의학석사 학위논문

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이 논문을 의학석사 학위논문으로 제출함

2022년 4월

서울대학교 대학원
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ABSTRACT

Real-world treatment burden and patterns of patients with myopic choroidal neovascularization: Common Data Model in Ophthalmology

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Background: Real-world studies on the use of anti-vascular endothelial growth factor (anti-VEGF) drugs in the treatment of myopic choroidal neovascularization (mCNV) using large-scale data sources were scarcely implemented.

Purpose: This study aimed at characterizing the real-world treatment burden and treatment patterns of patients with mCNV.

Methods: This is a retrospective, observational study using CDM database (more than 2 million patients) selecting only treatment-naïve patients with mCNV visiting Seoul National University Bundang Hospital over the

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* The author of this thesis is a Global Korea Scholarship scholar sponsored by the Korean Government

18-year period (2003-2020). Outcomes were treatment burden (time trends of total/average number of prescriptions, mean number of prescriptions in the first year and the second year after initiating treatment, proportion of patients with no treatment in the second year) and treatment patterns (subsequent patterns of treatment according to the initial treatment). R, SQL and software packages from OHDSI Methods Library was used to analyze.

Results: Our final cohort included 94 patients with at least 1-year observation period. Overall, 96.8% of patients received anti-VEGF drugs as first-line treatment, with most of injections from bevacizumab. There was an increase trend over time in the total number of anti-VEGF injections in each calendar year. There was a drop in mean number of prescriptions in the second year compared to first year after starting therapies, from 2.14 to 0.46 (2006-2017) and 1.67 to 0.56 (2017-2020); and 76.71% of patients receiving no treatment in the second year; and the trend was similar irrespective of drug types. A majority of patients (86.2%) followed non-switching monotherapy. Bevacizumab in general was the most popular choice, either in the first-line (68.1%) or in the second-line (53.8%). Aflibercept was increasingly used as first-line treatment for patients with mCNV.

Conclusion: Anti-VEGF drugs have been dominantly used to treat mCNV as both first-line and second-line for the last decades. The effectiveness

of anti-VEGF drugs has been also demonstrated: non-switching monotherapy is sufficient for most of cases, and the treatment burden decrease substantially from the second year of treatment.

Keywords: mCNV, pathologic myopia, treatment pathways, anti-VEGF drugs, bevacizumab, average injections, CDM, OHDSI, observational study

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LIST OF ABBREVIATIONS

mCNV: myopic choroidal neovascularization

nAMD: neovascular age-related macular degeneration

CDM: Common Data Model

DMO: diabetic macular oedema

EMR: Electronic Medical Record

OHDSI: Observational Health Data Sciences and Informatics

PDT: photodynamic therapy

PTCG: laser photocoagulation

RVO: retinal vein occlusion

SNUBH: Seoul National University Bundang Hospital

SQL: structured query language

Anti-VEGF: anti-vascular endothelial growth factor

본문

INTRODUCTION

Myopia (short-sightedness or near-sightedness) is increasingly becoming a disease of great concern due to its consequencing impacts on socio-economic aspects.[1,2] In East Asia, including South Korea, where its prevalence and incidence are higher than those in other regions of the world,[2] this disease might even gain more attentions. According to several studies examining the epidemiology of myopia in children and young adults of South Korea, the prevalence of myopia (a definition of diopters less than -0.5 D) was 65.4 - 96.5%, and that of high myopia (less than -6.0 D) was around 6.9 - 21.61%.[3,4] High myopia has been well-known as a risk factor for pathologic myopia, a condition that could endanger people' s visual function.[5] A systematic review carried by Wong et al.(2013) found that the prevalence of pathologic myopia was approximately 0.9%-3.1%, and that of pathologic myopia-attributed visual impairment varied around 0.2%-1.4% (based on studies from Asian countries).[6] Due to Covid-19, that trend is now being exacerbated with a growing speed of myopia progression.[7,8]

One of the serious complications of pathologic myopia is myopic choroidal neovascularization (mCNV).[9] Despite just being the second most prevalent cause of CNVs (after age-related macular degeneration), in people aged less than 50 years old (working age group), mCNV accounted for the largest percentage among the causes leading to CNV, thus a main contributor to visual impairment in this age group.[10] The expansion of macular dystrophy or fibrosis as a result of mCNV is among the most sight-threatening events to patients after 5 years from mCNV onset.[9,11,12] However, mCNV has not been fully understood regarding its pathogenesis (several hypothetical theories suggested as mechanical stress, single nucleotide polymorphism, or haemodynamic theory),[13] so does the modality for the preventation or delay in development of mCNV.[11]

Until the emergence of anti-vascular endothelial growth factor (anti-VEGF) therapies on the treatment of retina diseases, the choices of treatment of mCNV had been still restricted to photodynamic therapy (PDT) for subfoveal mCNV and laser photocoagulation (PTCG) for extra or juxtafoveal mCNV. While PTCG had been widely used without adequate evidences in favor of its usage;[9] PDT, however, was an approved treatment of mCNV, but it did not prove efficiency in maintaining visual function and anatomical features for in the long run, together with PTCG.[14,15] Recently, with regards to the

pathogenesis of retina diseases, the neutralization of VEGF has been the priority and the core principle in addressing retinal/sub-retinal/choroidal neovascularization and vascular leakage.[16] Anti-VEGF drugs (ranibizumab, bevacizumab and aflibercept), in line with the proved theories, have been shown to be effective in the treatment of mCNV in the improvement of the visual outcomes, the slowing down of disease progression and recurrences in several clinical trials and real-world studies.[17-24]

However, in the world, very few post-trial real-world observational studies were carried out to examine treatment patterns in patients with mCNV (Willis et al.,2017; Yang et al.,2017).[25,26] Those research works even did not take account of treatment pathways (switching or adding therapies), nor did they examine the usage of both on and off-label drugs. In other words, based on those current treatment modalities, without adequate systematic review of evidences, clinicans have been empirically treating patients according to a trial-and-error approach, thus their questions on how real-world use of anti-VEGF drugs on mCNV (e.g. how many patients underwent certain mix of therapies or how time-varying patterns are) were still mostly obscured. The interaction of invoved local (patient-doctor relations) and general stakeholders (social factors) could create a unique output for each

patient under certain circumstances, thus the real-world patterns might be far more different than being visualized.

In addition, when it comes to the use of anti-VEGF drugs, involved parties (doctors, patients…etc) always concern about treatment burden as most patients often need multiple injections. Although scientists hypothesize that less injection burden may be experienced by patients with mCNV, patients still need to be on a regular monthly followed up then every 3 months after the disease activity have regressed (according to the prorenata (PRN) regimen).[22] Also, such questions as how treatment regimens have been applied in real clinical settings, how the frequency of injections varies over time, and how many injections are sufficient for suppressing mCNV activities, have not been addressed in much detail in previous published studies (Wu and Kung, 2014; Willis et al., 2017; Wecker et al., 2017; Ohno-Matsui et al., 2018).[25,28-30] In particular, there should be more extensive research about the topic of the annual treatment burden of patients with mCNV.

When it comes to studies conducted in South Korea, there was hardly any study that addresses those questions. It should be noted that anti-VEGF drugs were not covered by National Health Insurance Scheme (NHIS) for a long time in South Korea, therefore the claim database of NHIS is not suitable. Even when the coverage was approved, no post-surveillance studies using large-scale data sources

(e.g. studies by Health Insurance Review and Assessment Service) had been done. Therefore, it is increasingly of necessity to conduct further research to describe the treatment burden and patterns of patients with mCNV.

Nevertheless, the traditional approach of observational research has somehow failed to address up-to-date real-word evidences, lagging behind the "vivid picture" in real life. Recently, thanks to the growing torrent of big data in this digital era (Ophthalmology field is not an exception[31]), scientists have useful materials to head towards evidence-based medicine; but the big-data driven approach is sometimes problematic due to the lack of scalability and transparency of much published research. To overcome that arduous journey from source data to reliable evidence, Observational Medical Outcomes Partnership – Common Data Model (OMOP - CDM) was born. The compass of OMOP was "open science" or "science 2.0", which means the transparency in every single step of research and the accessibility for every single stakeholders involved.[32] CDM, a product of OHDSI community, has been grabbing attention of medical scientists thanks to its standardized structures, inter-operational ability among time and places, and validity in research implementation.[32] CDM also offers the flexibility to deal with different types of observational data (populations, care settings, data capture process, health system) and

allows to produce different types of evidences desired as well.[32] Although CDM has been applied in various medical specialties worldwide (United States, Europe … etc) and nationwide (South Korea),[33-36] its application in the field of Ophthalmology is still restricted. It is important to take the first steps in actualizing the CDM application in Eye Research, making it as a norm.

In Seoul National University Bundang Hospital (SNUBH), our Retina research team with other collaborators has been implemented several multi-center CDM-related researches in the field of Ophthalmology.[37-39] We are taking advantage of the preexisting package of ATLAS (a web-based interface for implementation of CDM researches) to make preliminary studies using Characterization analysis. Recently, a CDM-based study on the incidence of endophthalmitis after anti-VEGF drugs has been published.[37] In this subsequent pilot study of CDM applicability in the field of Ophthalmology in South Korea using the electronic medical record (EMR)-derived OMOP CDM, the research objectives were as follows:

1. To characterize the treatment burden of patients with myopic choroidal neovascularization.
2. To characterize the treatment patterns of patients with myopic choroidal neovascularization.

MATERIALS AND METHODS

Observational Medical Outcomes Partnership (OMOP) and Common Data Model (CDM)

In this data-driven era, as the amount of health observational data continues to grow, medical scientists would like to take advantage of this invaluable real-world evidence to aid in their clinical decision. Despite certain concerns about the accuracy and validity of such those data, US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are the two pioneers on establishing a standardized observational data system,[40] and Observational Medical Outcomes Partnership (OMOP) was then introduced in the year of 2010.[41]

OMOP, initially born with a focus of drug safety study, then was utilized with the following major objectives:[32] (1) Providing a standardized approach to content, structure and semantics in order for study reproduction in every site that share the same method, (2) Creating an open-science community where all the procedures, codes, and designs are shared together with a goal of transparency, (3) Establishing a global network for clinicians, data engineers, customers, authorities to stay together to discuss, collaborate and aid in observational research implementation. See **Figure 1** for understanding more about OHDSI Community.

Common Data Model (CDM) is an entity under OMOP, in which a standardized data model facilitates the concurrent implementation of data analysis in discrete data sources. CDM is a person-centric relational database, which means the information of patients is distributed into different tables linking together and all joining into the PERSON table. A glance of the basic structure of this database was provided in **FIGURE 2** below.[32] Further knowledge of CDM could be elaborated through The Book of OHDSI, Chapter 4 – Common Data Model.[32]

Before conducting any CDM research, a relatively important step is to Extract – Transform – Load (ETL), which is merely transcribed as "harmonizing the original data (medical claims, or EMR) into the CDM". That will manipulate scientists to speak the same language when co-researching or discussing scientifically, regardless of the input of source data (different designs in different infrastructures, different types like structured, semi-structured, or unstructured data). This step is implemented with a collaboration of domain experts, data scientists, and informaticians.[32] Refer to Chapter 6 – Extract Transform Load of OHDSI book for further insights.[32] EMR, which mostly consists structured data, can be linked to CDM with less efforts than other kinds of data. For further complicated analysis, natural language processing (NLP) could be used to extract information from unstructured data such as doctors' notes or text laboratory results. Since CDM is not complete

at the beginning and is currently under development by our own users, Ophthalmologist ourselves have collaborated to create our own ETL process for specific ophthalmologic and ophthalmic measurements. Several research teams are working on this project. Remarkably, a research team in SNUBH and other collaborators has successfully created a new software for standardized, structured, and interoperable results in ophthalmic examinations (Mun et al., 2021).[38] They had initial success with Optical Coherence Tomography (OCT) images, which could be made applicable to images from other ophthalmic and medical devices, and could be augmented through a standardized database like CDM. When this study was being carried out, Ophthalmologic-specific data conversion was still incomplete; but thanks to the help of Department of Medical Informatics, current basic mappings are sufficient to perform several preliminary studies. In South Korea, a report of EMR-to-CDM conversion in a tertiary hospital has been published.[42]

When it comes to standard vocabularies, a range of standard nomenclature systems have been recognized, mostly taking advantages of preexisting vocabularies, such as Systematized Nomenclature of Medicine, clinical terms (SNOMED CT), RxNorm and RxNorm extension for drugs, and Logical Observation Identifiers Names and Codes (LOINC) for diagnosis codes, drug codes, and laboratory results and clinical measurements, respectively.[43,44] Those standardized vocabularies

are targeted in the so-called "standardizing mapping" process, in which the same vocabularies are shared regardless of the source data.

To enable CDM users to access to those standard vocabularies, OMOP community also provides ATHENA (https://athena.ohdsi.org) is a website that allows users to download standard terminologies to load into their source database.[32] Standard vocabularies are of course organized in hierarchial manner, with ancestors and descendants. This is beneficial in the domain of CONDITION and DRUGS (already completely organized), where we can retrieve all diagnoses which are smaller categories of a particular disease and all drugs with an ingredient. An example of hierarchial structure of CDM vocabularies in our research is shown in **Figure 4**. For our research, refer to **Table 1** for detailed standard vocabularies used.

Another prominent feature is ATLAS, a powerful open-source tool generated by OHDSI Community.[32] Scientists could define and create phenotypes (cohorts) by merely using ATLAS; but in cases of queries that are out of its power, they can either partially modify it by either utilizing provided source SQL codes from ATLAS, or even entirely create their own queries using SQL. There are two ways of creating a cohort: the rule-based or probabilistic approach. In our research, rule-based method was used with adequate components:[32] (1) Domain (which tables that data belong to; e.g. DRUG_EXPOSURE table for drugs); (2)

Concept set (a clinically meaningful definition made from concepts; e.g. **Table 1** shows the concept set of "anti-VEGF drugs" consisting of 3 concepts: Aflibercept, Bevacizumab, Ranibizumab); (3) Domain-specific attribute (additional attributes; e.g. in **Table 1,** Right eye Sphere Autorefractor.auto with VALUE_AS_NUMBER ≤ -6, this is just an example due to its insufficiency to denote the Spherical Equivalence) and temporal logic (occurring time; e.g. in **Table 1**, Myopic choroidal neovascularization within 365 days before and 365 days after the Entry event). Some of the features in ATLAS which were used in our research are introduced in **Figure 3.** We took advantage of ATLAS to create the initial cohort and use SQL to limit the Inclusion and Exclusion criteria to produce the final cohort.

Moreover, ATLAS provides several established R-based analytic packages for newbies in OHDSI CDM, which could address most of epidemiologic researches, such as Characterization, Population-Level Estimation, and Patient-Level Prediction.[32] In our study, only Characterization was used in three aspects: Database Level Characterization (to understand the characteristics of the database), Cohort Characterization (to produce baseline characteristics), and Treatment Pathways (to understand treatment patterns).[32]

Finally, evidence quality is also an aspect that should be taken into consideration whenever every CDM-based study comes out,[32] because the

majority of observational data is not generated for research purpose. Evidence quality can be classified as data quality (reviewing research process: from gathering, storing, analyzing and publishing), clinical validity (examining the characteristics of the data source, evaluating the performance of cohort in an analysis and assessing the generalizability), software validity (evaluating the adherence to programming practices, implementing code review/double coding) and method validity (testing the underlying assumptions, using control hypotheses to test the study design).[32] Taking advantages of provided tools developed OHDSI Community for checking evidence quality (details could be seen in Chapter 15-18, OHDSI Book[32]), we used ACHILLES software to check the data quality and Phevaluator package to check the clinical quality of our specific study. While ACHILLES allows us to check the accuracy of the mappings process by providing a detailed comparison of source code and standard code over time via checkCohortSourceCodes function, Phevaluator provides the examination of sensitivity, specificity, positive predictive value, negative predictive value of a generated cohort in comparison with the reality. Our software validity was re-evaluated by clinicians and data scientist involved in the study by means of double checking the generated codes.

