Edema Compared to Diabetes Mellitus After Propensity Score Matching

The primary outcomes showed that the DME group had significantly higher costs than the DM group in all categories, including total cost, reimbursement cost, non-reimbursement cost, out-of-pocket cost, and cost covered by insurance (P <.001). The total cost for the DME group was $2,359 more than the DM group, which was 2.09 times higher (95% CI: 1.78–2.47). Reimbursement costs were 1.89 times higher for the DME group compared to the DM group (95% CI: 1.57–2.28), while non-reimbursement costs were 2.54 times higher (95% CI: 2.12–3.06). The out-of-pocket and costs covered by insurance were also higher for the DME group compared to the DM group by a factor of 2.11 (95% CI: 1.58–2.59) and 2.01 (95% CI: 1.85–2.42), respectively. Age and pre-index cost were positively correlated with all costs, while the CCI was not significantly correlated with non-reimbursement costs but positively correlated with other costs. All unmatched covariates were insignificant (Table 2).

Table 2. The estimated incremental healthcare costs of the diabetic macular edema (DME) group compared to the diabetes mellitus (DM) group for 3 years after the index date from the exponential conditional models with propensity score matching in patients.

Exponential conditional model[a]	Total cost		Reimbursement categorization				Payment entity			
			Reimbursement cost		Non-reimbursement cost		Cost covered by insurance		Out-of-pocket cost	
Cost (US $, mean, (SE))										
DME group (number of patients: 454[b])	4,502.52 (251.79)		2,854.25 (192.85)		1,618.89 (76.39)		1,871.17 (177.34)		2,593.32 (114.72)	
DM group (number of patients: 1460[b])	2,142.56 (109.13)		1,525.78 (100.76)		627.52 (29.91)		970.01 (183.45)		1,208.88 (46.54)	
ΔCost	2,359.96		1,328.48		991.38		901.15		1,384.44	
Coefficient	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Intercept	*6.3596*	*<0.0001*	*5.7563*	*<0.0001*	*5.6721*	*<0.0001*	*4.8656*	*<0.0001*	*6.2848*	*<0.0001*
Group[c]	*0.7394*	*<0.0001*	*0.6364*	*<0.0001*	*0.9329*	*<0.0001*	*0.7005*	*<0.0001*	*0.7483*	*<0.0001*
Age[d]	*0.0142*	*<0.0001*	*0.0169*	*<0.0001*	*0.0090*	*0.0080*	*0.0227*	*<0.0001*	*0.0078*	*0.0019*
Sex[e]	0.1125	0.1122	0.1169	0.1473	0.1034	0.1943	*0.1161*	*0.2767*	0.1073	0.0673
Preindex cost (US $)[f]	*0.00008*	*<0.0001*	*0.00009*	*<0.0001*	*0.00004*	*0.0062*	*0.0001*	*<0.0001*	*0.00005*	*<0.0001*
Charlson comorbidity index	*0.0840*	*0.0047*	*0.1071*	*0.0016*	0.0285	0.3929	*0.0968*	*0.0306*	*0.0737*	*0.0027*
Rhegmatogenous retinal detachment	0.2098	0.7352	0.5303	0.4530	-0.5766	0.4088	0.7083	0.4486	-0.1739	0.7350
Degeneration of macula and posterior pole	-0.7872	0.1679	-1.1197	0.0851	-0.3211	0.6171	-1.5568	0.0703	-0.4344	0.3581

Discharge from eye	-0.5023	0.3471	-0.8284	0.1736	-0.0386	0.9488	-1.0515	0.1916	-0.1788	0.6861
Obstruction of nasolacrimal duct	-0.4781	0.4802	-0.5381	0.4855	-0.3361	0.6591	-0.1756	0.8865	-0.5049	0.3680
Lesion of eyelid	0.1415	0.8457	-0.0047	0.9955	0.3948	0.6295	-0.9050	0.4089	0.5853	0.3313
Hypertensive retinopathy	0.5335	0.4790	0.1840	0.8303	0.8669	0.3069	-0.0904	0.9366	0.7296	0.2425
Secondary glaucoma	0.0065	0.9933	-0.0738	0.9331	0.1137	0.8958	-0.3135	0.7874	0.1010	0.8743
Labyrinthine disorder	0.1522	0.8405	0.0551	0.9490	0.3323	0.6963	0.0740	0.9482	0.2516	0.6881
Diabetic foot	0.2552	0.3666	0.1356	0.6736	0.5071	0.1110	0.2031	0.6334	0.3030	0.1957

