Patient-centered Economic Burden of Non-proliferative Diabetic Retinopathy with Diabetic Macular Edema

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Background

Diabetic retinopathy is a common complication of diabetes mellitus (DM) that can lead to vision loss or blindness.[1] Non-proliferative diabetic retinopathy (NPDR) is an early stage of the disease, while proliferative diabetic retinopathy (PDR) is more advanced. Diabetic macular edema (DME) is a related condition characterized by fluid accumulation in the macula and the most common cause of vision loss in diabetic retinopathy. Effective management of DME is important to prevent vision loss. Anti-vascular endothelial growth factors (VEGFs) are commonly used to treat DME and PDR[2], but they are expensive, posing a financial burden on patients. Many previous studies addressed the high economic burden of patients with DR or PDR regardless of the presence of DME or DME itself; however, the economic burden of NPDR with DME patients has not been studied especially in the aspect of patient burden.[3, 4, 5]

The aim of this retrospective cohort study is to estimate the patient-centered economic burden of NPDR with DME patients compared to patients with DM. To analyze the economic burden of a patient, costs in different categories along with de-identification of the patient are essential. Observational Health Data Sciences and Informatics (OHDSI) Observational Medical Outcome Partners-Common Data Model (OMOP-CDM) has a cost vocabulary of various categories for cost analysis along with various de-identified data sources, and tools for cost analysis (HERMES) have been developed.[6] Furthermore, these costs can be validated by calculation and verification. With these characteristics, OHDSI's OMOP-CDM may be suitable for analyzing patient-centered economic burden.

Methods

This retrospective cohort study analyzed data from electronic health records of patients diagnosed with NPDR and DME. The study used the OMOP-CDM from Seoul National University Bundang Hospital. This database consisted of 1.90 million patients' data who visited the hospital from April 1931 to December 2020. Patients with NPDR and DME were compared to patients with DM only. Patients with NPDR and DME were defined by the prescription of intraocular anti-VEGF, triamcinolone, or dexamethasone from an ophthalmologist and the diagnosis of NPDR. Patients with DM were defined by the diagnosis of DM or DR and excluded those who had any prescription of intraocular anti-VEGF, triamcinolone, dexamethasone, or any occurrence of NPDR. Other ophthalmic diseases using intraocular anti-VEGFs, steroids, or severe disease (cancer, renal replacement, or severe cardiovascular disease (cerebrovascular accident, ischemic heart disease, and acute heart disease)) were excluded in both cohorts. To estimate patient-centered economic burden, we defined outcomes as direct medical healthcare costs, including reimbursement, non-reimbursement, insurance benefit, out-of-pocket costs, and health resource utilization (HRU) for a three-year period after the index date. For comparability, the propensity score matching with LASSO was performed and the covariates over 0.10 standardized mean difference were considered as unmatched covariates. The HERMES was used for the exponential conditional model (ECM)

with the generalized linear model to estimate the cost adjusting the confounders and positive skewness.[7, 8] HRU was also estimated by the HERMES with count model (e.g., Poisson or negative binomial model) after the propensity score matching. Age, sex, pre-index cost, and unmatched covariates from propensity score matching were considered as covariates in the ECM and count model, including the group variable. If the observed median was zero, a zero-inflated model was considered, and the covariates were selected by backward elimination.

Results

The study included 486 patients with NPDR and DME and 32,558 patients with DM. After propensity score matching, 454 patients in the NPDR and DME group and 1,646 patients in the DM group were included in the analysis. The NPDR and DME group had significantly higher costs in all categories compared to the DM group, including total cost, reimbursement cost, non-reimbursement cost, out-of-pocket cost, and insurance benefit cost ($p<0.001$) (Table 1). The total cost for the NPDR and DME group was $4,502 which was $2,360 higher than the DM group, representing a 2.09-fold increase. Reimbursement costs were 1.89 times higher, while non-reimbursement costs were 2.54 times higher in the NPDR and DME group. Out-of-pocket and insurance benefit costs were also higher for the NPDR and DME group (2.11, 2.01-fold increase).

Table 1. Three-year economic burden of patients with non-proliferative diabetic retinopathy and diabetic macular edema from results of exponential conditional models.