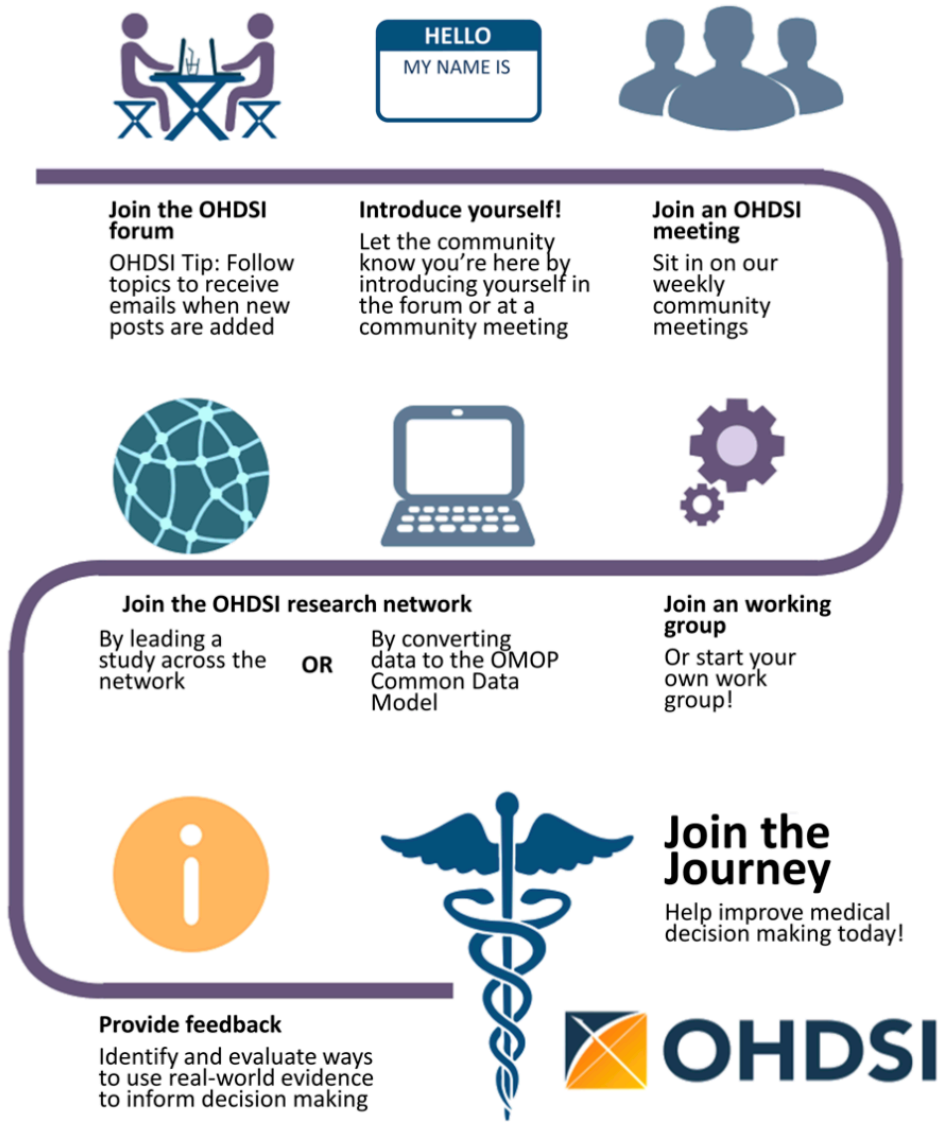


Figure 1. OHDSI Journey (OHDSI Community, 2019, p.12)[32]

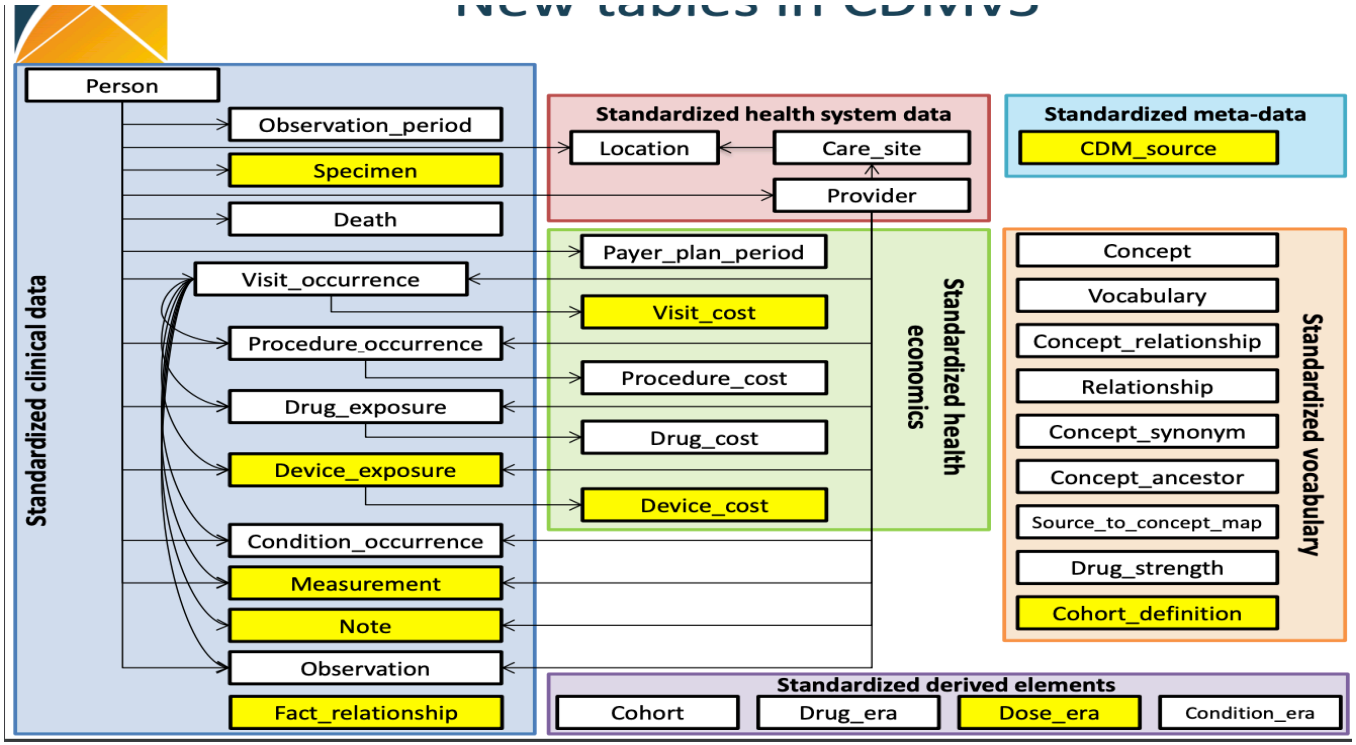


Figure 2. Overview of all tables in the CDM version 5.0. Not all relationships between tables are shown. The image was captured from OHDSI Tutorials (slide 6)

https://www.ohdsi.org/wp-content/uploads/2015/04/OHDSI-CDM-v4-to-v5-Conversion.pdf

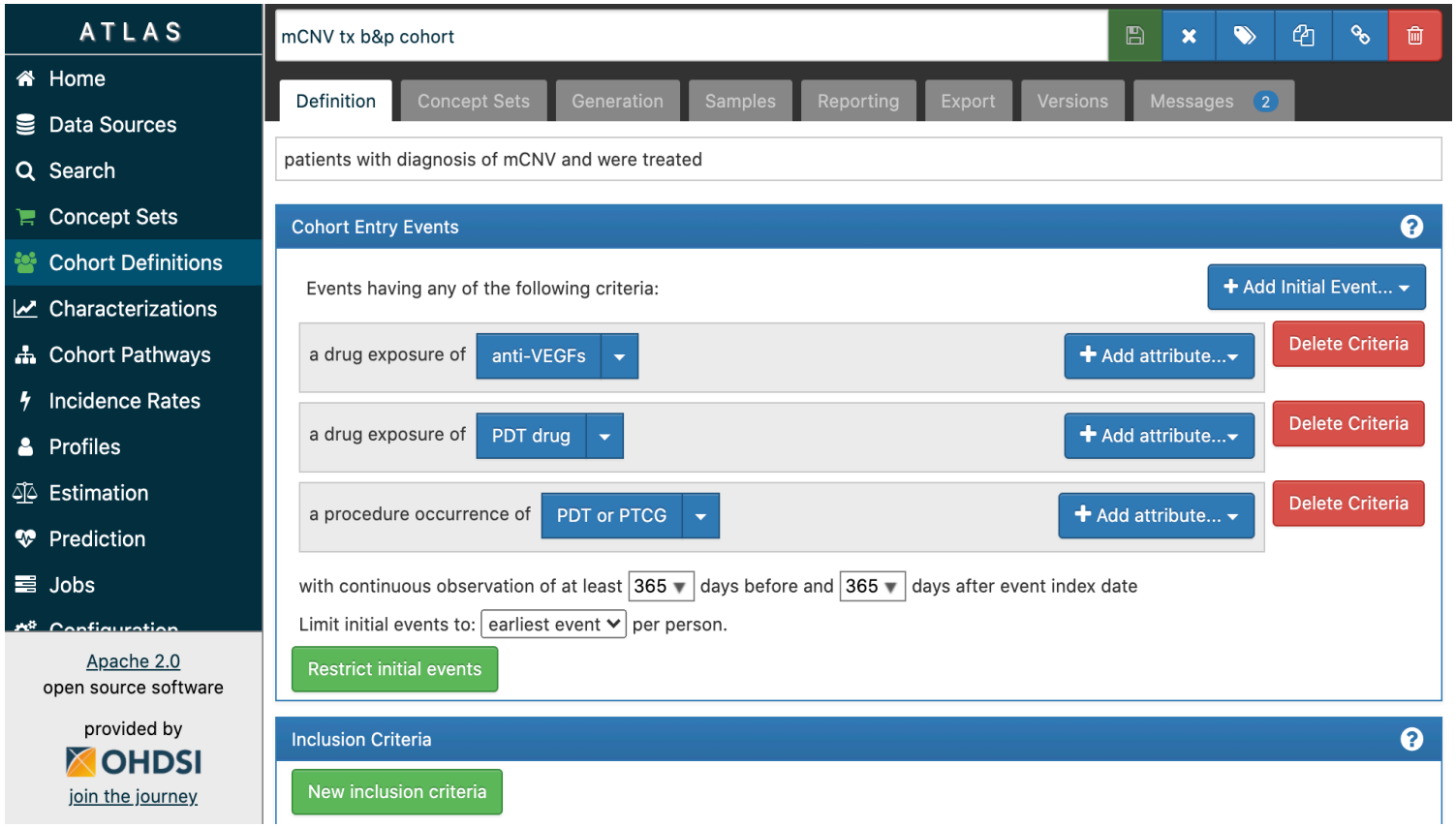


Figure 3. Creating a cohort of mCNV using web-based interface ATLAS

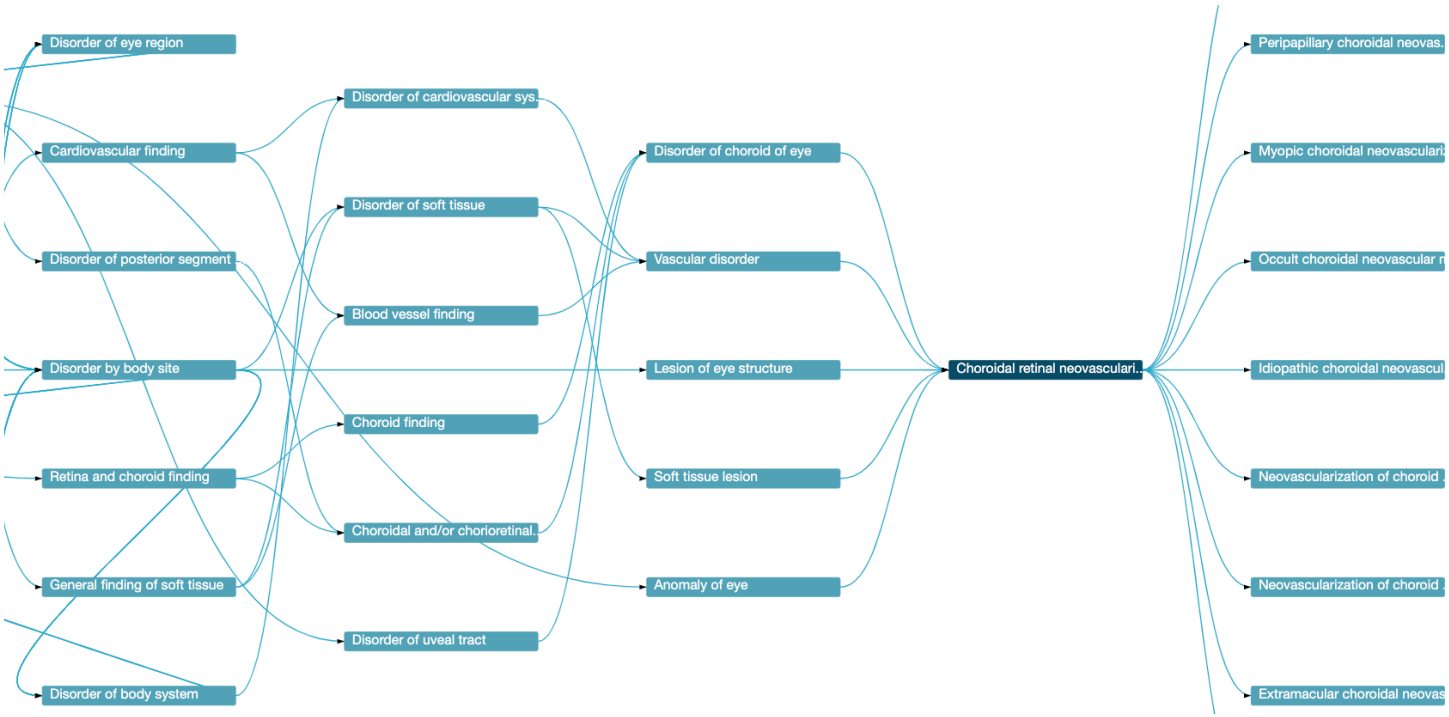


Figure 4. Hierarchy of the condition "choroidal neovascularization"

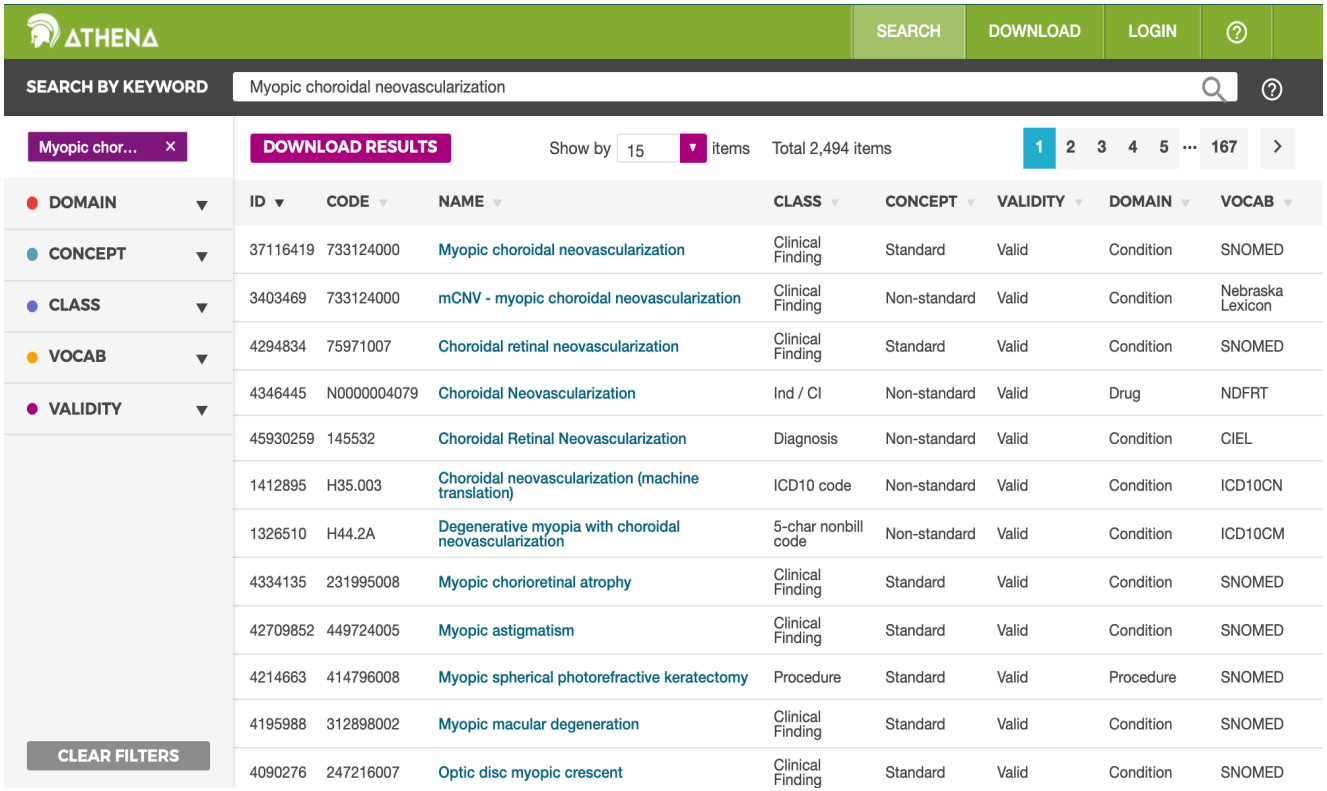


Figure 5. Searching a terminology using ATHENA

Study design and Data source

Our study was carried out in a retrospective, observational fashion. Electronic medical records (EMR) obtained from our tertiary hospital, Seoul National University Bundang Hospital (SNUBH), was readily harmonized into the standardized OMOP CDM (version 5.3.1) in a comprehensive way. Our EMR-derived database included a number of 2,006,478 patients in total, and the time period of recruitment was from 02/04/2013 to 31/12/2020. **Table 2** shows the characteristics of our database in detail.

Study population

The cohort of interest was created using open-source ATLAS in combination with SQL. This standardized way of cohort creation will alleviate the use of this process for further multi-center studies in the future.[45]

We created a rule-based cohort of patients with treated myopic choroidal neovascularization (mCNV) from the existing SNUBH database. All patients first exposed (treatment-naïve) to any of the three anti-VEGF drugs (ranibizumab, bevacizumab, and aflibercept) or any of the two procedures (laser photocoagulation (PTCG) and photodynamic therapy (PDT)) were included, and that was defined as the cohort entry event. The index date was defined as the date of first

exposure. We require the observation period should be 365 days before (to make sure those patients are treatment-naïve) and 365 days after the index date (long enough to observe the subsequent prescriptions, and based on the previous knowledge that after 1 year the number of treatment sessions for mCNV required decrease substantially[28]).

For inclusion criteria, those patients with either at least a diagnosis code of mCNV, or those who had a combination of CNV diagnoses together with Spherical Equivalence (SE) ≤ - 6.0 diopters or a diagnosis of high myopia/degenerative myopia, which were recorded within 365 days before or 365 days after, were included in the cohort. Those who had other anti-VEGF drugs required-treatment diseases were also excluded from the final cohort.[46] Refer **Table 1** for further details of the concepts' codes and **Supplementary** section regarding the process of creating the cohort using SQL. The Cohort Exit Event was the end of Observation Period.

Figure 6 demonstrates the Schematic diagram for cohort selection for mCNV treatment patterns, while **Figure 7** shows Patient selection flow chart.