[a]The exponential conditional models were conducted using a log link function with gamma distribution. The SEs of the estimated costs were calculated using bootstrapping.
[b]After propensity score matching, outliers were excluded.
[c]The reference group was the DM group.
[d]Age was reported in years and is preseonted as a continuous variable.
[e]Sex was represented as a binary variable, with a value of 1 indicating male and a value of 0 indicating female.
[f]Preindex cost was calculated for 1 year before the index date.

The Accumulative Cost and Health Resource Utilization for Diabetic Macular Edema After Propensity Score Matching

For the secondary outcomes, the accumulative cost differences between the DME group and the DM group gradually increased over time for all cost categories. The difference between the groups became more substantial as the follow-up date progressed, particularly for non-reimbursed and out-of-pocket costs (Figure 3). Furthermore, the DME group had higher average annual costs in years 1, 2, and 3 for all cost categories than the DM group (Multimedia Appendix 1).

When comparing HRUs over 3 years as secondary outcomes, the mean annual HRUs for years 1, 2, and 3, we found that the DME group had more outpatient and hospitalization visits than the DM group (Multimedia Appendix 2) and the mean annual HRUs in ophthalmology for outpatient and inpatient visits for years 1, 2, and 3 were also higher in the DME group than in the DM group (Multimedia Appendix 3). Overdispersion was observed in all cost categories in the Poisson model (Pearson chi2: from 1.5 to over 10). In the negative binomial model, the DME group showed 1.87 (95% CI: 1.66–2.12) times more outpatient visits. Age, CCI, and pre-index cost were significantly positively associated with the number of outpatient visits (Table 3). For inpatient visits and LOS, a zero-inflation negative binomial model was adapted and the DME group had 1.99 (95% CI: 1.49–2.67) times more inpatient visits over 3 years compared to the DM group (p-value < 0.05), and no between-group significance was observed for the LOS.

Table 3. The estimated incremental healthcare resource utilization of the diabetic macular edema (DME) group compared to the diabetes mellitus (DM) group for 3 years after the index date from the count models with propensity score matching in patients.

Count model[a]	Number of outpatient visits		Number of inpatient visits[b]				Length of stay[b]			
	Count model		Zero-inflation model		Count model		Zero-inflation model		Count model	
Count (mean, (SE))										
DME group (number of patients: 454[c])	18.4038 (0.9328)				0.4383 (0.0426)				1.8843 (0.3720)	
DM group (number of patients: 1460[c])	9.7246 (0.3190)				0.2480 (0.0158)				1.4148 (0.4037)	
ΔCount	8.6792				0.1903				0.4695	
Coefficient	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Intercept	1.7220	<0.0001	0.3053	0.6579	-1.8849	<0.0001	1.3035	0.0218	-0.2211	0.6216
Group[d]	0.6257	<0.0001	0.8670	0.0014	0.6915	<0.0001	0.0933	0.7050	0.0767	0.7074
Age[e]	0.0054	0.0184	0.0022	0.8197	0.0159	0.0043	-0.0068	0.3869	0.0188	0.0023
Sex[f]	-0.0301	0.5734	-0.1705	0.5222	0.1828	0.2074	-0.3052	0.1368	0.1148	0.5483
Pre-index cost (USD)[g]	0.00004	<0.0001	-0.0008	<0.0001	0.00002	N/A	-0.0008	<0.0001	0.00005	0.0509
Charlson comorbidity index	0.0706	0.0016	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Rhegmatogenous retinal detachment	-0.6900	0.1477	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Degeneration of macula and posterior pole	-0.6478	0.1383	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Discharge from eye	0.1973	0.6206	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Obstruction of nasolacrimal duct	-0.3816	0.4539	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Lesion of eyelid	0.0777	0.8862	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Hypertensive retinopathy	0.4509	0.4195	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Secondary glaucoma	-0.2024	0.7278	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Labyrinthine disorder	0.6377	0.2526	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]
Diabetic foot	-0.0606	0.7757	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]	N/A[h]