Exponential conditional model[a]		Total cost	Reimbursement categorization		Payment entity	
			Reimbursement cost	Non-reimbursement cost	Insurance benefit cost	Out-of-pocket cost
Cost (mean, (SE)), (USD)	NPDR and DME (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 (number of patients: 1,460[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[c]	Intercept	6.3596***	5.7563***	5.6721***	4.8656***	6.2848***
	Group	0.7394***	0.6364***	0.9329***	0.7005***	0.7483***
	Age	0.0142***	0.0169***	0.0090**	0.0227***	0.0078**
	Sex	0.1125	0.1169	0.1034	0.1161	0.1073
	Pre-index cost (USD)	0.00008***	0.00009***	0.00004**	0.0001***	0.00005***
	CCI	0.0840**	0.1071**	0.0285	0.0968*	0.0737**
	Rhegmatogenous retinal detachment	0.2098	0.5303	-0.5766	0.7083	-0.1739
	Degeneration of macula and posterior pole	-0.7872	-1.1197	-0.3211	-1.5568	-0.4344
	Discharge from eye	-0.5023	-0.8284	-0.0386	-1.0515	-0.1788
	Obstruction of nasolacrimal duct	-0.4781	-0.5381	-0.3361	-0.1756	-0.5049
	Lesion of eyelid	0.1415	-0.0047	0.3948	-0.9050	0.5853
	Hypertensive retinopathy	0.5335	0.1840	0.8669	-0.0904	0.7296
	Secondary glaucoma	0.0065	-0.0738	0.1137	-0.3135	0.1010
	Labyrinthine disorder	0.1522	0.0551	0.3323	0.0740	0.2516
	Diabetic foot	0.2552	0.1356	0.5071	0.2031	0.3030

CCI, Charlson comorbidity index; DM, diabetes mellitus; DME, diabetic macular edema; NPDR, non-proliferative diabetic retinopathy; SE, standard error; USD, united states dollar

* p<0.05, ** p<0.01, *** p<0.001

a Exponential conditional model was conducted with gamma distribution with log link function, and standard error was calculated by bootstrapping.

b Number of patients estimated after propensity score matching and outlier removal.

c Variable with an inclusive relationship was excluded from the ECM due to multicollinearity ("degeneration of posterior pole of eye").

The accumulative cost differences by group and follow-up date gradually increased over time for all cost categories. The difference between the groups became more substantial as the follow-up date progressed for non-reimbursement costs and out-of-pocket costs (Figure 1).