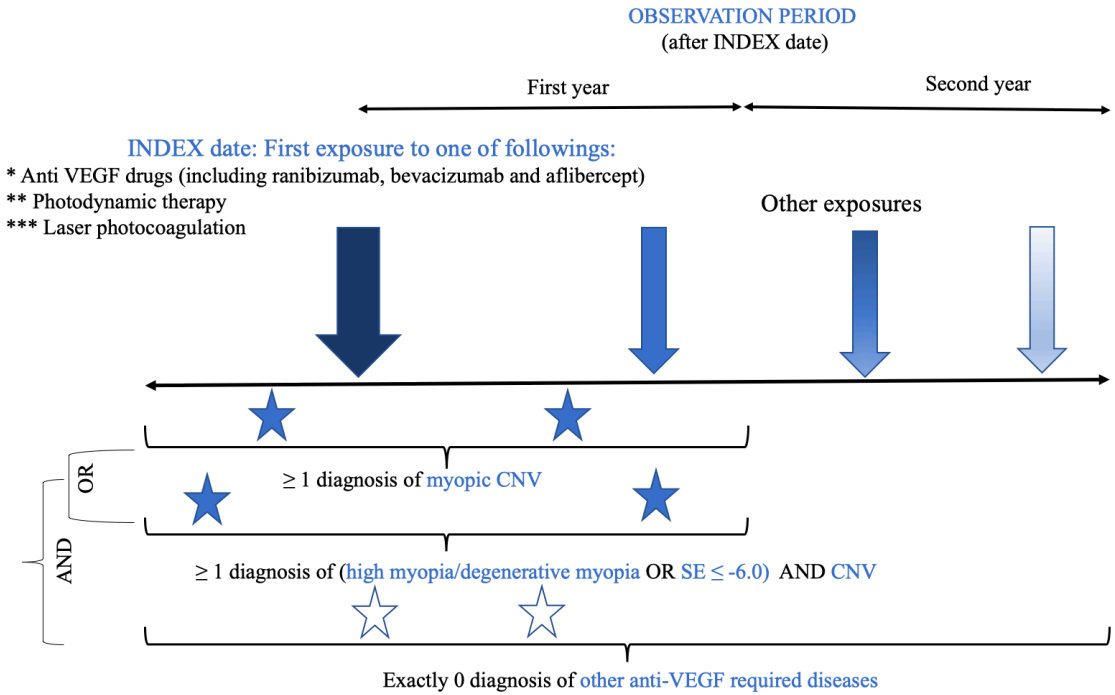


Figure 6. Diagram of cohort selection for treated mCNV patients.
Down arrows represent the exposures, filled/empty stars illustrate the presence/absence of diagnoses.
SE: Spherical Equivalent, CNV: choroidal neovascularization

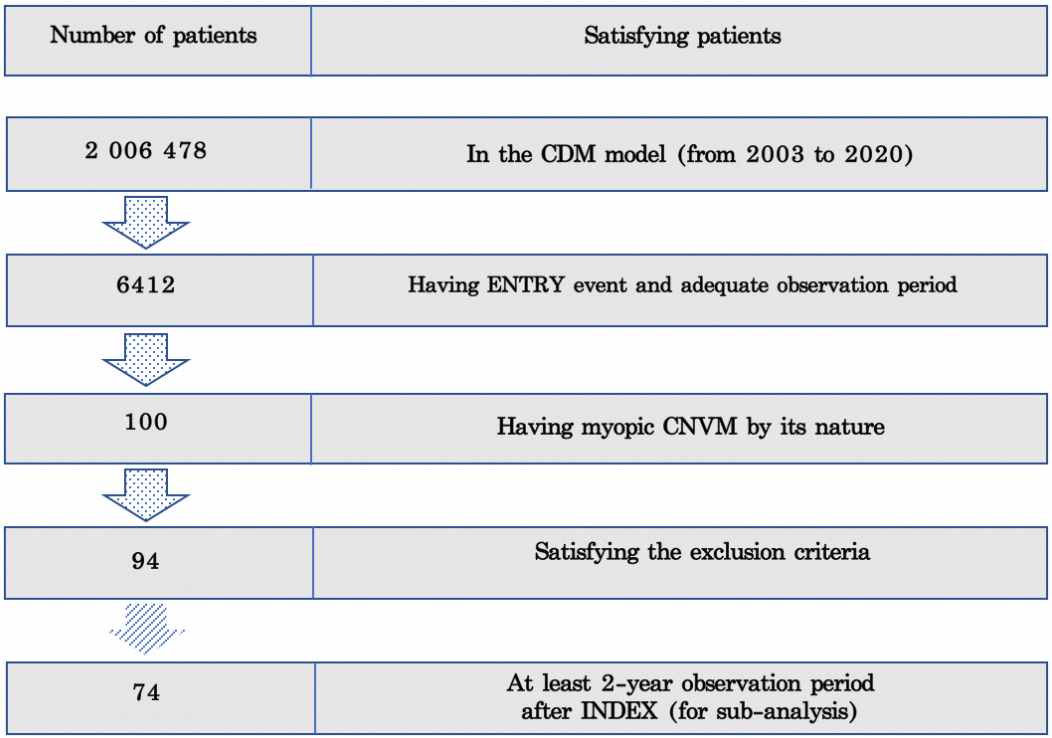


Figure 7. Patient selection flow chart

Table 1. Identification for concepts in CDM

	Concept ID	Concept Name	Domain	Standard Concept Caption	Exclude	Descendant	Mapped
Anti-VEGF drugs	19080982	Ranibizumab	Drug	Standard	X	O	O
	1397141	Bevacizumab	Drug	Standard	X	O	O
	40244266	Aflibercept	Drug	Standard	X	O	O
Procedure of laser photocoagulation	4232642	Photocoagulation of eye	Procedure	Standard	X	O	O
Procedure of photodynamic therapy	4117979	Photodynamic therapy	Procedure	Standard	X	O	O
Use of photosensitizer drugs	1593778	Verteporfin 15MG	Drug	Standard	X	O	O
mCNV Diagnosis	37116419	Myopic choroidal neovascularization	Condition	Standard	X	O	O
CNV Diagnosis	4294834	Choroidal retinal neovascularization	Condition	Standard	X	O	O
	4143622	Severe myopia	Condition	Standard	X	O	O

High myopia Detection through Diagnosis input	381281	Degenerative progressive high myopia	Condition	Standard	X	O	O
High myopia Detection through Spherical Equivalent	3000744	Right eye Sphere Autorefractor.auto	Measurement	Standard	X	O	O
	3003500	Left eye Sphere Autorefractor.auto	Measurement	Standard	X	O	O
	3033346	Right eye Cylinder Autorefractor.auto	Measurement	Standard	X	O	O
	3022777	Left eye Cylinder Autorefractor.auto	Measurement	Standard	X	O	O
Visual Acuity Calculation	2061000007	Corrected Visual Acuity (Decimal) Right Eye	Measurement	Non-standard	X	O	O
	2061000008	Corrected Visual Acuity (Decimal) Left Eye	Measurement	Non-standard	X	O	O
	21491746	Visual acuity uncorrected Right eye by Snellen chart	Measurement	Standard	X	O	O

	21491747	Visual acuity uncorrected Left eye by Snellen chart	Measurement	Standard	X	O	O
Exclusion of other retinal diseases requiring anti-VEGF drugs	4028363	Uveitis	Condition	Standard	X	O	O
	4174977	Retinopathy due to diabetes mellitus	Condition	Standard	X	O	O
	440392	Retinal vascular occlusion	Condition	Standard	X	O	O
	4334245	Retinal artery occlusion	Condition	Standard	X	O	O
	377270	Hereditary retinal dystrophy	Condition	Standard	X	O	O
	376966	Exudative age-related macular degeneration	Condition	Standard	X	O	O
	372894	Central serous chorioretinopathy	Condition	Standard	X	O	O

Vocabularies used for these concepts were SNOMED for Diagnosis, RxNorm for Drug, and LOINC/SNOMED for Procedure. Mapping from EMR to CDM vocabularies were entirely done beforehand in a comprehensive way in order not to miss any concepts. An "O" in the Descendants means all Descendants concepts were also included in the selection. An "O" in the Mapped allows us to search for non-standard concepts so that we do not miss any events. An "X" in the Exclude just means we include this concept for searching.

Study outcomes

Baseline characteristics of patients including in the cohort were characterized by using the Characterization function in ATLAS. It allows us to describe the baseline features (at the time of entering the cohort) by counting as follows: age (grouped per 5-year interval), gender (male vs female), race (Korean vs others), medical history (general, cardiovascular diseases, neoplasm; mainly describing concepts of diseases usually occurring in the pilot study of CDM). Self-coding R language was used to produce the myopic status (displayed in diopters) and the visual acuity at baseline (maximum values among values measured at index date or at the most recent date before the index date, presented in LogMAR).

The patterns of exposures to anti-VEGF drugs and/or PTCG/PDT of patients were analyzed. To begin with, treatment pathways were defined based on the sequences of these prescriptions, including the switching to a new prescription.[45] Next, the patterns were derived from these pathways by removing duplications of previously occurring prescriptions at subsequent steps: such duplications were not counted. To visually describe the patterns, Sunburst and Sankey diagrams were utilized to demonstrate these sequences. In the Sunburst, the first ring depicts the proportions of patients following each type of therapies defined by ENTRY events, and the subsequent rings describe the percentages of patients having other

therapies among those who followed a certain first-line therapy. The Sankey diagram include two columns, between which each bar is connected together, and its meaning is relatively similar to Sunburst plot.

Also, treatment burden was also examined. The definition of treatment burden may vary and include numerous domains to be perfectly conceptualized.[47] With the available data that we have, we focused on the workload that patients and doctors have to confront when guidelines are enacted. Therefore, the number of patients receiving prescriptions and the number of prescriptions given are two parameters to be investigated, as well as the average number per patient that could be inferred. In our research, based on the time that prescriptions were performed (drug exposure date), we first calculated the annual total number and the average number of prescriptions per patient in each calendar year during the analysis period to display the time trends. Second, according to the index date of each patient, the frequencies of exposures to those prescriptions in the first year and the second year after index date were then calculated, then the mean and the standard deviation (SD) number of prescriptions were drawn 〔In this second analysis, SD is not an important aspect from our perspective. It is important to note that CDM offers us the ability to summarize the aggregated results without individual data of each database.[32] Therefore, the pooled SD can only be calculated like what are done in meta-analysis, which could be sometimes time-

consuming and decelerate the speed of multi-center research on the treatment burden〕.

Sub-analysis included: (1) Dividing the patients into two groups, those with observation periods of 1 year versus 2 years (as we calculated the burden in year 1 and year 2, it is essential for a sub analysis of those completed the 2-year observation period), (2) Classifying the patients into different groups according to their initial treatment, (3) Dividing the patients according to three time periods depending on when their index date was. As the era of anti-VEGF drugs use in eyes for retinal diseases first started in 2005 after its approval in the previous year,[18] the first analysis period would be from 02/04/2013 to 31/12/2004. The middle period should be from 01/01/2005 to 30/11/2017 since the hallmark of 01/12/2017 was when ranibizumab and aflibercept were approved and reimbursed by insurance companies on using for mCNV in South Korea; and then came the remaining period (01/02/2017 to 31/12/2020).

Lastly, in treated mCNV patients with at least 2-year observation period, we calculated the proportion of patients who experienced no prescriptions in the second year after their index dates. We also divided this analysis into different time periods and different initial treatment.

Data Analysis

Our study merely provided a descriptive summary of data without specific assumptions. Validated methods are readily available in OHDSI Methods Library. In this study, we used the preexisting function in ATLAS (version 2.10.1) with modification the source code (using open-source R package) for treatment pathway. R (R Studio version 3.6.3) and SQL (PostgreSQL version 8.0.2) was also utilized to display the treatment burden. See **Supplementary** section for detailed analysis code. The edited or self-developed source codes could be made publicly available to either be run on local system or other participating databases.[33,45]

Ethics

Our study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice Guidelines. Institutional Review Board (IRB) was obtained from SNUBH Committee (IRB Number X-2112-727-902, acceptance date 09/12/2021) and because of CDM's nature of anonymizing the identities of patients and the retrospective observational design itself, informed consent was waived.

RESULTS

Patients' selection flow

Figure 7 illustrates the patient selection flowchart. Our final cohort includes a total of 94 patients, 74 of which had at least 2 years of follow-up.

Patients' characteristics

The detailed baseline characteristics of each group at first exposure are shown in **Table 3.** The age distribution of treated patients with mCNV varied widely, from the age of adolescent (10-19 years old) to elderly people (80-84 years old). However, a majority of patients aged from 50 years old above (67.38%), with the group of 50-59 accounted for the most of the cases (34.04%). Female individuals dominated the number of patients, with more than two-thirds of the cases (73.4%). Interestingly, no patients were foreigners, mean that 100% had Korean nationality. The overall medical history of participants was generally good, with less than 5% having chronic diseases such as diabetes or hypertension as well as other cardiovascular diseases; despite the accompanied visual system disorder were high (87.23%) due to the obvious nature of the study population of mCNV. The visual acuity of patients at baseline were 0.29 ± 0.31 (n=84), and myopia status were -5.79 ± 5.04 (n=73).

Treatment burden

A vast majority of people received anti-VEGF drugs as the initial treatment, with 3 out of 94 as an exception. When it comes to time trends for treatment burden according to drug exposure date, the total number of injections performed each year generally increased over the time (despite a slight decrease in the last analysis period, maybe due to few patients), in which bevacizumab injections were more popular compared to other therapies. Regarding the average number of prescriptions over the years, a similar trend was witnessed. While the figure in the second analysis period ranged from 1.5 to 2.5 prescriptions per patients per year, that in the third period approximately approached an average of 3 per patient. **Figure 9** and **Figure 10** show time trends of the total and the average number of prescriptions per patient during the study period.

Table 4 shows the number of prescriptions calculated based on each patient's index date regardless of the duration of observation period. Because the figure for PDT and PTCG was relatively small in our study, treatment burden mainly focused on the number of anti-VEGF injections. Since anti-VEGF drugs were not widely used in the first analysis period (1/2003-12/2005), visible changes in the treatment burden are apparently shown in the second and third period rather than the first

one. As is clearly seen in the table, there was a dramatic decline in the treatment burden in the second year in comparison to the first year after treatment. For instance, the mean number of injections per patient saw a substantial decline in the year two after initiating treatment, from 2.14 to 0.46, from 1.67 to 0.56 in the second and third analysis period, respectively. With regards to the trends of each distinctive anti-VEGF drugs, they all show the same trend with the overall figure; in the second period, patients initiating bevacizumab still had the highest mean number of injections (2.20 injections in the first year of treatment), then dropping to just 0.63 in the second year; that of the third period was from 1.00 to 0 injections, respectively. Ranibizumab and aflibercept first-users, however, needed a smaller number of injections in the first year, with a mean of 2.11 and 1.67 during the second analysis period. It is noted that in the third period, aflibercept outnumbered bevacizumab in the mean number of injections in the first year (2.20 vs 1.00). Patients treated with those two drugs even needed an optimal mean number of injections in the second year after treatment, ranging from 0 to 0.05 in the second analysis period. The treatment burden within first year after initiating treatment also followed a slightly decreasing pattern over time. While the mean number of injections per person within first year after initiating treatment in the second analysis period stood at around 2.14, there was a sudden drop to just 1.67 in the last analysis period.

Table 5 demonstrated the sub-analysis of those who underwent at least 2 years follow-up. Due to the insufficient observation period of patients enrolled in the third period, we mainly assessed the second period in this sub analysis. As a part of sensitive analysis, similar trends were seen in the changes from first year of treatment to second year of treatment, as well as in each kind of drugs.

Table 6 denoted the proportion of patients without any prescriptions given in the second year after index date among those who had at least 2 years of observation period. In the second analysis period (which contained adequate number of patients to assess), it was clearly seen that a large majority (76.71%) did not undergo any treatment episodes in the second year. The figure for bevacizumab was 67.31% and perfectly 100% in case of ranibizumab, aflibercept and PDT.

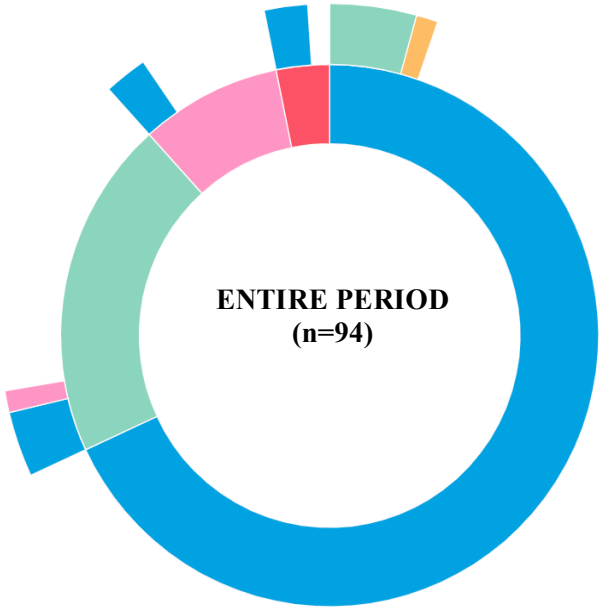
Treatment patterns

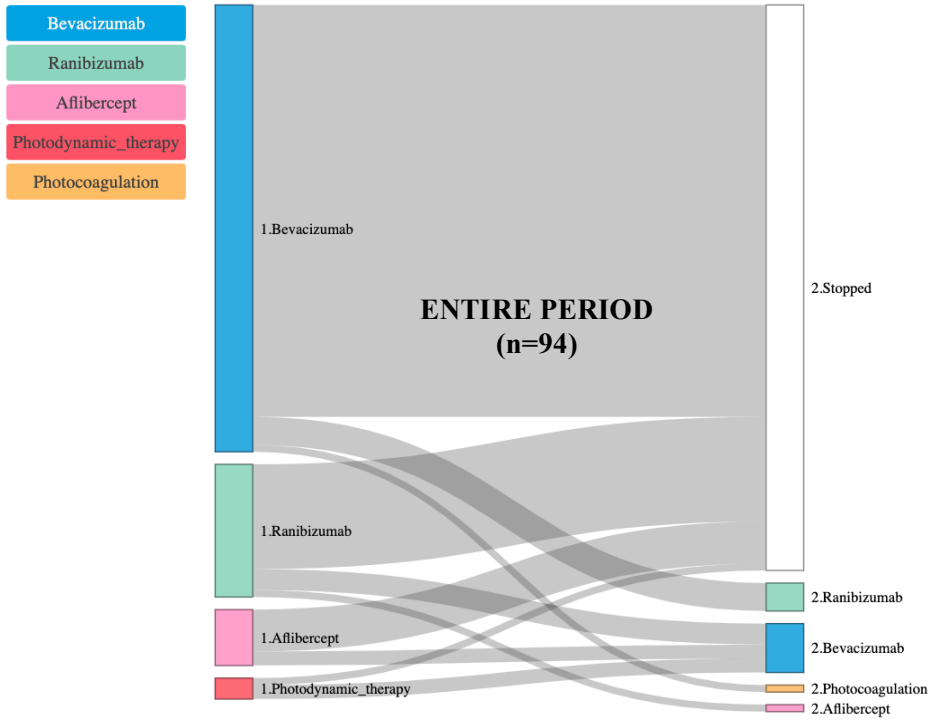
Ten unique treatment patterns of patients with mCNV were identified during the study period. Refer to **Figure 8** for the entire period presentation of treatment pathways from a minimum of one to a maximum of two prescriptions. The most prevalent first-line treatment for patients with mCNV belonged to bevacizumab (68.1%), whose figure was far higher than the second most popular, ranibizumab (20.2%). Aflibercept only accounted for a small figure of first-line treatments, at 8.51%; and

PDT was also rarely selected, at a modest figure of 3.19%. Interestingly, PTCG was not used at a first-line treatment in any cases. It was found that bevacizumab was still the most common choice of second-line anti-VEGF drugs among all patients with multitherapy regardless of their first-line treatment status, at 53.8%; which outnumbered the figure for ranibizumab (30.8%), PTCG (7.7%), and aflibercept (7.7%).