[a]Count model conducted with negative binomial distribution, and standard error was calculated by bootstrapping.
[b]Since the observed median is zero, a zero-inflation model was applied. The zero- inflation model was estimated as a binomial with a logit link function. Covariates were selected by backward elimination due to a lack of variation by groups.
[c]After propensity score matching, outliers were excluded.
[d]The reference group was the DM group.
[e]Age was reported in years and is presented as a continuous variable.
[f]Sex was represented as a binary variable, with a value of 1 indicating male and a value of 0 indicating female.
[g]Preindex cost was calculated for 1 year before the index date.
[h]Variables were removed by backward elimination to address convergence issue.

Discussion

Principal Findings

This retrospective cohort study evaluated the economic burden of DME using real-world data. The economic burdens of DME were significantly higher than those of DM without DME (P<.001 in all cases). Comparing the total cost over 3 years through the ECM, the DME group were 2.09 times higher. In particular, the patient burden was higher than that of insurance or reimbursement due to non-reimbursement items. Reimbursement costs and costs covered by insurance were 1.89 and 2.01 times higher, respectively, while non-reimbursement and out-of-pocket costs, the direct economic burden of patients, were 2.54 and 2.11 times higher. Age and pre-index cost were significantly and positively associated with all costs, and CCI was significantly and positively associated with all costs, except non-reimbursement costs. When compared by follow-up period, patients with DME had consistently higher costs, not only in the first year but also in the second and third years. As a result of the count model, the number of outpatient and inpatient visits over 3 years was also significantly higher in the DME group than in the DM group (P <.001 in all cases).

Comparison with Previous Studies

Since ophthalmic conditions significantly constitute the medical costs associated with diabetes [14] and diabetic ophthalmic conditions are diseases that can lead to vision loss or blindness with a high economic burden to patients, a few previous studies have studied the burden of diabetic ophthalmic conditions, such as DME or DR [15, 20-28]. However, these studies were unable to estimate the patient-centered economic burden of patients with DME due to the following: 1) difficulty distinguishing the analyzed population as a mix of DME and DR, including PDR without DME or NPDR without DME as well as other ophthalmic conditions, due to the absence of diagnosis of DME in ICD-10 and the overlap in treatment modalities between PDR and DME [25, 26]; 2) outdated data before the introduction of anti-VEGF and a descriptive analysis rather than a marginal economic burden compared to a quasi-experimental control [20-23, 29]; 3) a short analysis period of 1 year [15, 24]; and 4) reimbursed drugs and tests such as aflibercept and ranibizumab, excluding patients and physician choice of non-reimbursement treatments such as bevacizumab, and underestimating patient burden [15, 26]. Therefore, previous studies have highlighted the high descriptive economic burden of DR or DME but have faced challenges in accurately estimating the patient-centered long-term economic burden, specifically for patients with DME. Our study has several strengths. Firstly, we precisely defined DME patients, excluding PDR patients, using EMR data converted to OMOP-CDM. We validated the clinical and cost data with clinicians, data scientists, and economists. This is the only real-world data that met fit-for-use, including non-reimbursed medication, measurements, and ophthalmology information. Using EMR data converted to OMOP-CDM, we could not only define the patient with DME but also analyze the economic burden from a patient perspective. Secondly, we implemented LASSO and ECM models to estimate the marginal patient burden, minimizing selection

bias and confounders. Third, we compared multiple categories of long-term (3-year) direct medical costs between DME patients and DM patients. With these strengths, our study provides valuable real-world evidence by demonstrating a significant patient-centered incremental economic burden, including non-reimbursement care, compared to DM.