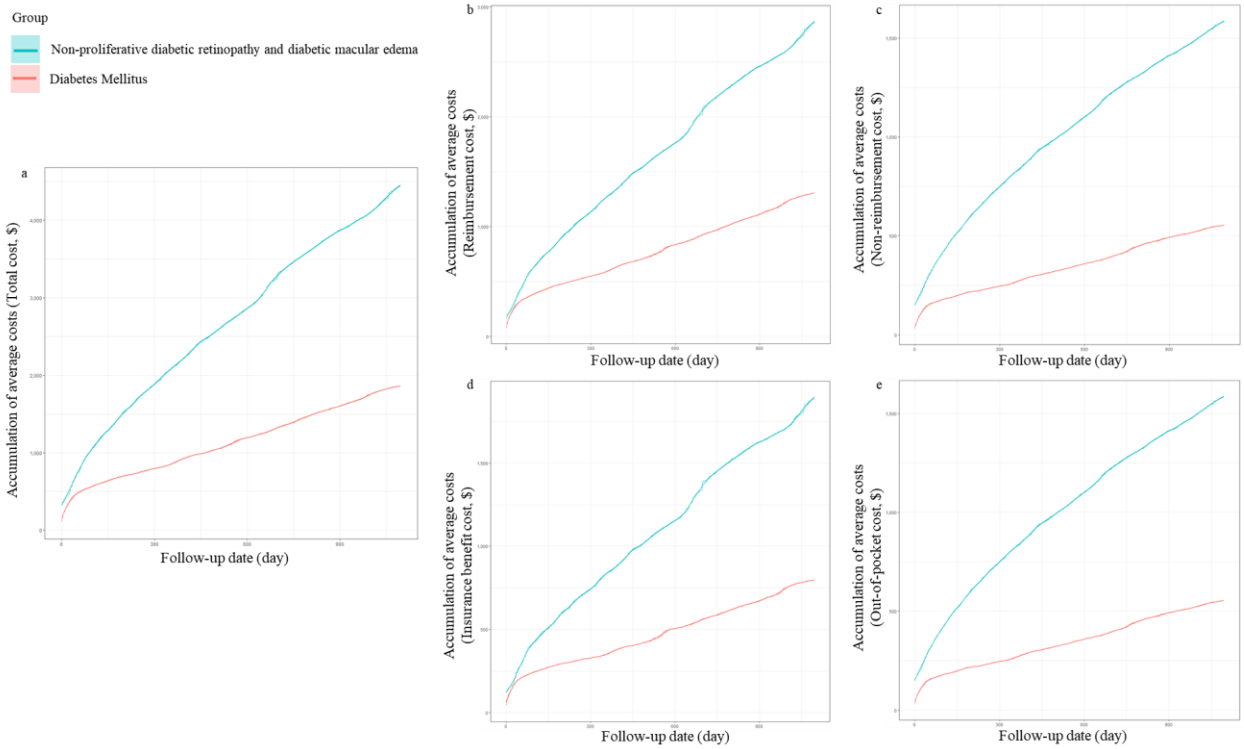

Figure 1. Accumulative costs by follow-up date for patients with non-proliferative diabetic retinopathy and diabetic macular edema compared to patients with diabetes mellitus: (a) total costs and breakdown by (b) reimbursement, (c) non-reimbursement, (d) insurance benefit, and (e) out-of-pocket costs over three-year follow-up Period.

In the count model (Table 2), HRU analysis showed significant differences in outpatient visits and inpatient visits ($p<0.01$), but the length of stay was not significantly different ($p>0.05$). NPDR and DME group showed 1.87 (95% CI: 1.66 – 2.12) times more outpatient visits and 1.99 (95% CI: 1.46 – 2.67) times more inpatient visits for three years.

Table 2. Three-year health resource utilization of patients with non-proliferative diabetic retinopathy and diabetic macular edema derived from results of a count model.

Count model[a]		Number of outpatient visits	Number of inpatient visits[b]		Length of stay[b]	
			Zero-inflated model	Count model	Zero-inflated model	Count model
Count (mean, (SE))	NPDR and DME (number of patients: 454[c])	18.4038 (0.9328)		0.4383 (0.0426)		1.8843 (0.3720)
	DM (number of patients: 1,460[c])	9.7246 (0.3190)		0.2480 (0.0158)		1.4148 (0.4037)
	ΔCount	8.6792		0.1903		0.4695
Coefficient[d]	Intercept	1.7220***	0.3053	-1.8849***	1.3035*	-0.2211
	Group	0.6257***	0.8670**	0.6915***	0.0933	0.0767
	Age	0.0054*	0.0022	0.0159**	-0.0068	0.0188**
	Sex	-0.0301	-0.1705	0.1828	-0.3052	0.1148
	Pre-index cost (USD)	0.00004***	-0.0008***	0.00002	-0.0008***	0.00005
	CCI	0.0706**	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Rhegmatogenous retinal detachment	-0.6900	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Degeneration of macula and posterior pole	-0.6478	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Discharge from eye	0.1973	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Obstruction of nasolacrimal duct	-0.3816	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Lesion of eyelid	0.0777	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Hypertensive retinopathy	0.4509	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Secondary glaucoma	-0.2024	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Labyrinthine disorder	0.6377	N/A[e]	N/A[e]	N/A[e]	N/A[e]
	Diabetic foot	-0.0606	N/A[e]	N/A[e]	N/A[e]	N/A[e]

CCI, Charlson comorbidity index; DM, diabetes mellitus; DME, diabetic macular edema; N/A, not applicable; NPDR, non-proliferative diabetic retinopathy; SE, standard error; USD, united states dollar

* p<0.05, ** p<0.01, *** p<0.001

a Count model was conducted with negative binomial distribution, and standard error was calculated by bootstrapping.

b Since the observed median is zero, so a zero-inflated model was applied. The zero-inflated 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 Number of patients estimated after propensity score matching and outlier removal.

d Variable with an inclusive relationship was excluded from the ECM due to multicollinearity ("degeneration of posterior pole of eye").

e Variables were removed by backward elimination.

Conclusion

This retrospective cohort study estimated the economic burden of NPDR with DME patients compared to DM patients using real-world data in the aspect of patient-centered economic burden. The findings demonstrate significantly higher direct medical healthcare costs for NPDR with DME patients especially non-reimbursement costs and out-of-pocket costs. There is a limitation that the findings should be interpreted in the context of the specific study population and setting, as it uses data from a single hospital. However, these results provide valuable insights for healthcare policymakers, clinicians, and researchers working towards improving the management and prevention of diabetic retinopathy in developing cost-effective reimbursement strategies and accessible treatment options. Also, we found that OMOP-CDM allows for efficient cost analysis because of its well-organized vocabulary and tools including HADES and HERMES. We expect that various cost studies using the OMOP-CDM and the HERMES, including cost-effectiveness studies, will be possible in the future.

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