Among types of first-line drugs' users, loyal-to-one-drug users stood at a large percentage (86.2%) and the rest 13.8% of patients opted for a switch in therapies to second-line therapy. No third-line ones were seen in the treatment pattern of patients with mCNV. Of those patients who initiated their treatment with bevacizumab (68.1% of total cases), a vast majority of patients (92.2%) did not need alternative therapy, as only a small number of patients switched to ranibizumab (6.25%) or PDT (1.5%). The same pattern was seen in other therapies, with only small proportion of patients in need of surrogate therapy. In detail, in the case of first-line treatment with ranibizumab, the percentages of patients continuing the same therapy, switching to bevacizumab and aflibercept were 78.9%, 15.8%, and 5.3%, respectively. With regards to aflibercept, while mono-therapy was seen in 75%, 25% of patients had their treatment modalities changing to bevacizumab. In contrast, patients who began with PDT had a higher rate of therapy alteration, at 66.6%.

Regarding sub-analysis in the divided period. Before 01/2006, PTCG seemed to be the only treatment of mCNV although only 1 case of treatment was included in this period. In that only one case, there was an initial treatment of PDT and then switching to bevacizumab. The second analysis period saw the same pattern with bevacizumab still dominating the popular treatment' s league. In detail, during the period from 01/2006 to 11/2017, bevacizumab first-line users accounted for 72.6%. The period of 12/2017 to 12/2020 witnessed an absolute preference of anti-VEGF treatments, when no sessions of PTCG or PDT were performed. Interestingly, the novel aflibercept took place of bevacizumab to be the dominant choice of first-line treatment (55.6% vs 33.3%) in this period.


ENTIRE PERIOD
(n=94)


Bevacizumab
Ranibizumab
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(n=94)
2.Stopped
2.Ranibizumab
2.Bevacizumab
2.Photocoagulation
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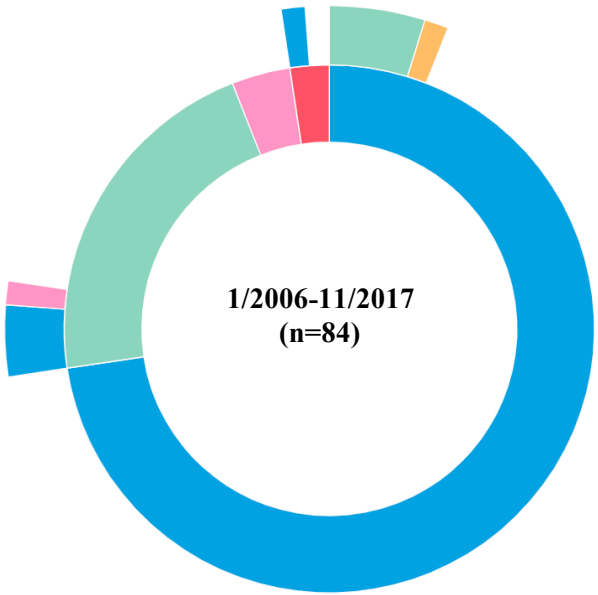
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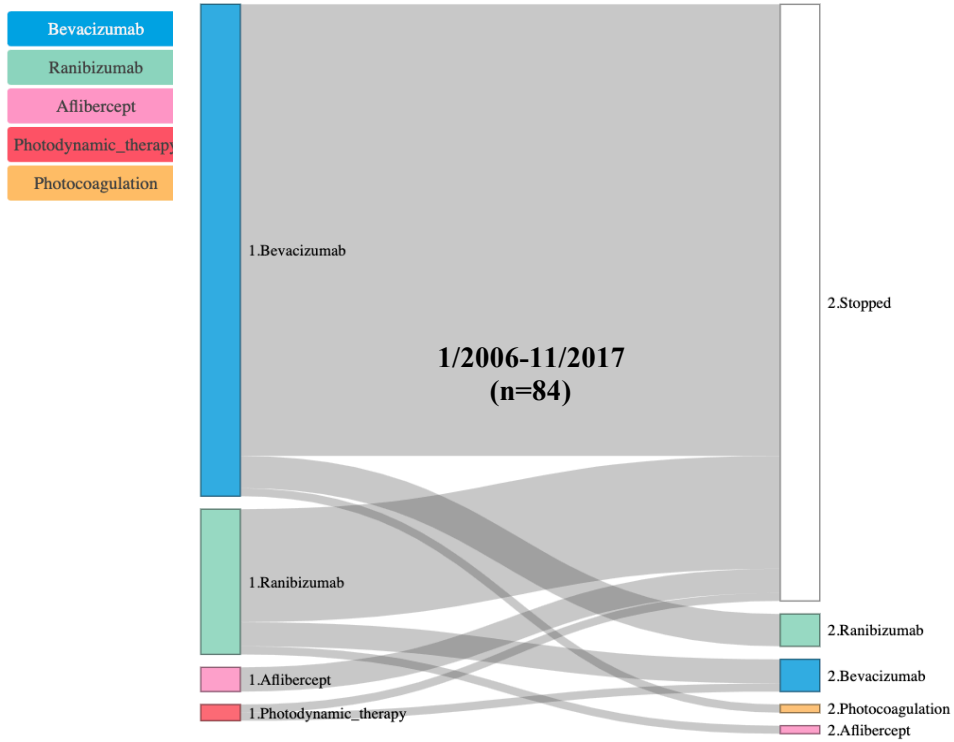
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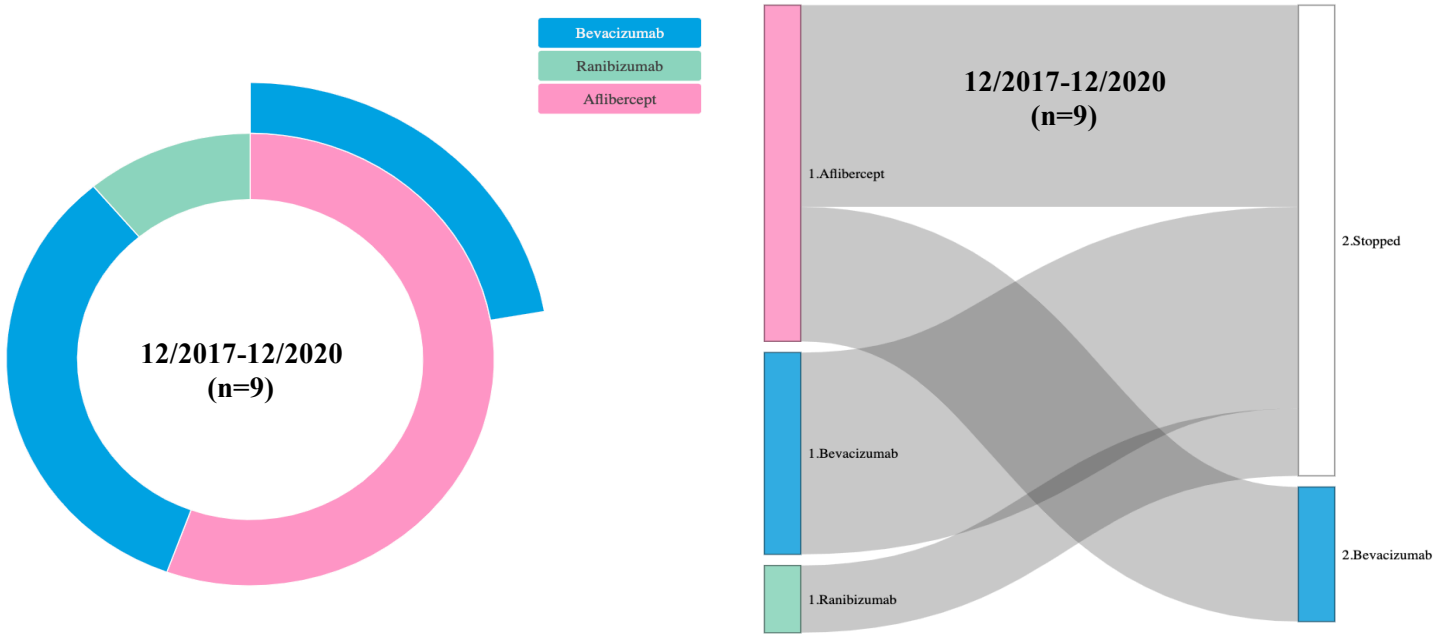

Figure 8. Sunburst and Sankey diagram of treatment pathways of patients with mCNV. First ring/column indicated the first-line treatment. The second ring/the connected second column described the subsequent treatments among those following the certain first line ones. Each period was plotted according to index date of each patient, subsequent treatment episodes were counted until the end of observation period (cohort exit date).

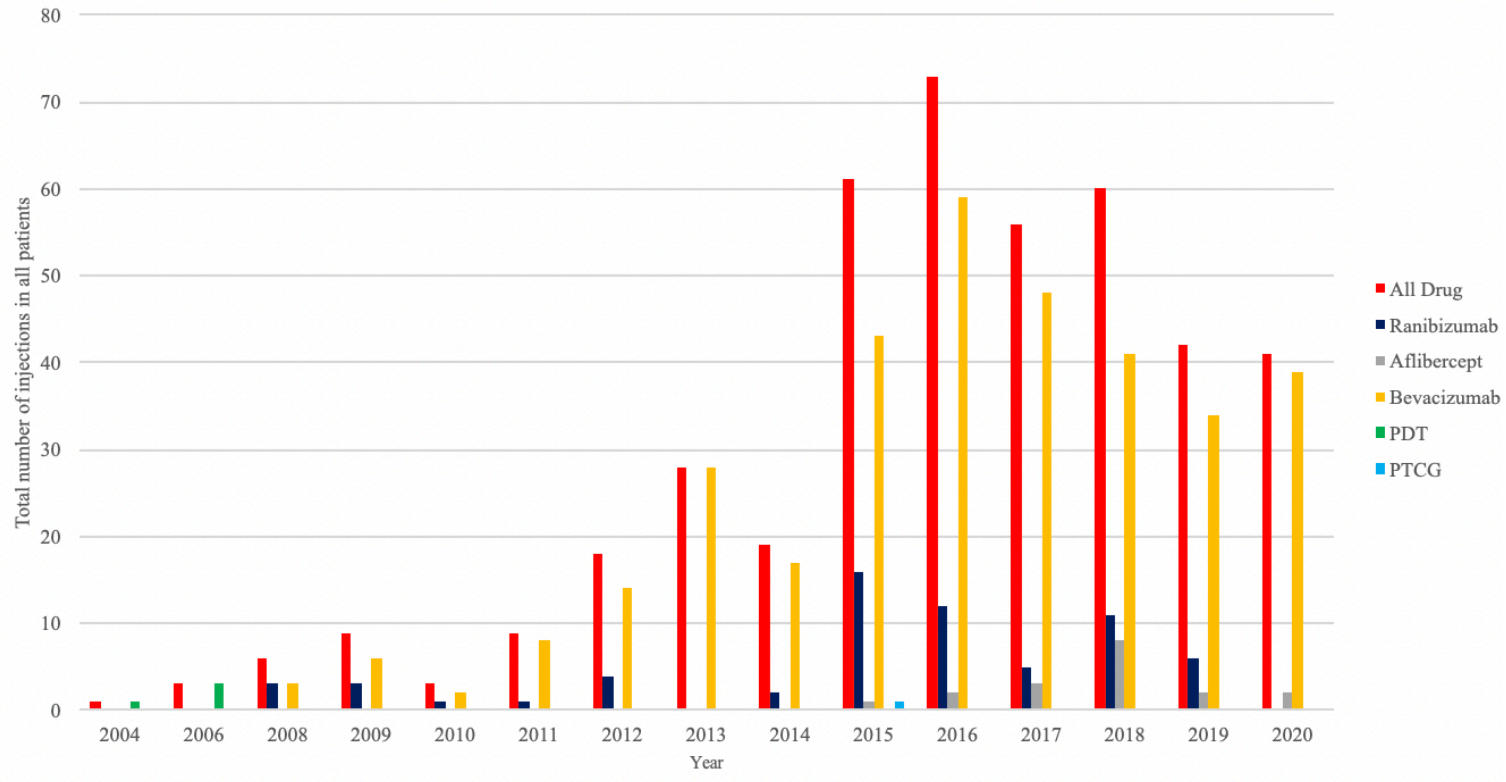

Figure 9. Time trends for total number of prescriptions of patients with mCNV during all time period
PDT: Photodynamic therapy, PTCG: laser photocoagulation

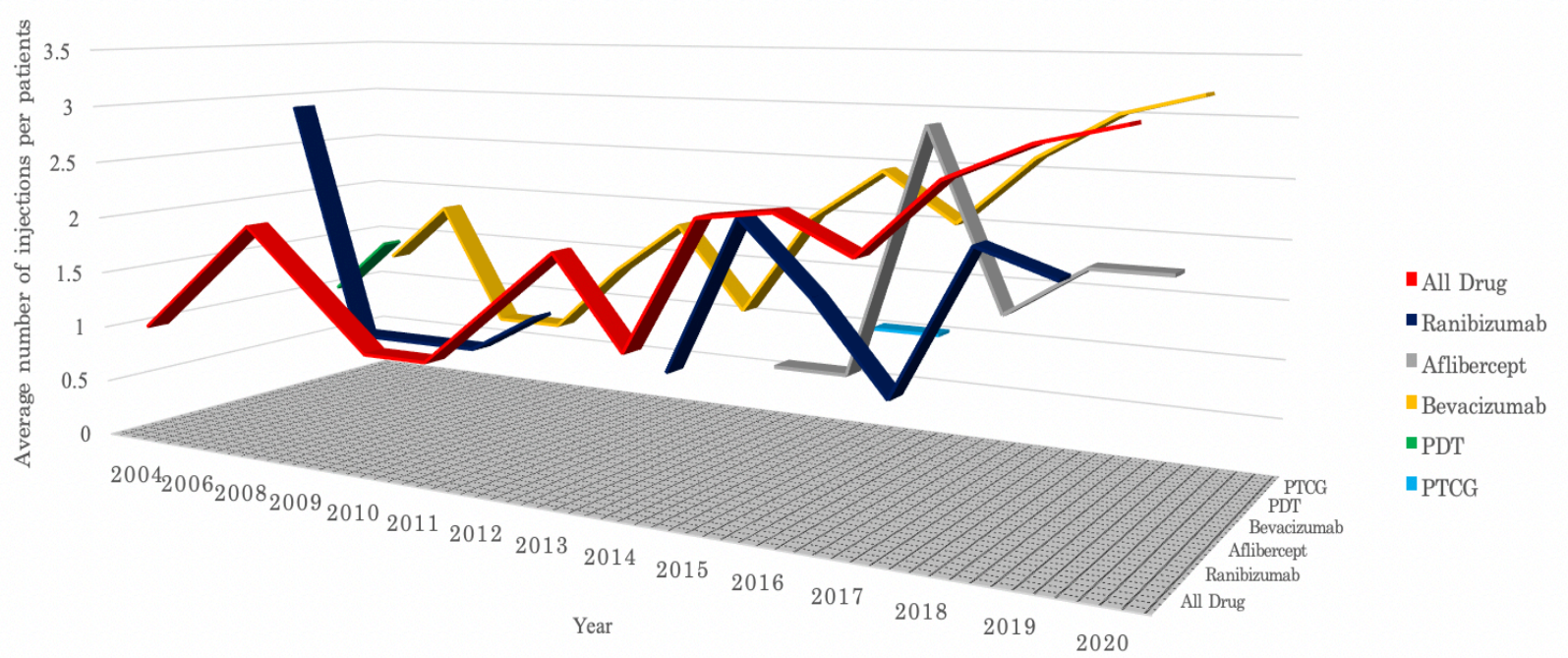

Figure 10. Time trends for average number of prescriptions per patient with mCNV during all time period
PDT: Photodynamic therapy, PTCG: laser photocoagulation

Table 2. Overall characteristic of the database

Data Source	Number of patients	Number of male	Start Date (yyyy/mm/dd)	End Date (yyyy/mm/dd)
SNUBH	2,006,478	955,106	2003/04/02	2020/12/31

SNUBH: Seoul National University Bundang Hospital

Table 3. Baseline characteristics of all patients with mCNV in the final cohort

Characteristics	Count	% (n =94)
Age group		
10 - 19	4	4.26
20 - 29	2	2.13
30 - 39	6	6.38
40 - 49	19	20.21
50 - 59	32	34.04
60 - 69	16	17.02
70 - 79	10	10.64
80 - 84	5	5.32
Gender: Female	69	73.40
Race		
Korean	94	100
Unknown	0	0
Medical history: General		
Diabetes mellitus	3	3.19
Gastroesophageal reflux disease	1	1.06
Hyperlipidemia	0	0
Hypertensive disorder	3	3.19

Osteoarthritis	1	1.06
Renal impairment	0	0
Visual system disorder	82	87.23
Medical history: Cardiovascular disease		
Cerebrovascular disease	1	1.06
Coronary arteriosclerosis	1	1.06
Heart disease	3	3.19
Ischemic heart disease	0	0
Venous thrombosis	0	0
Medical history: Neoplasms		
Malignant neoplastic disease	2	2.13
Characteristics	Mean ± SD	n
Myopia status (spherical diopter)	-5.79 ± 5.04	73
Visual acuity (logMAR)	0.29 ± 0.31	84

Table 4. The number of prescriptions in all patients with mCNV regardless of observation period (n=94): Patients were categorized into three different analysis periods based on their index date, and into different groups based on which therapies initiated first. The mean and the standard deviation (SD) of prescriptions in the first year and in the second year after index date was calculated.