Policies for DME

Effective management strategies are crucial for patients with DME to prevent disease progression to PDR or vision loss, which is associated with a higher economic burden and a poorer prognosis [25, 30]. The high costs of medications, coupled with uncompensated and out-of-pocket expenses, may create economic burdens for patients in the DME group, leading to hesitation in seeking treatment. To prevent a greater treatment burden in the future, active reimbursement policies, such as relaxation of reimbursement criteria or reimbursing bevacizumab, along with comprehensive disease prevention and management strategies, should be considered. In the United States, bevacizumab is reimbursed to patients through the Centers for Medicare and Medicaid Services, ensuring broader access to this treatment option and reducing the financial burden on patients. However, globally, in Central and Eastern Europe, there is a lack of clinical practice guidelines for DME, and the accessibility and reimbursement of anti-VEGF treatments differ widely by region [31]. This discrepancy results in many patients remaining untreated or receiving inappropriate treatment. Similarly, in the UK and South Korea, bevacizumab is not reimbursed or even licensed. In South Korea, unlike other similarly treated conditions, such as exudative age-related macular degeneration, there is no special calculation system for exempted health insurance policies to reduce the burden on patients. These limitations highlight the urgent need for appropriate economic equity and the development of reimbursement policies to address the high out-of-pocket costs experienced by patients with DME. In addition to these policies, new drugs and technologies need to be developed to relieve the patient burden. The development and reimbursement of novel drugs have the potential to significantly improve patient outcomes, leading to better prognosis, enhanced quality of life, and reduced economic burden [32]. Additionally, leveraging artificial intelligence for eye examinations with ophthalmologists can facilitate the early detection and treatment of DR patients, offering promising avenues for efficient and cost-effective care [28].

In addition, the current reimbursement policy for regulating expensive drug costs might exacerbate patients' clinical and economic burdens. A narrow drug reimbursement pathway, rather than a stringent drug authorization process, combined with international reference pricing system, can lead to pharmaceutical companies skipping or withholding reimbursement in low-income countries. Consequently, patients in those countries may be compelled to pay for the drug out-of-pocket, thereby worsening their economic and clinical burdens. Addressing this issue requires various policy interventions, one of which involves implementing a two-stage reimbursement process with a revalidation process using real-world data alongside expedited approval mechanisms. This approach not only promotes the use of fast-track reimbursement and real-world data fit-for-use in those countries but also ensures that drug pricing reflects accurate revalidation and appropriate statistical methodologies.

Limitations

This study had several limitations. First, EMR data were used to accurately define. Due to the nature of EMR data, the data are unstructured and missing records and deaths in other hospitals; however, we used EMR data converted and validated with OMOP-CDM and matched both groups comparably using LASSO and negative control to reduce bias such as missingness from a selection bias perspective. In addition, the control group was defined as patients with DM who visited a tertiary care hospital, which is a more severe group of patients than general DM patients. We made efforts to reduce selection bias in this study, and the incremental economic burden of DME patients was robust and substantial in all costs and HRUs for 3 years. Second, both the number of hospitalizations and the number of hospital days were often zero for many patients. We used the zero-inflation model and selected variables by backward elimination because of the small variation in covariates across groups. Even with the addition of some variables, the group for the number of hospitalizations was always significant and the added unmatched covariates were not significant in any of the models. Third, the type and status of patient insurance were not available because there were no data. However, in South Korea, national health insurance services cover the majority of the population, and only 3% of patients are supported by medical aid programs. Nevertheless, our study is the only real-world evidence of the economic burden from the perspective of patients with DME, showing that DME are associated with a significant economic burden compared to DM alone, highlighting the need for healthcare resource allocation and policy planning to address this issue. These findings may be of interest to healthcare providers, policymakers, and payers in their efforts to manage and reduce the economic impact of these conditions. Lastly, in this study we included the direct medical costs measurable from the single-center EMR. However, we did not include data from other centers, direct non-medical costs (such as transportation costs), and indirect costs (such as productivity loss costs). Consequently, the patients' economic burden might be underestimated.