	Time period	Year after treatment initiation	Overall (n=94)	Initial treatment				
				Bevacizumab (n=63)	Ranibizumab (n=20)	Aflibercept (n=8)	PTCG (n=0)	PDT (n=3)
Number of prescriptions (mean ± SD)			(n=1)	(n=0)	(n=0)	(n=0)	(n=0)	(n=1)
	04/2003-12/2005	1st year	1.00±0.00	NA	NA	NA	NA	1.00±0.00
		2nd year	0.00±0.00	NA	NA	NA	NA	0.00±0.00
			(n=84)	(n=60)	(n=19)	(n=3)	(n=0)	(n=2)
	01/2006-11/2017	1st year	2.14±1.91	2.20±2.07	2.11±1.52	1.67±0.94	NA	1.50±0.50
		2nd year	0.46±1.24	0.63±1.43	0.05±0.22	0.00±0.00	NA	0.00±0.00
			(n=9)	(n=3)	(n=1)	(n=5)	(n=0)	(n=0)
	12/2017-12/2020	1st year	1.67±0.82	1.00±0.00	1.00±0.00	2.20±0.75	NA	NA
		2nd year	0.56±1.07	0.00±0.00	0.00±0.00	1.00±1.26	NA	NA

PTCG: laser photocoagulation, PDT: photodynamic therapy, NA: not available

Table 5. The number of prescriptions in patients with mCNV with at least 2 years of observation period after index date (n=74): Patients were categorized into three different analysis periods based on their index date, and into different groups based on which therapies initiated first. The average number of prescriptions in the first year and in the second year after index date was calculated.

	Time period	Year after treatment initiation	Overall (n=74)	Initial treatment				
				Bevacizumab (n=52)	Ranibizumab (n=17)	Aflibercept (n=2)	PTCG (n=0)	PDT (n=3)
Number of prescriptions (mean ± SD)			(n=1)	(n=0)	(n=0)	(n=0)	(n=0)	(n=1)
	04/2003-12/2005	1st year	1.00±0.00	NA	NA	NA	NA	1.00±0.00
		2nd year	0.00±0.00	NA	NA	NA	NA	0.00±0.00
			(n=73)	(n=52)	(n=17)	(n=2)	(n=0)	(n=2)
	01/2006-11/2017	1st year	2.23±2.00	2.27±2.18	2.24±1.55	2.00±1.00	NA	1.50±0.50
		2nd year	0.52±1.31	0.73±1.51	0.00±0.00	0.00±0.00	NA	0.00±0.00
			(n=0)	(n=0)	(n=0)	(n=0)	(n=0)	(n=0)
	12/2017-12/2020	1st year	NA	NA	NA	NA	NA	NA
		2nd year	NA	NA	NA	NA	NA	NA

PTCG: laser photocoagulation, PDT: photodynamic therapy, NA: not available

Table 6. Proportion of patients without any prescriptions given in the second year after the index date among those who had at least 2 years of observation period. Patients were categorized into three different analysis periods based on their index date, and into different groups based on which therapies initiated first.

Time period	Overall (n=74)	Bevacizumab (n=52)	Ranibizumab (n=17)	Aflibercept (n=2)	PTCG (n=0)	PDT (n=3)
01/2003 - 12/2005	100% (1/1)	NA	NA	NA	NA	100% (1/1)
01/2006 - 11/2017	76.71% (56/73)	67.31% (35/52)	100% (17/17)	100% (2/2)	NA	100% (2/2)
12/2017 - 12/2020	NA	NA	NA	NA	NA	NA

PTCG: laser photocoagulation, PDT: photodynamic therapy, NA: not available

DISCUSSION

In the current study, we found that only 10 unique treatment pathways were detected, and most of the sequences stopped at the second step of treatment. Bevacizumab demonstrated its dominant therapy of choices when treating mCNV, at above 60%, either in the first line or in the second line of treatment. The total number of prescriptions tended to increase year by year along with the increasingly prevalent use of anti-VEGF drugs. Individually, there was a reduction in the mean number of prescriptions in the second year of treatment compared with the previous year, at 1.67-2.14 for the first year and around 0.5 for the second year of treatment processes. To the best of our knowledge, our studies are among the very first studies that describe the treatment burden and patterns of patients with mCNV in South Korea, and among very few studies in the world that provided insights into this area. The study also aimed at evaluating the feasibility of applying OHDSI CDM into observational research in the field of Ophthalmology to give a big picture of real-world practice.

Principal findings

In our study, the characteristics of patients best reflects those in literature of mCNV. Most of included individuals were above 50 years

old as age is a risk factor for developing mCNV.[10,48] However, as age varied widely, it may limit the interpretation of further findings. Females accounted for 73.4%, which might be justified by the preponderance of female gender in developing mCNV.[49,50] Although the female predilection is not clearly in older population,[49,50] this might be because a significant 32.98% of patients in our study aged under 60 years old. The visual acuity and myopia status at baseline were just for reference to know the characteristics of cohort as there still exists incompleteness in the data. We only included in the cohort those patients have been treated and excluded those with observation (no offered treatment), justifying that only 94 out of more than 2 million patients in the database were selected. Some patient may also be missed due to comorbid retina diseases that fell into our exclusion criteria. The number of people with 2 years of observation was 72/94, which was relatively high. We did not evaluate the outcome of visual acuity or patients' symptoms due to the inherent limitations of secondary data, but the high rate of patients' return in this case may be as a result of our clinicians' choice and patients' obedience to undergo follow-up.

Our study showed that anti-VEGFs ruled the league of treatment choice with 91/94 patients opting for as first-line treatment. Over the years, both the trends for using anti-VEGF agents and the number of anti-VEGF injections increased. It was consistent with current knowledge,[26]

because up to now, anti-VEGF agents have been proving its efficiency and safety in the treatment of mCNV, in both anatomic and functional outcomes,[21,51-53] and they are also superior to other modalities (demonstrated by two studies: RADIANCE[21] and BRILLIANCE[54]). Before 2005, when anti-VEGFs were not introduced, extremely few patients were included in the study as most of them would be in the observation population (due to limited options of treatment and patients' disobedience) and the rest would be no choice but undergoing PDT or PTCG, yet not often. In the pre-anti-VEGF era, several studies found that the effectiveness of PDT and PTCG in the treatment of sub-foveal and extra- or justa-foveal mCNV, respectively. However, PTCG accelerates the process of scaring and atrophy, thus deteriorating the visual functions and increasing the recurrent rate.[15,55] Photodynamic therapy (PDT), tend to be more beneficial to patients than placebo, but could only maintain visual acuity rather than improving it (in both short-term and long-term).[56,57] It is known as the culprit of subsequent chorioretinal atrophy in the long run.[58] The scarce usage of PDT after anti-VEGF era could further be cemented by its failure to demonstrate its effectiveness in a combined protocol with Triamcinolone compared to PDT alone in the treatment of mCNV in a study by Chan et al. (2006).[59]

There was a remarkable decline of treatment burden from the first to the second year in our study: the mean number of injection dropped from

around 2 to just 0.5 and the proportion of patients without prescriptions given in the second year after index date was 76.71%; suggesting that one episode of initial treatment may be sometimes adequate to deactivate the disease. It was in accordance with the established guideline of PRN (prorenata) treatment without loading phases regimen (1 injection in the first episode and then as needed) in treating patients with mCNV.[44] Several studies supported this result as in a five-year real-life PRN injection patterns study in AMD, DMO, RVO and mCNV patients performed by Wecker et al.(2016), the median number of injections of mCNV decreased from more than 3 to just under 0.5 in the subsequent year.[28] And when it comes to examining the association between injections in year 1 and consecutive year, it suggested that the injection number of following years was lower than year 1, and the velocity of injection accumulation over 5-year period became lower as time passed by.[28] In the real-world IRIS study, which used cloud-based ophthalmic data registry (a sort of big data like our study), among those who received at least 1 injection within one year after diagnosis, nearly 50% of injection frequencies felt into the first month, and 20% in the second month.[25] In a 12-month observational study on ranibizumab-naïve patients with mCNV by Ohno-Matsui et al.(2018), more than half (52.2%) of patients received just one injection in the study period, almost 90% of patients took less or equal than three.[29] In a 24-month follow up

observational study on ranibizumab by Wu and Kung (2014), a decline in the mean number of injections from 2.82 in the first year to 0.5 in the second year was seen.[30] Luckily, when we only assessed those patients with at least 2-year observation period (n=74), no significant difference was seen in the treatment burden between the first and the second year. This means there was probably no loss-to-follow-up bias in this case (characteristics of those losing follow-up did not differ from those remain in the cohort till end).

In our study, the number of injections within 1 year after initiating the treatment varied from 1.67-2.14 depending on the analysis period (before and after approval of ranibizumab and aflibercept), which was in accordance with results of previous studies[20,21,25,60,61]. Indeed, being different from other diseases (such as AMD and DMO) that required at least 3 loading doses,[62,63] the PRN-without-loading-doses treatment regimen- which showed its effectiveness on the treatment mCNV in a two famous clinical trials (RADIANCE and MYRROR)[20,21]- allows patients to receive less frequent injections.[19] In the RADIANCE study, a median number of injection of 2.0 was witnessed in the group of 1 episode of (ranibizumab or PDT) followed by PRN;[21] and MYRROR study depicted similar results with a median of 2.0 injections in the aflibercept group.[20] With regards to real-world study, our results were not so far from that of IRIS study, where 2.8 was the mean number of injections for anti-

VEGFs in mCNV.[25] The consistence in the results in favor of a less intensive treatment was also seen in a study with just 23 subjects in Japan conducted by Nakanishi et al.(2011): mean: 1.35 ± 0.71 injections (within 24 months);[61] or in a retrospective study examining the number of injections until the resolution of mCNV by Okuma et al.(2021): mean: 1.18 ± 0.44.[60] It is remarkably to note that real-world practice is not only individualized to each patient by its nature but also is influenced by treatment guideline and updates, and is decided by insurance companies' rules and government policies. Although the comparison was challenging, given that clinical trials recruited patients in a stringent fashion than observational studies and different studies have different research settings and have different baseline characteristics of patients; we can confidently conclude that the treatment burden of mCNV was less heavy than other diseases in real-world settings.[23,28]

It should be noticed that our study did not have baseline data related to the location and the size of mCNV (e.g. extra-foveal mCNV may not require treatment[64]), and other concomitant features such as macular schisis that can eventually affect the need for further injections.[65] Also, a tertiary hospital like SNUBH have accepted referrals from other provinces, thus the far distance between patients' homes and the retina clinic should be questioned on the assessment of patients' compliance because it may affect the observed number of injections. Our study did

not include data of patients' location, and such association between patients' locations and hospitals was not observed in a study by Wecker et al.(2016).[28] Finally, whether under-treatment (non adherence or non persistence of patients) may drive the underestimation of treatment burden still remain uncertain. The lack of data in visual outcomes - still be ongoing towards proper mapping to CDM in our hospital- refrained us to evaluate the adequateness of the provided amount of injections. We did not know for sure whether it was the case that patients experienced a more favorable prognosis or it was due to the irreversible scarring as a subsequent episode of CNV after treating anti-VEGF drugs (45.3% by 2 year in a study in nAMD patients by Daniel et al.(2014)[66]). Real-world performance of anti-VEGF therapy was not that good as indicated in the clinical trials: there was an association between poor outcomes and less-than-needed treatment frequency.[67]

Our study revealed a slight disparity, but not statistically significant, between three anti-VEGF agents in the mean number of injections in the first year. In 2006-2017, the mean number of aflibercept first users was lower than that of bevacizumab and ranibizumab ones (1.67 vs 2.20, 2.11; respectively). This may be as a result of the later introduction of aflibercept and its superiority over two former drugs.[68,69] Interestingly, in 2017-2020, an opposite pattern was seen: aflibercept users even received more injections. However, the number of patients of each subgroup in this

period was small and data may not be properly input with adequate observation period, which may eventually undermine the interpretation of this finding. A study by Corazza et al. (2020), which retrospectively analyzed 96 eyes in a 3-year follow-up period, supported our result. They demonstrated no difference in the average number of injections between three anti-VEGF drugs (bevacizumab, ranibizumab, and aflibercept).[70] But it should be noted that only patients with monotherapy were included in the study, therefore, a switching in therapies was ignored, which may omit the counting of second or maybe third-line drugs. Taking a look at the mean number of injections in the second year after index date, we can see a higher prevalence of bevacizumab than the rest in both second and third analysis period; but as the number of patients was relatively small in other drugs and the standard deviations was overlapped, not much inference could be drawn from that disparity.

Due to less options for treatment of mCNV compared with AMD or DMO, it was obvious that less unique treatment pathways (10) were observed. In our study, bevacizumab proved to be the most prominent choice of mCNV for both first and second line of treatment. This drug is more prevalent administered off-label thanks to it affordable prices and non-inferiority in the treatment of mCNV.[22,61] It also allows retina specialists to use freely in individualized patients without strict restrictions on disease activity evidences (worsened visual acuity, newly-developed

metamorphopsia, hemorrhage on fundus image, retina fluids on OCT, and leakage on FA).[13] Therefore, it was preferable in case of long-term treatment or arising problems with insurance companies or poor financial status of patients. Ranibizumab appeared in the market earlier and has been more affordable than aflibercept, reasonably justified why it outweighed the latter in the drug of choices (20.2% versus 10%). PDT has been shown not to be efficient in terms of improving outcomes or sustaining its long-term effect[54], therefore less likely to be used over time (only 3.19%).

Most of the patients in the study were candidates for pure monotherapy (non-switching, non-adding monotherapy), at 86.2%, which could be justified just by the effectiveness of mCNV therapies, particularly the good adaptive response in mCNV in comparison with in other anti-VEGF required diseases.[23,52] Okuma et al. (2021) demonstrated that the duration to achieve the resolution of mCNV by anti-VEGF agents was just 1.12-1.50 months.[60] Biases in favor of pure monotherapy, but meanwhile patients abandoning their treatment or following disguised monotherapy conversion in reality, may have little chance to happen. For example, it may be not reasonable if patients stop their treatment (because of sight-threating complications of mCNV probably interfering their visual functions), seeking for other hospitals (as study was conducted in a tertiary level hospital with high-end retina services), or searching for

surrogate treatments provided outside of official medical facilities (as little was known except orthodox treatment). Regarding conversion to another monotherapy, literature on this problem has been still in its infancy. In our study, there were not only users switching to more potent anti-VEGF molecules (e.g. bevacizumab < ranibizumab < aflibercept),[71] but also users undergoing the opposite way. First, the reason why patients switched from bevacizumab to ranibizumab/aflibercept, or ranibizumab to aflibercept might be attributed to a number of etiologies: a trial of more potent agents to replace the poorer response one, the availability and the affordability of ranibizumab and aflibercept thanks to its approval and license in Korea. Bevacizumab receivers in place of ranibizumab or aflibercept might have their non-medical reasons, either due to the financial problem (off-label bevacizumab is much more affordable than the rest[72]), the rigid rules of medical insurance coverage limit, or a shortage of drugs supplies. These reasons behind switching could be addressed in future studies as current CDM database still lacks information on this matter. When it comes to adding therapies to the preexisting therapies, our study did not examine this issue entirely because it needs certain strict definition of temporal criteria to know when a new therapy appears, is it either a switching or an adding therapy? In fact, there is no reason to use a combination of anti-VEGF drugs since they share the same mechanism of action. Unlike the case of central serous chorioretinopathy (CSC) or polypoidal choroidal

vasculopathy (PCV) which demonstrated the additive effects of concomitant use of PDT plus anti-VEGF drug,[73,74] PDT and PTCG themselves are not a suitable regimen for mCNV. Therefore, in our study, there were cases that switched from PDT to anti-VEGF drugs, which could be justified by the increase in visual acuity after switching proved in RADIANCE trial.[21]

Sub-period analysis demonstrated that before 1/2006, no treatment of anti-VEGF agents was provided, which was consistent with the date of introduction of those agents. The same treatment patterns were produced in the second analysis period compared to the entire period, which may be a result of the plausible subgroup effects. After 12/2017, the novel therapy aflibercept outnumbered bevacizumab in terms of the most popular first-line treatment for mCNV. It may be justified by aflibercept's superiority against ranibizumab in terms of better final visual outcomes,[68] and against bevacizumab in terms of less treatment burden during 12-month period.[69]

Strengths and limitations

There are certain strengths and limitations of the study that should be admitted. The first and foremost strength of this study is that we can assess off-label use and non-reimbursement options. Most of the previously conducted studies neglected this usage due to the limited

strength of the data. In South Korea, the National Health Insurance claim database could not capture the treatment of mCNV because aflibercept and ranibizumab were not covered until 2017, while bevacizumab is an off-label drug. Our study used EMR data which was completely eligible to cover the real-world treatment in a comprehensive way. In this case, it would be selection bias without assessing bevacizumab because it did, in reality, dominate treatment patterns over the period. After 2017, due to the small number of patients (probably the data was not perfectly updated with enough observation period), we cannot see the clear changes in treatment patterns. But when a large multi-center study was conducted based on this pilot study, knowing that 2017 was when the completion of licensing of ranibizumab and aflibercept in South Korea, a difference in the treatment modalities of choice would be forecasted to be seen.

Second, using CDM to address the research question in our study is a notable advantage because of its eligibility with big data. Currently, available traditional sampling and statistical methods have been insufficient to characterize the real-world practice while treatment patterns and burden would be the key to deepen our understandings of what have been and are happening in clinical settings and also be the tools for evaluating the applications of guidelines into reality. Our study included a large EMR-based CDM of SNUBH with 2,006,478 patients being input to produce 94 patients that satisfied the target population of

study. Compared with the traditional sampling method, it would take us 18 years to finish collecting enough samples in case of prospective studies, or if we just review the EMR in a retrospective fashion, it would be very time-consuming, labor-intensive, and more prone to human errors. CDM provides us with the very flexible searching and dealing with the queries, which are standardized and are able to extend to other databases sharing the same CDM structure.[75] In addition to the well-known criteria of ensuring the quality of evidence, namely repeatable, reproducible, replicable, generalizable, robust, and calibrated,[32] CDM may create a so-called "reusable" characteristic as concepts, cohorts and analysis in a study could be reused for another research that needs those kinds of "puzzle pieces", thus accelerate the implementation of a new study. For example, well-understood concepts (anti-VEGF drugs, PDT, laser photocoagulation) and cohort (treatment naïve patients with exposure to those concepts ± having diagnosis of mCNV) could be swiftly extracted to be reused for another study related to treatment of mCNV; or the analysis of treatment burden and patterns could be re-delivered meaningfully in the same investigation of another disease (especially retina diseases).

In addition, our study is among rare studies underlining the treatment burden and patterns of mCNV in the world. The results of our study could contribute to the overall picture of treatment burden. In the future, when taking into account the humane perspectives when enacting clinical

guidelines, treatment burden may play an important role in the decision making. It is because there are considerable consequences of overburden: non adherence to the treatment regimen, and negligibility to medical consults in the future.[76] Also, patients bear the burden in different ways, depending on their socio-demographic and clinical characteristics.[76] However, drug companies have no interests and motives in the investment of evaluating this perspective, making it being scarcely investigated. Further qualitative studies on the topic of treatment burden of mCNV as well as diseases requiring anti-VEGF drugs could base on our preliminary data to progress. Second, treatment patterns have been changing a lot. Adamis et al.(2020) argues that recent clinical trials have demonstrated an efficacy ceiling for anti-VEGF agents,[18] which means that we already achieved the maximum potential effects (with the highest dose and potency) of anti-VEGFs on the improvement of outcomes. In the future, more modalities for the treatment of mCNV would be introduced. In addition to VEGF, other molecular signals have been of interest in targeting, such as placental growth factor, Tie2 pathway, or platelet-derived growth-factor B...etc.[16] Even with the current mechanism, several other potential therapies may be added into the treatment regimen of mCNV in the future. Recently, Conbercept, a novel VEGFR 1&2 inhibitor drug sharing the same mechanism with aflibercept, has proved its effectiveness and safety in nAMD (Nie et al.,2021).[77] Byooviz

(ranibizumab-nuna, Samsung Bioepis) – a biosimilar drug - is a good example made in Korea, which gained approval from FDA in 09/2021.[78] Or long-acting Susvimo (ranibizumab implant, 100mg/ml), which are believed to be a "game changer" in terms of reducing the treatment burden, was approved for treatment of wet, neovascular age-related macular degeneration.[79] We can add those treatment variants into our study frame in the future to optimize current treatment strategies with the current real-world practice.

Nevertheless, certain limitations still exist due to the pristine EMR-based CDM model and our retrospective observational design of study. First, not fully-mapped CDM database prevented us to assess further outcomes, and other related variables for the robustness of the data. For example, we do not differentiate between the left eye and the right eye because data on this is still not complete. But the fellow eye does not always share the same problem with the affected eye, and analysis on separate eyes should be done to produce meaningful results. Additional injections might happen in the fellow eye due to the new development of another anti-VEGF drugs required diseases, which might be not recorded in the EMR due to uncertainty of diagnosis.

Second, retrospective design could result in missing data in the measurement of patients' exposure without giving us the chances to rescue it. Although we only included in study those patients with at least

1 year of observation period, some people may experience recurrent mCNV events - which may need addition injections – falling out of the observation period. Okuma et al.(2021) found an overall time to recurrence of mCNV of 24 months ± 28.8, especially longer for those treated with bevacizumab, at 46.7 ± 35.4.[60] Study assessing only bevacizumab treatment for mCNV in South Korea discovered that there was a large number patients having relapse episodes (39.5%), and the time to first relapse was 19.5 ± 15.4 months (Lee et al., 2019).[80] Although the standard deviation of time relapse was high, it implied that the recurrence of mCNV was not easily to be predicted. Those events could not be observed in our study due to lack of time (included later near the end day of EMR database) or loss to-follow-up. The issue of loss-to-follow-up is also another limitation of EMR because EMR is not integrated in a united manner across hospitals, therefore, we could not know the history of patients in other health care facilities.

Third, the de-identified CDM analysis could not offer the accuracy to the single individual because of the secondary use and large volume of data. The number of patients could be not sufficient (missing) despite the fact that we tried to avoid every single small error by properly identifying the mCNV patients with multiples criteria of inclusion and exclusion. In detail, we performed the detection process in a comprehensive way (requirement of the more robust treatment code first and an additional

confirmation of diagnosis code) to assure that all patients with mCNV were accurately identified. A justification for our handling is that in a study carried out by Stein et al.(2019), to estimate the accuracy of detection of exfoliation syndrome, they declared that 60% of sample size would have been missed if the searching was merely based on diagnosis code.[81] Moreover, because of the less reliability in the diagnosis code input (doctors do not necessarily need to include a diagnosis code if not related to financial problems) than the treatment code input (doctors need to include what they did to patients in the EMR), the target population in our study cannot be all patients with mCNV regardless of their treatment status (including those undergoing observation). Ultimately, despite all efforts having been made, since the man-made input of diagnosis code of patients was prone to errors with regards to time and presence, such current studies could not effectively estimate the incidence and prevalence of mCNV. Therefore, in the future, if there is a need for insights into that area, there should be a stricter and more trustworthy accuracy of diagnosis input. Finally, this preliminary study had the drawbacks of inadequate heterogeneity due to single center sampling, leading to the limited generalization of the findings. It would be erroneous to draw the conclusion from single databases or even multiple database in a single nation, which is prone to many subsequent errors.[82]

Future work

Our study so far merely characterized the treatment burden and patterns of mCNV without considering the factors associated with that observation (due to the small number of patients detected from our database, the treatment burden and pattern were not stratified according to baseline clinically relevant characteristics). In the future, a scenario when all the EMR information of a certain number of health care institutions, insurance claims, national surveys and registries are already properly mapped to CDM, even up to real-time mapping, could enable the ability of detection of those potential association. This approach also allows us to get real-time updates with any newly emerged treatment options provided in real-world evidences. In addition, further CDM-based studies using machine learning approach to provide predictive parameters for the number of injections needed for each patient over time based on their baseline characteristics (clinical profiles, para-clinical indexes) as what Bogunovic et al. (2017) did in nAMD,[83] and to estimate the treatment regimen suitable for each individual should be carried out. Also, treatment burden should not be restricted to the concepts of the number of injections. Among various related studies, Alsadah et al.(2020) conceptualized treatment burden as (a) being a patient preventing themselves from well-functioning in their lives, and (b) bearing an "opportunity cost" of

allocating human and financial resources on the treatment.[47] Therefore, another feasible approach could be to map the insurance claim data to the COST table in CDM according to the availability of data sources, thus we can estimate the financial treatment burden of mCNV as some studies had done in other diseases.[84] Finally, a multicenter study should be carried out soon to enhance the external validity of the results.

Conclusion

In conclusion, anti-VEGF drugs have been increasingly prevalently prescribed and off-label drug bevacizumab has been even the most popular, therefore it should be confident to prescribe these drugs to patients after considering other clinical and non-clinical profiles of patients. The anti-VEGF drugs are effective in treating mCNV: non-switching monotherapy is sufficient in most cases and the need for treatment in the second year after initiating therapy decreased substantially, which enables doctors and patients to be aware of the less intensive treatment journey compared with other diseases sharing similar regimens. It is also worth noticing that our study is among the first utilizing CDM database to assess the treatment burden and patterns of mCNV. As long as the feasibility of this approach was confirmed, the novelty in the use of CDM would be our advantage to validate the real-

world settings by further multi-center studies and even multi-national ones.

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SUPPLEMENTARY

R codes (pasted in bordered paragraph) and SQL codes (plain text) for

Cohort Definition and Treatment Burden & Pattern Analysis

```
/*********************************************************************/
/********** 1. COHORT CREATION (Figure 6 & Figure 7) **********/
/*********************************************************************/


/* cohort entry event : drug exposure to anti-VEGF drugs, PDT, PTCG*/
/* cohort_definition_id : 102 */

/*mCNV condition*//*N=72*/
create table snubh_researcher.mcnv_desc_1 as
select a.person_id from cdm_2020.condition_occurrence a
inner join result_cdm_2020.cohort b
on a.person_id = b.subject_id
where 1=1
and b.cohort_definition_id in (102) --entry cohort
and a.condition_concept_id in (select vc.descendant_concept_id from
cdm_voca_2020.concept_ancestor vc where vc.ancestor_concept_id in
(37116419)) --mCNV condition_concept_id
and a.condition_start_date - b.cohort_start_date <=365;

/*CNV condition and SE <-6*/*N=80*/
create table snubh_researcher.mcnv_desc_2 as
select c.person_id from cdm_2020.condition_occurrence c
inner join cdm_2020.measurement d
on c.person_id = d.person_id
where
c.person_id in (select person_id from cdm_2020.condition_occurrence a inner join
result_cdm_2020.cohort b on a.person_id = b.subject_id
where b.cohort_definition_id in (102) --entry cohort
```

```
and a.condition_concept_id in (select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc where vc.ancestor_concept_id in (4294834)
--CNV condition_concept_id
and a.condition_start_date - b.cohort_start_date <=365)
and d.measurement_concept_id in (select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc where vc.ancestor_concept_id in (3000744,3006500)) --right/left eye sphere autorefractor.auto
and d.value_as_number <= -6;

/*exclusion*//*N=6*/
create table snubh_researcher.mcnv_exc as
select person_id from cdm_2020.condition_occurrence
where condition_concept_id in (select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc where vc.ancestor_concept_id in (4028363,4174977,440392,4334245,377270,376966,372894))
and (person_id in (select person_id from snubh_researcher.mcnv_desc_1) or person_id in (select person_id from snubh_researcher.mcnv_desc_2));

/*(mCNV condition) or (CNV condtion and SE <-6)*//*N=100*/
create table snubh_researcher.mcnv_id_list as
select person_id from snubh_researcher.mcnv_desc_1;
insert into mcnv_id_list (person_id)
select person_id from snubh_researcher.mcnv_desc_2;


/*(mCNV condition) or (CNV condtion and SE <-6) + exclusion*//*N=94*/
create table snubh_researcher.mcnv_id_list_exc_done as
select distinct person_id from snubh_researcher.mcnv_id_list
where person_id not in (select person_id from snubh_researcher.mcnv_exc);

/*Final*//*N=94*/
select count(distinct person_id) from snubh_researcher.mcnv_id_list_exc_done;

create table snubh_researcher.mcnv_person as
select distinct person_id from snubh_researcher.mcnv_id_list_exc_done;
```

```
/*************************************************************************/
/********** 2. SUNBURST AND SANKEY PLOT (Figure 8) ************/
/*************************************************************************/

/* Drug Exposure Table : 19080982, 1397141, 40244266, 912803*//*count = 428*/
create table snubh_researcher.mcnv_drug_exposure as
select drug_exposure_id, person_id, drug_concept_id, drug_exposure_start_date
from cdm_2020.drug_exposure
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person)
and drug_concept_id in (select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (19080982, 1397141, 40244266, 912803))

/* PROCEDURE OCCURRENCE TABLE : 4117979, 4232642 *//*count = 429*/
insert into snubh_researcher.mcnv_drug_exposure (drug_exposure_id, person_id, drug_concept_id, drug_exposure_start_date)
select procedure_occurrence_id as drug_exposure_id,
person_id as person_id ,
procedure_concept_id as drug_concept_id,
procedure_date as drug_exposure_start_date
from cdm_2020.procedure_occurrence
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person)
and procedure_concept_id in
(select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (4117979, 4232642));
```

➔ **R CODE FOR SUNBURST AND SANKEY DIAGRAM AS FOLLOWS:**

```
###################################
#         Sunburst Plot           #
###################################

rm(list = ls())
Sys.setlocale(category = "LC_ALL", locale = "us")

library(devtools)
library(SqlRender)
library(DatabaseConnector)
library(dplyr)
library(sunburstR)

connectionDetails <- createConnectionDetails(dbms=dbms,
                                             server=server,
                                             user=user,
                                             password=pw,
                                             port=port,
                                             pathToDriver = "C:/
Program Files/sqldeveloper/jdbc/lib")


conn <- connect(connectionDetails)
#disconnect(conn)

# Parameters Setting
# drug_list - Bevacizumab / Ranibizumab / Aflibercept / Verteporfin
# procedure - Photocoagulation

drug_beva <- c('1397141') #beva
drug_rani <- c('43286611') #rani
drug_afli <- c('35606176') #afli
drug_vert <- c('1593778') #PDT
drug_coag <- c('4334592') #photocoagulation

drug_all <- c(drug_beva, drug_rani, drug_afli, drug_vert, drug_coag)

# Drug exposure table
options(scipen = 100)
treatment_pathway <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_drug_exposure;")
length(unique(treatment_pathway$PERSON_ID))
unique(treatment_pathway$DRUG_CONCEPT_ID)

treatment_pathway$DRUG_EXPOSURE_START_DATE <-
as.Date(treatment_pathway$DRUG_EXPOSURE_START_DATE)
treatment_pathway$DRUG_EXPOSURE_END_DATE <-
as.Date(treatment_pathway$DRUG_EXPOSURE_END_DATE)
str(treatment_pathway)

# DRUG_CLASS
treatment_pathway<-treatment_pathway %>%
  mutate(DRUG_CLASS = ifelse(DRUG_CONCEPT_ID %in% drug_beva,
'Bevacizumab',
```

```
                              ifelse(DRUG_CONCEPT_ID %in% drug_rani,
'Ranibizumab',
                                     ifelse(DRUG_CONCEPT_ID %in%
drug_afli, 'Aflibercept',
                                            ifelse(DRUG_CONCEPT_ID
%in% drug_vert, 'Photodynamic_therapy',

ifelse(DRUG_CONCEPT_ID %in% drug_coag,
'Photocoagulation','Others'))))))

# min date
treatment_pathway <- treatment_pathway %>%
group_by(PERSON_ID,DRUG_CLASS) %>%
summarise(MIN_DATE=min(DRUG_EXPOSURE_START_DATE))
treatment_pathway <-
treatment_pathway[order(treatment_pathway$PERSON_ID,treatment_pathwa
y$MIN_DATE),]

# PERSONAL_DRUG_ASD_NUMBER
treatment_pathway <- treatment_pathway %>% group_by(PERSON_ID) %>%
arrange(MIN_DATE) %>% mutate(PERSONAL_DRUG_ASD_NUMBER =
row_number())


TxPathwayDf <- data.frame(treatment_pathway %>% group_by(PERSON_ID)
%>% mutate(TxPathway = paste(DRUG_CLASS, collapse = '-')))
sunburstDf <- TxPathwayDf %>% select('PERSON_ID', 'TxPathway') %>%
distinct()

sunburstTxPathway<-c()
for (j in sunburstDf$TxPathway){
  txPathway<-c()
  treatment<-unlist(strsplit(j, '-'))

  for (i in 1:length(treatment)){
    txPathway <- c(txPathway, treatment[i])
  }
  sunburstTxPathway<-c(sunburstTxPathway, paste(txPathway, collapse
= '-'))
}
sunburstTxPathway <- data.frame(table(sunburstTxPathway))

sum(sunburstTxPathway$Freq) ##RVO COHORT n수와 일치하는지 확인

# sunburst plot
legend_items <- c('Bevacizumab', 'Ranibizumab', 'Aflibercept',
'Photodynamic_therapy', 'Photocoagulation')
cols <- c('Bevacizumab', 'Ranibizumab', 'Aflibercept',
'Photodynamic_therapy', 'Photocoagulation')
cols[legend_items=='Bevacizumab'] = "#984ea3"
cols[legend_items=='Ranibizumab'] = "#ff7f00"
cols[legend_items=='Aflibercept'] = "#377eb8"
cols[legend_items=='Photodynamic_therapy'] = "#008379"
cols[legend_items=='Photocoagulation'] = "#ccccc"
```

```
maintitle = "mCNV Tx pathway" # Plot main title
subtitle = paste0(sum(sunburstTxPathway$Freq),' patients;
',length(sunburstTxPathway$sunburstTxPathway),' unique paths')
plottitle = "All_mCNV" # plot file name


sb = sunburstTxPathway %>% sunburst(colors=list(range=cols,
domain=legend_items),
                                    legendOrder = legend_items,
                                    valueField = "size",
                                    percent = TRUE,
                                    count = TRUE,
                                    legend = list(w=150),
                                    width = 700,
                                    height = 700,
                                    withD3=TRUE,
                                    sortFunction = htmlwidgets::JS(
                                      "
                                      function(a,b){
                                        abb = {
                                          Bevacizumab:1,
                                          Ranibizumab:2,
                                          Aflibercept:3,
                                          Photodynamic_therapy:4,
                                          Photocoagulation:5
                                        }
                                        return abb[a.data.name] -
abb[b.data.name];
                                      }
                                      "
                                    )
                                    )


sb = htmlwidgets::onRender(sb,
                           "
          function(el, x) {
          d3.selectAll('.sunburst-legend text').attr('font-size',
'15px');
    d3.select(el).select('.sunburst-
togglelegend').property('checked',true);
    d3.select(el).select('.sunburst-togglelegend').on('click')();
    d3.select(el).select('.sunburst-togglelegend').remove();
          }
          "
)
#sb = htmlwidgets::prependContent(sb, htmltools::h1(maintitle),
htmltools::h2(subtitle))

sb
```

```
# csv file
firstyearDf<-treatment_pathway %>%
filter(PERSONAL_DRUG_ASD_NUMBER==1) %>% select('PERSON_ID',
'MIN_DATE')
FUN <- function(x){
  substr(as.character(x), 1, 4)
}
firstyearDf['MIN_DATE'] <- lapply(firstyearDf['MIN_DATE'], FUN)
csvfiledf<-merge(firstyearDf, sunburstDf, by='PERSON_ID')
csvfiledf<-data.frame(csvfiledf %>% group_by(MIN_DATE, TxPathway)
%>% summarise(count = n()))
write.csv(csvfiledf, file='./count_mCNV.csv')


####################################
#          Sankey Plot             #
####################################

rm(list = ls())

Sys.setlocale(category = "LC_ALL", locale = "us")

library(devtools)
library(dplyr)
library(sunburstR)
library(remotes)
library(drat)
library(tidyr)
library(stringr)
library(networkD3)
library(htmlwidgets)
library(webshot)

dataset <- read.csv('./count_mCNV.csv')
sum(dataset$count)

dataset2 <- dataset %>% group_by(TxPathway) %>% summarize(count =
sum(count))
sum(dataset2$count)

dataset2 <- dataset2[order(-dataset2[,2]),]

dataset3 <- dataset2 %>% separate(TxPathway, c('path1','path2'),'-')
dataset3[is.na(dataset3)] <- 'Stopped'

dataset3$event_cohort_name1 <- paste0("1.",dataset3$path1)
dataset3$event_cohort_name2 <- paste0("2.",dataset3$path2)

results1 <- dataset3 %>%
  dplyr::group_by(event_cohort_name1,event_cohort_name2) %>%
  dplyr::summarise(count = sum(count))


# Format in prep for sankey diagram
```

```
colnames(results1) <- c("source", "target", "value")
links <- as.data.frame(rbind(results1))
links <- links[order(-links[,3]),]

nodes <- data.frame(
  name=c(as.character(links$source),
         as.character(links$target)) %>% unique()
)

links$IDsource <- match(links$source, nodes$name)-1
links$IDtarget <- match(links$target, nodes$name)-1

my_color <- 'd3.scaleOrdinal() .domain(["2.Stopped",
"1.Bevacizumab", "1.Ranibizumab", "2.Bevacizumab", "1.Aflibercept",
"1.Photodynamic_therapy", "2.Ranibizumab", "2.Aflibercept",
"2.Photocoagulation", "3.Stopped"]) .range(["#cccccc", "#984ea3",
"#ff7f00", "#984ea3", "#377eb8", "#008379", "#ff7f00", "#377eb8",
"#ccccc", "#cccccc"])'


p <- sankeyNetwork(Links = links, Nodes =nodes,
                   Source = "IDsource", Target = "IDtarget",
                   Value = "value", NodeID = "name",
colourScale=JS(my_color),
                   fontSize= 12, nodeWidth = 30,
                   iterations = FALSE,
                   sinksRight = FALSE)

p
```

```
/********************************************************************/
/**************** 3. DEMOGRAPHICS (Table 3) *********************/
/********************************************************************/

/*COHORT*/
create table snubh_researcher.mcnv_cohort as
select a.*
from result_cdm_2020.cohort a
where a.cohort_definition_id in (102)
and a.subject_id in (select person_id from snubh_researcher.mcnv_person);

/*AGE*/
create table snubh_researcher.mcnv_age as
select a.*,round((a.cohort_start_date - b.birth_datetime)/365.25,0) as age
from snubh_researcher.mcnv_cohort a
left join snubh_researcher.mcnv_person b
on a.subject_id = b.person_id;

/*GENDER AND RACE*/
create table snubh_researcher.mcnv_gend_race as
select a.*, b.gender_concept_id , b.ethnicity_concept_id
from snubh_researcher.mcnv_cohort a
left join snubh_researcher.mcnv_person b
on a.subject_id = b.person_id;

/*CONDITION*/
create table snubh_researcher.mcnv_condi_hist as
select a.subject_id as person_id,
(case when a.subject_id in (select a.person_id from (select * from
cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where
ancestor_concept_id in (201820))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
```

```
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as diabetes,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (318800))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as gastro,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (432867))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as hyperlipidemia,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (316866))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as hypertensive,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (80180))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
```

```
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as osteoarthritis,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (4030518))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as renal,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (4134440))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as visual
,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (381591))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as cerebrov
,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (317576))) as a
left join snubh_researcher.mcnv_cohort as b
```

```
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as coronary
,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (321588))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as heart
,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (4185932))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as ischemic
,
(case when a.subject_id in (select a.person_id from (select * from cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (444247))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as venous
,
(case when a.subject_id in (select a.person_id from (select * from
```

```
cdm_2020.condition_occurrence where condition_concept_id in
(select descendant_concept_id from cdm_voca_2020.concept_ancestor where ancestor_concept_id in (443392))) as a
left join snubh_researcher.mcnv_cohort as b
on a.person_id = b.subject_id
where b.cohort_start_date - a.condition_start_date < 365*2
and b.cohort_start_date - a.condition_start_date > 0) then 1 else 0 end) as malignant
from snubh_researcher.mcnv_cohort a ;

select min(observation_period_start_date), max(observation_period_end_date)
from cdm_2020.observation_period
where person_id in (select subject_id from snubh_researcher.mcnv_cohort_2yr);
select min(observation_period_start_date), max(observation_period_end_date)
from cdm_2020.observation_period;
```

```
/*VISUAL ACUITY*/
create table snubh_researcher.mcnv_va as
select * from cdm_2019.measurement
where person_id in (select subject_id from snubh_researcher.mcnv_cohort)
and measurement_concept_id in (2061000007, 2061000008, 21491746, 21491747); -- Corrected visual acuity (Decimal) Right/Left eye and Visual acuity uncorrected Right/Left eye by Snellen eye chart

create table snubh_researcher.mcnv_va_todo as
selet aa.*, bb.measurement_date, bb.measurement_concept_id, bb.value_as_number, bb.value_source_value
from snubh_researcher.mcnv_cohort aa
inner join (select person_id, measurement_date, measurement_concept_id, value_as_number, value_source_value from snubh_researcher.mcnv_va where measurement_concept_id in (3000744, 3003500)) bb
on aa.subject_id = bb.person_id;

create table snubh_researcher.mcnv_va_diff as
select *, (measurement_date - cohort_start_date) as date_diff from nubh_researcher.mcnv_va_todo;

create table snubh_researcher.mcnv_va_diff_bf as
select * from snubh_researcher.mcnv_va_diff
where date_diff <=0;

create table snubh_researcher.mcnv_va_max as
select aa.* from snubh_researcher.mcnv_va_diff_bf aa
inner join (select subject_id, max(date_diff) as max_date from snubh_researcher.mcnv_va_diff_bf group by subject_id) bb
on aa.subject_id = bb.subject_id and aa.date_diff = bb.max_date;

/*MYOPIA STATUS*/
create table snubh_researcher.mcnv_diop as
select * from cdm_2019.measurement
where person_id in (select subject_id from snubh_researcher.mcnv_cohort)
```

```
and measurement_concept_id in (3000744, 3003500); -- Right/Left eye Sphere Autorefractor.auto

create table snubh_researcher.mcnv_diop_todo as
select aa.*, bb.measurement_date, bb.measurement_concept_id, bb.value_as_number, bb.value_source_value
from snubh_researcher.mcnv_cohort aa
inner join (select person_id, measurement_date, measurement_concept_id, value_as_number, value_source_value from snubh_researcher.mcnv_diop where measurement_concept_id in (3000744, 3003500)) bb
on aa.subject_id = bb.person_id;

create table snubh_researcher.mcnv_diop_diff as
select *, (measurement_date - cohort_start_date) as date_diff from nubh_researcher.mcnv_diop_todo;

create table snubh_researcher.mcnv_diop_diff_bf as
select * from snubh_researcher.mcnv_diop_diff
where date_diff <=0;

create table snubh_researcher.mcnv_diop_max as
select aa.* from snubh_researcher.mcnv_diop_diff_bf aa
inner join (select subject_id, max(date_diff) as max_date from snubh_researcher.mcnv_diop_diff_bf group by subject_id) bb
on aa.subject_id = bb.subject_id and aa.date_diff = bb.max_date;
```