Further Research for DME patients

Further research is needed. First, a detailed analysis of the underlying economic burden of DME patients should be conducted, which includes a breakdown of medical costs by source, such as medications, procedures, and tests. This comprehensive approach will provide valuable insights into specific areas that contribute to the economic burden beyond the scope of payer and entity analysis. Particularly, leveraging OMOP-CDM with HERMES will facilitate the seamless generation of real-world evidence, supporting evidence-based decision-making in clinical, economic, and regulatory contexts with validated patient-centered data [33]. Second, further research could analyze the correlation between policy measures, such as the strengthening of coverage for severe diseases in South Korea, and their impact on economics and clinical outcomes related to non-reimbursement and hospitalization. Understanding these policy correlations will shed light on potential interventions and strategies to optimize patient care and financial stress, and even clinical outcomes. Finally, further research is needed to enhance our

understanding and preparedness for managing the cycle of DME patients. Specifically, investigations focusing on patient measurements, subsequent therapy, and factors contributing to the sudden worsening of symptoms can provide valuable insights into optimizing patient care and resource allocation. We observed that the speed of cost growth increased at 700 and 1000 days in the DME group compared to that in the DM group, which could be due to patient measurement, subsequent therapy, or sudden worsening of symptoms.

Lastly, future research urgently needs to provide a policy rationale and recommendations with appropriate statistical methods aimed at reducing the clinical economic burdens on both patients and the country, while preventing pharmaceutical companies from skipping or delaying drug reimbursement onto specific countries. For example, there is a need for future research to reach consensus on statistical methods for appropriately handling discrepancies between results from randomized clinical trials and real-world evidence, as well as on how to incorporate these methods into economic evaluations for drug-cost regulation.

Conclusions

Our study findings indicate that DME, even in the absence of PDR, are associated with significantly higher healthcare costs and HRU than DM alone. This emphasizes the substantial patient-centered economic burden posed by DME. Regulatory and economic policies with innovative drugs and technology should be implemented to address the challenges presented by DME, prevent vision deterioration, and mitigate the high economic burden on society. These insights have significant implications for healthcare providers and policymakers, highlighting the crucial need for enhanced surveillance and management of patients with DR. By prioritizing disease progression prevention and mitigating associated healthcare costs, we can effectively improve patient outcomes and allocate healthcare resources more efficiently to reduce financial stress in patients with DME.

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Data Availability

As OMOP-CDM is a distributed research network, access to the data is restricted to internal private networks, and the data is not publicly available.

Conflicts of Interest

None declared.

Abbreviations

CCI: Charlson comorbidity index
DM: diabetes mellitus

DME: diabetic macular edema
DR: diabetic retinopathy
ECM: exponential conditional model
HERMES: health resources econometric analysis tool
HRU: health resource utilization
LASSO: least absolute shrinkage and selection operator
LOS: length of stay
OHDSI: observational health data sciences and informatics
OMOP-CDM: observational medical outcomes partnership-common data model
SNUBH: Seoul National University Bundang Hospital
VEGF: vascular endothelial growth factor