→ R CODE FOR DEMOGRAPHICS AS FOLLOWS:

```
rm(list = ls())
Sys.setlocale(category = "LC_ALL", locale = "us")

library(devtools)
library(SqlRender)
library(DatabaseConnector)
library(dplyr)


connectionDetails <- createConnectionDetails(dbms=dbms,
                                             server=server,
                                             user=user,
                                             password=pw,
                                             port=port,
                                             pathToDriver = "C:/
Program Files/sqldeveloper/jdbc/lib")

conn <- connect(connectionDetails)
#disconnect(conn)

mcnv_age <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_age;")

library(dplyr)
library(devtools)
mcnv_age$gp <- ifelse(mcnv_age$AGE>=80, 1,
                  ifelse(mcnv_age$AGE>=75, 2,
                     ifelse(mcnv_age$AGE>=70, 3,
                        ifelse(mcnv_age$AGE>=65, 4,
                           ifelse(mcnv_age$AGE>=60, 5,
                                ifelse(mcnv_age$AGE>=55, 6,
                                     ifelse(mcnv_age$AGE>=50, 7,
                                            ifelse(mcnv_age$AGE>=45,
8,

ifelse(mcnv_age$AGE>=40, 9,

ifelse(mcnv_age$AGE>=35, 10,

ifelse(mcnv_age$AGE>=30, 11,

ifelse(mcnv_age$AGE>=25,12,

ifelse(mcnv_age$AGE>=20, 13,

ifelse(mcnv_age$AGE>=15, 14,

ifelse(mcnv_age$AGE>=10, 15,16))))))))))))))

age <- mcnv_age %>%
  group_by(gp) %>%
  summarise(count_n = n_distinct(SUBJECT_ID))

mcnv_gend_race <- querySql(conn, "SELECT * FROM
```

```
snubh_researcher.mcnv_gend_race;")
gender <- mcnv_gend_race %>%
  group_by(GENDER_CONCEPT_ID) %>%
  summarise(count_n = n_distinct(SUBJECT_ID))

mcnv_condi <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_condi;")
mcnv_condi <- mcnv_condi[,-1]
colSums(mcnv_condi)

mcnv_condi_hist <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_condi_hist;")
mcnv_condi_hist <- mcnv_condi_hist[,-1]
colSums(mcnv_condi_hist)

mcnv_va_sql <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_va_max;")
mcnv_va_sql_value <- mcnv_va_sql %>% group_by(SUBJECT_ID) %>%
slice(which.max(VALUE_AS_NUMBER))

#################################################################2022-
04-13 start
#mean(mcnv_va_sql_value$VALUE_AS_NUMBER)
#sd(mcnv_va_sql_value$VALUE_AS_NUMBER)

# Decimal -> logMAR
mcnv_va_sql_value$logMAR <- round(log10(1/
mcnv_va_sql_value$VALUE_AS_NUMBER),2)

mean(mcnv_va_sql_value$logMAR)
sd(mcnv_va_sql_value$logMAR)
#################################################################2022-
04-13 end

mcnv_diop_sql <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_diop_max;")
mcnv_diop_sql_value <- mcnv_diop_sql %>% group_by(SUBJECT_ID) %>%
slice(which.max(VALUE_AS_NUMBER))

mean(mcnv_diop_sql_value$VALUE_AS_NUMBER)
sd(mcnv_diop_sql_value$VALUE_AS_NUMBER)
```

```
/*************************************************************************/
/************* 4. BURDEN TABLE (Figure 9 & Figure 10) *************/
/*************************************************************************/

/* Drug Exposure Table : 19080982, 1397141, 40244266, 912803*//*count
= 428*/
create table snubh_researcher.mcnv_drug_exposure as
select drug_exposure_id, person_id, drug_concept_id, drug_exposure_start_date
from cdm_2020.drug_exposure
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person)
and drug_concept_id in (select vc.descendant_concept_id from
cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (19080982, 1397141, 40244266, 912803))

/* PROCEDURE OCCURRENCE TABLE : 4117979, 4232642 *//*count =
429*/
insert into snubh_researcher.mcnv_drug_exposure (drug_exposure_id, person_id,
drug_concept_id, drug_exposure_start_date)
select procedure_occurrence_id as drug_exposure_id,
person_id as person_id ,
procedure_concept_id as drug_concept_id,
procedure_date as drug_exposure_start_date
from cdm_2020.procedure_occurrence
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person)
and procedure_concept_id in
(select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (4117979, 4232642));
```

→ R CODE FOR BURDEN TABLE AS FOLLOWS:

```
rm(list = ls())
Sys.setlocale(category = "LC_ALL", locale = "us")

library(devtools)
library(SqlRender)
library(DatabaseConnector)
library(dplyr)

connectionDetails <- createConnectionDetails(dbms=dbms,
                                             server=server,
                                             user=user,
                                             password=pw,
                                             port=port,
                                             pathToDriver = "C:/
Program Files/sqldeveloper/jdbc/lib")

conn <- connect(connectionDetails)
#disconnect(conn)

mcnv_all <- querySql(conn, "SELECT * FROM
snubh_researcher.mcnv_drug_exposure;")
length(unique(mcnv_all$PERSON_ID))

####################################
#       Parameters Setting         #
####################################
drug_beva <- c('1397141') #beva
drug_rani <- c('43286611') #rani
drug_afli <- c('35606176') #afli
drug_vert <- c('1593778') #PDT
drug_coag <- c('4334592') #photocoagulation

drug_all <- c(drug_beva, drug_rani, drug_afli, drug_vert, drug_coag)

####################################YEO


# PERSONAL_DRUG_ASD_NUMBER
mcnv_all  <- mcnv_all  %>%
  group_by(PERSON_ID) %>%
  arrange(DRUG_EXPOSURE_START_DATE) %>%
mutate(PERSONAL_DRUG_ASD_NUMBER = row_number())
mcnv_all  <- mcnv_all[order( mcnv_all[,2],mcnv_all[,4] ),]


mcnv_all$year <- format(as.Date(mcnv_all$DRUG_EXPOSURE_START_DATE),
"%Y")


all <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_all) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())
```

```
rani <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_rani) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())

afli <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_afli) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())

beva <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_beva) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())

vert <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_vert) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())

ptcg <- mcnv_all %>%
  filter(DRUG_CONCEPT_ID %in% drug_ptcg) %>%
  group_by(year) %>%
  summarise(count_n = n_distinct(PERSON_ID), count_inj = n())

#merge(all, beva, by = 'year', all = TRUE)

mergeAll <- merge(merge(merge(merge(merge(
  all,
  rani, by = 'year', all = TRUE),
  afli, by = 'year', all = TRUE),
  beva, by = 'year', all = TRUE),
  vert, by = 'year', all = TRUE),
  ptcg, by = 'year', all = TRUE)


colnames(mergeAll) <- c("YEAR",
                        "ALLDRUG_N", "ALLDRUG_INJ",
                        "RANI_N", "RANI_INJ",
                        "AFLI_N", "AFLI_INJ",
                        "BEVA_N", "BEVA_INJ",
                        "PDT_N", "PDT_INJ",
                        "PTCG_N", "PTCG_INJ")
mergeAll

write.csv(mergeAll, file = "./mcnv_txburden.csv")
```

```
/*************************************************************************/
/********* 5. AVERAGE TABLE (Table 4 & Table 5 & Table 6) **********/
/*************************************************************************/

/*2YR COHORT*/
create table snubh_researcher.mcnv_cohort_2yr as
select a.*
from result_cdm_2020.cohort a
where a.cohort_definition_id in (108)
and a.subject_id in (select person_id from snubh_researcher.mcnv_person);

/* Drug Exposure Table : 19080982, 1397141, 40244266, 912803*/
create table snubh_researcher.mcnv_drug_exposure_2yr as
select drug_exposure_id, person_id, drug_concept_id, drug_exposure_start_date
from cdm_2020.drug_exposure
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person_2yr)
and drug_concept_id in (select vc.descendant_concept_id from
cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (19080982, 1397141, 40244266, 912803))

/* PROCEDURE OCCURRENCE TABLE : 4117979, 4232642 */
insert into snubh_researcher.mcnv_drug_exposure_2yr (drug_exposure_id,
person_id, drug_concept_id, drug_exposure_start_date)
select procedure_occurrence_id as drug_exposure_id,
person_id as person_id ,
procedure_concept_id as drug_concept_id,
procedure_date as drug_exposure_start_date
from cdm_2020.procedure_occurrence
where 1=1
and person_id in (select person_id from snubh_researcher.mcnv_person_2yr)
and procedure_concept_id in
(select vc.descendant_concept_id from cdm_voca_2020.concept_ancestor vc
where vc.ancestor_concept_id in (4117979, 4232642));
```