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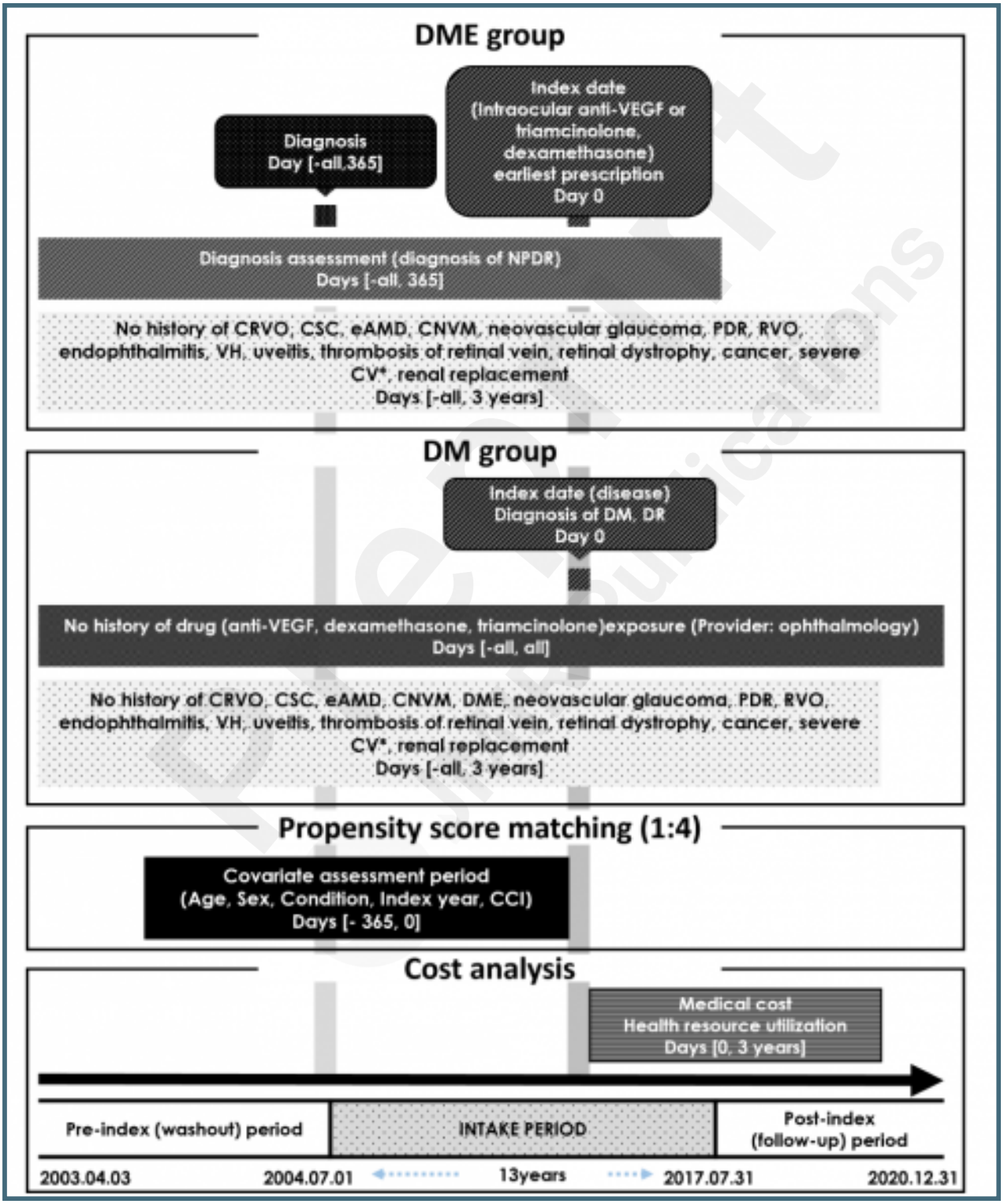
Supplementary Files

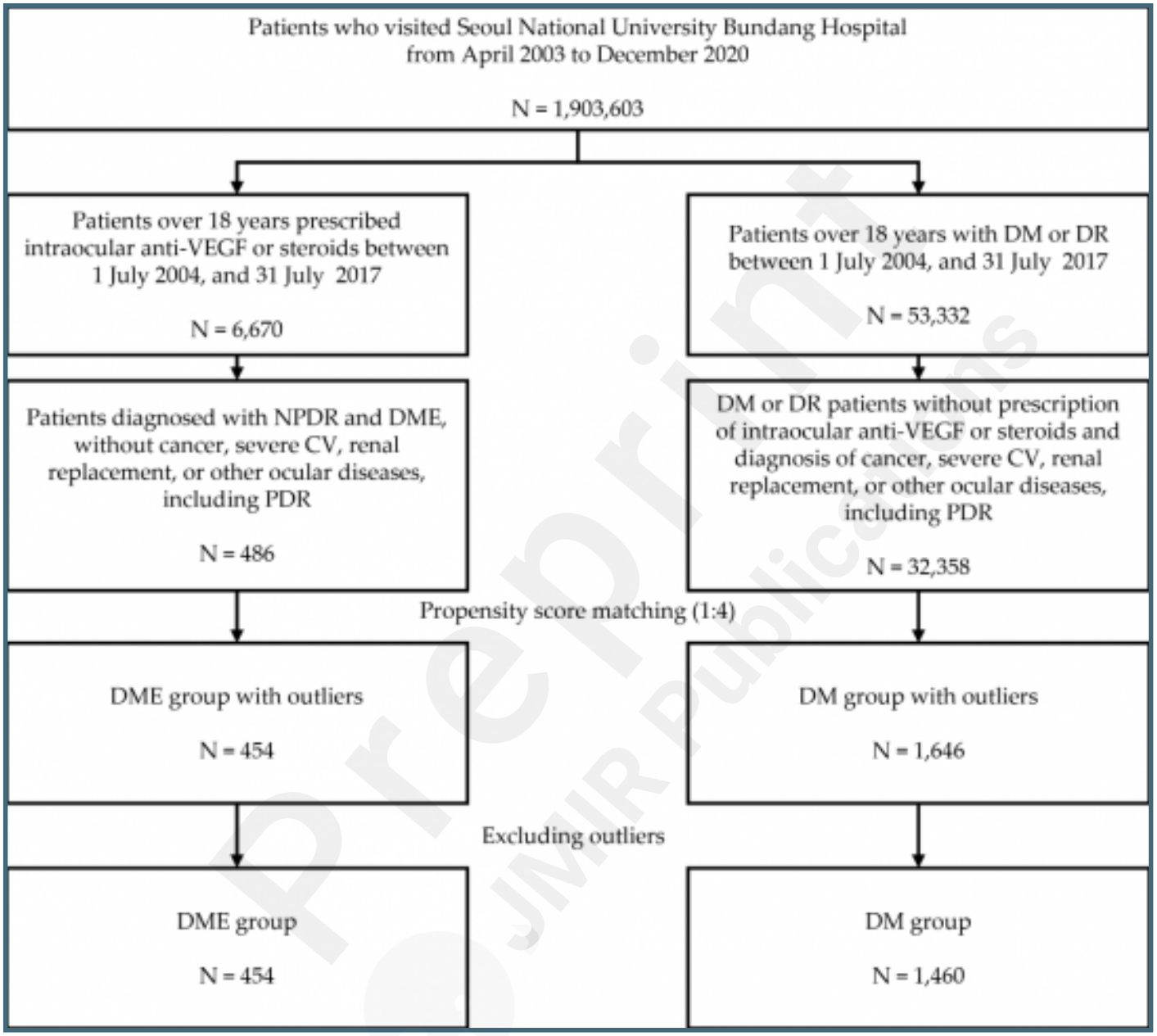
Untitled.
URL: http://asset.jmir.pub/assets/fa6d476fad79420e7c42e46c44852efc.docx

Figures

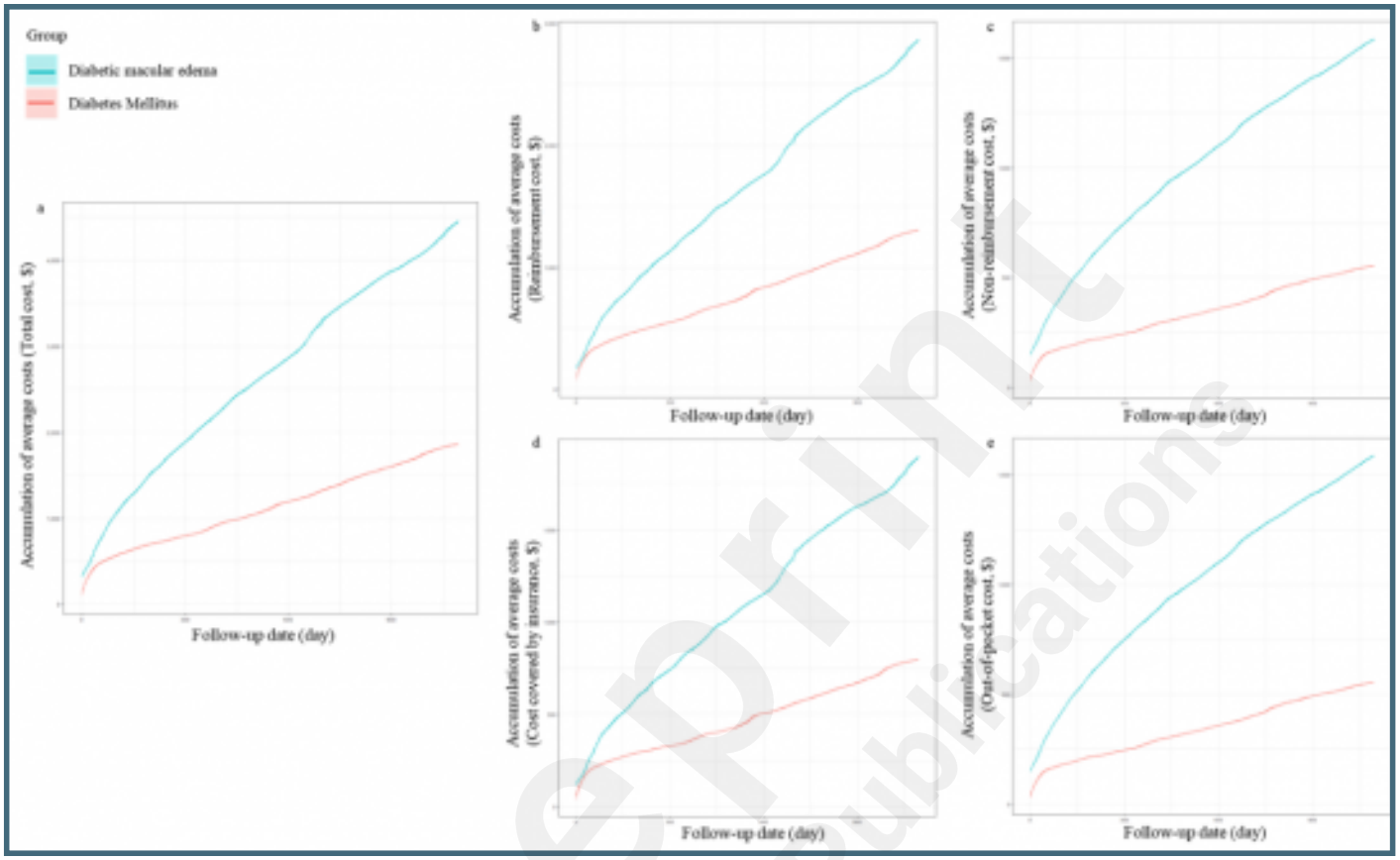
Analysis scheme. Data were included from June 2003 to December 2020. The intake period was defined as July 1, 2004, to July 31, 2017. The follow-up period was 3 years from the index date. CCI, Charlson comorbidity index; CNV, choroidal neovascularization; CSC, central serous chorioretinopathy; CV, cardiovascular disease; DM, diabetes mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; eAMD, exudative age-related macular degeneration; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor; VH. variceal hemorrhage.



Selection flow of patients with diabetic macular edema (DME) group and diabetes mellitus (DM) group from June 2003 to December 2020. CV, cardiovascular; DM, diabetic mellitus; DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.



Accumulative costs by follow-up date for patients with diabetic macular edema when compared to that for patients with diabetes mellitus: (a) total costs and breakdown by (b) reimbursement costs, (c) non-reimbursement costs, (d) Costs covered by insurance, and (e) out-of-pocket costs over the three-year follow-up Period.



Multimedia Appendixes

The three-year observed economic burden of patients with diabetic macular edema by reimbursement categorization and payment entity.
URL: http://asset.jmir.pub/assets/6d910dfcbdbf47cee564dea19d1643bf.docx

The three-year observed health resource utilization of patients with diabetic macular edema.
URL: http://asset.jmir.pub/assets/e1f662fb15ca4f8688c2119c5527a6a8.docx

The three-year observed health resource utilization of patients with diabetic macular edema in ophthalmology.
URL: http://asset.jmir.pub/assets/ed5629c93a58cb91c721bbb9520dc83c.docx

CONSORT (or other) checklists

STROBE checklist.
URL: http://asset.jmir.pub/assets/dc64c4694f51c2c75a425b68e231ec53.pdf