→ R CODE FOR AVERAGE TABLE AS FOLLOWS:

```
rm(list = ls())
Sys.setlocale(category = "LC_ALL", locale = "us")

library(devtools)
library(SqlRender)
library(DatabaseConnector)
library(dplyr)

connectionDetails <- createConnectionDetails(dbms=dbms,
                                             server=server,
                                             user=user,
                                             password=pw,
                                             port=port,
                                             pathToDriver = "C:/
Program Files/sqldeveloper/jdbc/lib")

conn <- connect(connectionDetails)
#disconnect(conn)

###################################
#       Parameters Setting        #
###################################
drug_beva <- c('1397141') #beva
drug_rani <- c('43286611') #rani
drug_afli <- c('35606176') #afli
drug_vert <- c('1593778') #Verteportin / PDT
drug_coag <- c('4334592') #photocoagulation

drug_all <- c(drug_beva, drug_rani, drug_afli, drug_vert, drug_coag)

first_anti <- c(drug_beva, drug_rani, drug_afli)
first_pdt <- c(drug_vert, drug_coag)
first_all <- drug_all

yr1 <- query(conn, "SELECT * FROM
snubh_researcher.mcnv_drug_exposure;") #429건, 94명
yr2 <- query(conn, "SELECT * FROM
snubh_researcher.mcnv_drug_exposure_2yr;") #386건, 74명

{
  yr1 <- yr1 %>%
    group_by(PERSON_ID) %>%
    arrange(DRUG_EXPOSURE_START_DATE) %>%
mutate(PERSONAL_DRUG_ASD_NUMBER = row_number())
  yr1 <- yr1[order(yr1[,2], yr1[,4]),]


  yr2 <- yr2 %>%
    group_by(PERSON_ID) %>%
    arrange(DRUG_EXPOSURE_START_DATE) %>%
mutate(PERSONAL_DRUG_ASD_NUMBER = row_number())
  yr2 <- yr2[order(yr2[,2], yr2[,4]),]
}
{
```

```
  yr1_first <- yr1 %>% filter(PERSONAL_DRUG_ASD_NUMBER==1) %>%
select('PERSON_ID','DRUG_EXPOSURE_START_DATE','DRUG_CONCEPT_ID')
  colnames(yr1_first) <- c("PERSON_ID",
'FIRST_DRUG_EXPOSURE_START_DATE', "FIRST_TREATMENT")
  yr1 <- merge(yr1, yr1_first , by='PERSON_ID')
  yr1['dayDiff'] <- yr1['DRUG_EXPOSURE_START_DATE'] -
yr1['FIRST_DRUG_EXPOSURE_START_DATE']
  yr1['year_gp'] <- ifelse(yr1$dayDiff<=365, 1,
ifelse(yr1$dayDiff<=730, 2, ifelse(yr1$dayDiff<=1095,3,9999)))

  yr2_first <- yr2 %>% filter(PERSONAL_DRUG_ASD_NUMBER==1) %>%
select('PERSON_ID','DRUG_EXPOSURE_START_DATE','DRUG_CONCEPT_ID')
  colnames(yr2_first) <- c("PERSON_ID",
'FIRST_DRUG_EXPOSURE_START_DATE', "FIRST_TREATMENT")
  yr2 <- merge(yr2, yr2_first , by='PERSON_ID')
  yr2['dayDiff'] <- yr2['DRUG_EXPOSURE_START_DATE'] -
yr2['FIRST_DRUG_EXPOSURE_START_DATE']
  yr2['year_gp'] <- ifelse(yr2$dayDiff<=365, 1,
ifelse(yr2$dayDiff<=730, 2, ifelse(yr2$dayDiff<=1095,3,9999)))
}

table4 <- matrix(ncol = 12, byrow = T)
table4 <- data.frame(table4)
colnames(table4) <- c("Overall_mean","Overall_sd",
                      "Beva_Ini_mean","Beva_Ini_sd",
                      "Rani_Ini_mean","Rani_Ini_sd",
                      "Afli_Ini_mean","Afli_Ini_sd",
                      "Ptcg_Ini_mean","Ptcg_Ini_sd",
                      "PDT_Ini_mean","PDT_Ini_sd")

table4_sup <- matrix(ncol = 18, byrow = T)
table4_sup <- data.frame(table4_sup)
colnames(table4_sup) <-
c("Overall_Tot_Count","Overall_ID_Count","Overall_noinjcnt",

"Beva_Tot_Count","Beva_ID_Count","Beva_noinjcnt",

"Rani_Tot_Count","Rani_ID_Count","Rani_noinjcnt",

"Afli_Tot_Count","Afli_ID_Count","Afli_noinjcnt",

"Ptcg_Tot_Count","Ptcg_ID_Count","Ptcg_noinjcnt",

"PDT_Tot_Count","PDT_ID_Count","PDT_noinjcnt")

# PERIOD
period1 <- yr1 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2005-12-31"))) %>%
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2003-01-01")))
period2 <- yr1 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2017-11-30"))) %>%
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2006-01-01")))
period3 <- yr1 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2019-12-31"))) %>%
```

```
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2017-12-01")))

### Rcode mcnv_average_rep.R, mcnv_average_sup.R

write.csv(table4, file = './table4.csv')
write.csv(table4_sup, file = './table4_sup.csv')

#########################################################################
#########################################################################
########
#### Table 5
period1 <- yr2 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2005-12-31"))) %>%
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2003-01-01")))
period2 <- yr2 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2017-11-30"))) %>%
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2006-01-01")))
period3 <- yr2 %>% filter(FIRST_DRUG_EXPOSURE_START_DATE <=
as.Date(c("2019-12-31"))) %>%
  filter(FIRST_DRUG_EXPOSURE_START_DATE >= as.Date(c("2017-12-01")))

### Rcode mcnv_average_rep.R, mcnv_average_sup.R

write.csv(table4, file = './table5.csv')
write.csv(table4_sup, file = './table5_sup.csv')
```

```
{
  ######################################period1
  ###All
  period1_1yr <- period1 %>% filter(year_gp == 1)
  period1_2yr <- period1 %>% filter(year_gp == 2)
  #1yr
  period1_1yr_all <- data.frame(table(period1_1yr$PERSON_ID))
  table4[1,1] <- round(sum(period1_1yr_all$Freq)/
length(period1_1yr_all$Freq),2)
  table4[1,2] <- round(sqrt(sum((period1_1yr_all$Freq)^2)/
length(period1_1yr_all$Freq)-(sum(period1_1yr_all$Freq)/
length(period1_1yr_all$Freq))^2),2)

  period1_2yr_all <- data.frame(table(period1_2yr$PERSON_ID))
  table4[2,1] <- round(sum(period1_2yr_all$Freq)/
length(period1_1yr_all$Freq),2)
  table4[2,2] <- round(sqrt(sum((period1_2yr_all$Freq)^2)/
length(period1_1yr_all$Freq)-(sum(period1_2yr_all$Freq)/
length(period1_1yr_all$Freq))^2),2)

  ###beva
  #1yr
  period1_1yr_beva <- period1_1yr %>% filter(FIRST_TREATMENT %in%
drug_beva)
  period1_1yr_beva_cnt <-
data.frame(table(period1_1yr_beva$PERSON_ID))
  table4[1,3] <- round(sum(period1_1yr_beva_cnt$Freq)/
length(period1_1yr_beva_cnt$Freq),2)
  table4[1,4] <- round(sqrt(sum((period1_1yr_beva_cnt$Freq)^2)/
length(period1_1yr_beva_cnt$Freq)-(sum(period1_1yr_beva_cnt$Freq)/
length(period1_1yr_beva_cnt$Freq))^2),2)
  #2yr
  period1_2yr_beva <- period1_2yr %>% filter(FIRST_TREATMENT %in%
drug_beva)
  period1_2yr_beva_cnt <-
data.frame(table(period1_2yr_beva$PERSON_ID))
  table4[2,3] <- round(sum(period1_2yr_beva_cnt$Freq)/
length(period1_1yr_beva_cnt$Freq),2)
  table4[2,4] <- round(sqrt(sum((period1_2yr_beva_cnt$Freq)^2)/
length(period1_1yr_beva_cnt$Freq)-(sum(period1_2yr_beva_cnt$Freq)/
length(period1_1yr_beva_cnt$Freq))^2),2)

  ###rani
  #1yr
  period1_1yr_rani <- period1_1yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period1_1yr_rani_cnt <-
data.frame(table(period1_1yr_rani$PERSON_ID))
  table4[1,5] <- round(sum(period1_1yr_rani_cnt$Freq)/
length(period1_1yr_rani_cnt$Freq),2)
  table4[1,6] <- round(sqrt(sum((period1_1yr_rani_cnt$Freq)^2)/
length(period1_1yr_rani_cnt$Freq)-(sum(period1_1yr_rani_cnt$Freq)/
length(period1_1yr_rani_cnt$Freq))^2),2)
  #2yr
```

```
  period1_2yr_rani <- period1_2yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period1_2yr_rani_cnt <-
data.frame(table(period1_2yr_rani$PERSON_ID))
  table4[2,5] <- round(sum(period1_2yr_rani_cnt$Freq)/
length(period1_1yr_rani_cnt$Freq),2)
  table4[2,6] <- round(sqrt(sum((period1_2yr_rani_cnt$Freq)^2)/
length(period1_1yr_rani_cnt$Freq)-(sum(period1_2yr_rani_cnt$Freq)/
length(period1_1yr_rani_cnt$Freq))^2),2)

  ###afli
  #1yr
  period1_1yr_afli <- period1_1yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period1_1yr_afli_cnt <-
data.frame(table(period1_1yr_afli$PERSON_ID))
  table4[1,7] <- round(sum(period1_1yr_afli_cnt$Freq)/
length(period1_1yr_afli_cnt$Freq),2)
  table4[1,8] <- round(sqrt(sum((period1_1yr_afli_cnt$Freq)^2)/
length(period1_1yr_afli_cnt$Freq)-(sum(period1_1yr_afli_cnt$Freq)/
length(period1_1yr_afli_cnt$Freq))^2),2)
  #2yr
  period1_2yr_afli <- period1_2yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period1_2yr_afli_cnt <-
data.frame(table(period1_2yr_afli$PERSON_ID))
  table4[2,7] <- round(sum(period1_2yr_afli_cnt$Freq)/
length(period1_1yr_afli_cnt$Freq),2)
  table4[2,8] <- round(sqrt(sum((period1_2yr_afli_cnt$Freq)^2)/
length(period1_1yr_afli_cnt$Freq)-(sum(period1_2yr_afli_cnt$Freq)/
length(period1_1yr_afli_cnt$Freq))^2),2)

  ###ptcg
  #1yr
  period1_1yr_ptcg <- period1_1yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period1_1yr_ptcg_cnt <-
data.frame(table(period1_1yr_ptcg$PERSON_ID))
  table4[1,9] <- round(sum(period1_1yr_ptcg_cnt$Freq)/
length(period1_1yr_ptcg_cnt$Freq),2)
  table4[1,10] <- round(sqrt(sum((period1_1yr_ptcg_cnt$Freq)^2)/
length(period1_1yr_ptcg_cnt$Freq)-(sum(period1_1yr_ptcg_cnt$Freq)/
length(period1_1yr_ptcg_cnt$Freq))^2),2)
  #2yr
  period1_2yr_ptcg <- period1_2yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period1_2yr_ptcg_cnt <-
data.frame(table(period1_2yr_ptcg$PERSON_ID))
  table4[2,9] <- round(sum(period1_2yr_ptcg_cnt$Freq)/
length(period1_1yr_ptcg_cnt$Freq),2)
  table4[2,10] <- round(sqrt(sum((period1_2yr_ptcg_cnt$Freq)^2)/
length(period1_1yr_ptcg_cnt$Freq)-(sum(period1_2yr_ptcg_cnt$Freq)/
length(period1_1yr_ptcg_cnt$Freq))^2),2)
```

```
  ###vert
  #1yr
  period1_1yr_vert <- period1_1yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period1_1yr_vert_cnt <-
data.frame(table(period1_1yr_vert$PERSON_ID))
  table4[1,11] <- round(sum(period1_1yr_vert_cnt$Freq)/
length(period1_1yr_vert_cnt$Freq),2)
  table4[1,12] <- round(sqrt(sum((period1_1yr_vert_cnt$Freq)^2)/
length(period1_1yr_vert_cnt$Freq)-(sum(period1_1yr_vert_cnt$Freq)/
length(period1_1yr_vert_cnt$Freq))^2),2)
  #2yr
  period1_2yr_vert <- period1_2yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period1_2yr_vert_cnt <-
data.frame(table(period1_2yr_vert$PERSON_ID))
  table4[2,11] <- round(sum(period1_2yr_vert_cnt$Freq)/
length(period1_1yr_vert_cnt$Freq),2)
  table4[2,12] <- round(sqrt(sum((period1_2yr_vert_cnt$Freq)^2)/
length(period1_1yr_vert_cnt$Freq)-(sum(period1_2yr_vert_cnt$Freq)/
length(period1_1yr_vert_cnt$Freq))^2),2)

  ########################################period2
  ###All
  period2_1yr <- period2 %>% filter(year_gp == 1)
  period2_2yr <- period2 %>% filter(year_gp == 2)
  #1yr
  period2_1yr_all <- data.frame(table(period2_1yr$PERSON_ID))
  table4[3,1] <- round(sum(period2_1yr_all$Freq)/
length(period2_1yr_all$Freq),2)
  table4[3,2] <- round(sqrt(sum((period2_1yr_all$Freq)^2)/
length(period2_1yr_all$Freq)-(sum(period2_1yr_all$Freq)/
length(period2_1yr_all$Freq))^2),2)

  period2_2yr_all <- data.frame(table(period2_2yr$PERSON_ID))
  table4[4,1] <- round(sum(period2_2yr_all$Freq)/
length(period2_1yr_all$Freq),2)
  table4[4,2] <- round(sqrt(sum((period2_2yr_all$Freq)^2)/
length(period2_1yr_all$Freq)-(sum(period2_2yr_all$Freq)/
length(period2_1yr_all$Freq))^2),2)

  ###beva
  #1yr
  period2_1yr_beva <- period2_1yr %>% filter(FIRST_TREATMENT %in%
drug_beva)
  period2_1yr_beva_cnt <-
data.frame(table(period2_1yr_beva$PERSON_ID))
  table4[3,3] <- round(sum(period2_1yr_beva_cnt$Freq)/
length(period2_1yr_beva_cnt$Freq),2)
  table4[3,4] <- round(sqrt(sum((period2_1yr_beva_cnt$Freq)^2)/
length(period2_1yr_beva_cnt$Freq)-(sum(period2_1yr_beva_cnt$Freq)/
length(period2_1yr_beva_cnt$Freq))^2),2)
  #2yr
  period2_2yr_beva <- period2_2yr %>% filter(FIRST_TREATMENT %in%
```

```
drug_beva)
  period2_2yr_beva_cnt <-
data.frame(table(period2_2yr_beva$PERSON_ID))
  table4[4,3] <- round(sum(period2_2yr_beva_cnt$Freq)/
length(period2_1yr_beva_cnt$Freq),2)
  table4[4,4] <- round(sqrt(sum((period2_2yr_beva_cnt$Freq)^2)/
length(period2_1yr_beva_cnt$Freq)-(sum(period2_2yr_beva_cnt$Freq)/
length(period2_1yr_beva_cnt$Freq))^2),2)

  ###rani
  #1yr
  period2_1yr_rani <- period2_1yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period2_1yr_rani_cnt <-
data.frame(table(period2_1yr_rani$PERSON_ID))
  table4[3,5] <- round(sum(period2_1yr_rani_cnt$Freq)/
length(period2_1yr_rani_cnt$Freq),2)
  table4[3,6] <- round(sqrt(sum((period2_1yr_rani_cnt$Freq)^2)/
length(period2_1yr_rani_cnt$Freq)-(sum(period2_1yr_rani_cnt$Freq)/
length(period2_1yr_rani_cnt$Freq))^2),2)
  #2yr
  period2_2yr_rani <- period2_2yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period2_2yr_rani_cnt <-
data.frame(table(period2_2yr_rani$PERSON_ID))
  table4[4,5] <- round(sum(period2_2yr_rani_cnt$Freq)/
length(period2_1yr_rani_cnt$Freq),2)
  table4[4,6] <- round(sqrt(sum((period2_2yr_rani_cnt$Freq)^2)/
length(period2_1yr_rani_cnt$Freq)-(sum(period2_2yr_rani_cnt$Freq)/
length(period2_1yr_rani_cnt$Freq))^2),2)

  ###afli
  #1yr
  period2_1yr_afli <- period2_1yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period2_1yr_afli_cnt <-
data.frame(table(period2_1yr_afli$PERSON_ID))
  table4[3,7] <- round(sum(period2_1yr_afli_cnt$Freq)/
length(period2_1yr_afli_cnt$Freq),2)
  table4[3,8] <- round(sqrt(sum((period2_1yr_afli_cnt$Freq)^2)/
length(period2_1yr_afli_cnt$Freq)-(sum(period2_1yr_afli_cnt$Freq)/
length(period2_1yr_afli_cnt$Freq))^2),2)
  #2yr
  period2_2yr_afli <- period2_2yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period2_2yr_afli_cnt <-
data.frame(table(period2_2yr_afli$PERSON_ID))
  table4[4,7] <- round(sum(period2_2yr_afli_cnt$Freq)/
length(period2_1yr_afli_cnt$Freq),2)
  table4[4,8] <- round(sqrt(sum((period2_2yr_afli_cnt$Freq)^2)/
length(period2_1yr_afli_cnt$Freq)-(sum(period2_2yr_afli_cnt$Freq)/
length(period2_1yr_afli_cnt$Freq))^2),2)

  ###ptcg
```

```
  #1yr
  period2_1yr_ptcg <- period2_1yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period2_1yr_ptcg_cnt <-
data.frame(table(period2_1yr_ptcg$PERSON_ID))
  table4[3,9] <- round(sum(period2_1yr_ptcg_cnt$Freq)/
length(period2_1yr_ptcg_cnt$Freq),2)
  table4[3,10] <- round(sqrt(sum((period2_1yr_ptcg_cnt$Freq)^2)/
length(period2_1yr_ptcg_cnt$Freq)-(sum(period2_1yr_ptcg_cnt$Freq)/
length(period2_1yr_ptcg_cnt$Freq))^2),2)
  #2yr
  period2_2yr_ptcg <- period2_2yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period2_2yr_ptcg_cnt <-
data.frame(table(period2_2yr_ptcg$PERSON_ID))
  table4[4,9] <- round(sum(period2_2yr_ptcg_cnt$Freq)/
length(period2_1yr_ptcg_cnt$Freq),2)
  table4[4,10] <- round(sqrt(sum((period2_2yr_ptcg_cnt$Freq)^2)/
length(period2_1yr_ptcg_cnt$Freq)-(sum(period2_2yr_ptcg_cnt$Freq)/
length(period2_1yr_ptcg_cnt$Freq))^2),2)

  ###vert
  #1yr
  period2_1yr_vert <- period2_1yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period2_1yr_vert_cnt <-
data.frame(table(period2_1yr_vert$PERSON_ID))
  table4[3,11] <- round(sum(period2_1yr_vert_cnt$Freq)/
length(period2_1yr_vert_cnt$Freq),2)
  table4[3,12] <- round(sqrt(sum((period2_1yr_vert_cnt$Freq)^2)/
length(period2_1yr_vert_cnt$Freq)-(sum(period2_1yr_vert_cnt$Freq)/
length(period2_1yr_vert_cnt$Freq))^2),2)
  #2yr
  period2_2yr_vert <- period2_2yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period2_2yr_vert_cnt <-
data.frame(table(period2_2yr_vert$PERSON_ID))
  table4[4,11] <- round(sum(period2_2yr_vert_cnt$Freq)/
length(period2_1yr_vert_cnt$Freq),2)
  table4[4,12] <- round(sqrt(sum((period2_2yr_vert_cnt$Freq)^2)/
length(period2_1yr_vert_cnt$Freq)-(sum(period2_2yr_vert_cnt$Freq)/
length(period2_1yr_vert_cnt$Freq))^2),2)

  ########################################period3
  ###All
  period3_1yr <- period3 %>% filter(year_gp == 1)
  period3_2yr <- period3 %>% filter(year_gp == 2)
  #1yr
  period3_1yr_all <- data.frame(table(period3_1yr$PERSON_ID))
  table4[5,1] <- round(sum(period3_1yr_all$Freq)/
length(period3_1yr_all$Freq),2)
  table4[5,2] <- round(sqrt(sum((period3_1yr_all$Freq)^2)/
length(period3_1yr_all$Freq)-(sum(period3_1yr_all$Freq)/
length(period3_1yr_all$Freq))^2),2)
```

```
  period3_2yr_all <- data.frame(table(period3_2yr$PERSON_ID))
  table4[6,1] <- round(sum(period3_2yr_all$Freq)/
length(period3_1yr_all$Freq),2)
  table4[6,2] <- round(sqrt(sum((period3_2yr_all$Freq)^2)/
length(period3_1yr_all$Freq)-(sum(period3_2yr_all$Freq)/
length(period3_1yr_all$Freq))^2),2)

  ###beva
  #1yr
  period3_1yr_beva <- period3_1yr %>% filter(FIRST_TREATMENT %in%
drug_beva)
  period3_1yr_beva_cnt <-
data.frame(table(period3_1yr_beva$PERSON_ID))
  table4[5,3] <- round(sum(period3_1yr_beva_cnt$Freq)/
length(period3_1yr_beva_cnt$Freq),2)
  table4[5,4] <- round(sqrt(sum((period3_1yr_beva_cnt$Freq)^2)/
length(period3_1yr_beva_cnt$Freq)-(sum(period3_1yr_beva_cnt$Freq)/
length(period3_1yr_beva_cnt$Freq))^2),2)
  #2yr
  period3_2yr_beva <- period3_2yr %>% filter(FIRST_TREATMENT %in%
drug_beva)
  period3_2yr_beva_cnt <-
data.frame(table(period3_2yr_beva$PERSON_ID))
  table4[6,3] <- round(sum(period3_2yr_beva_cnt$Freq)/
length(period3_1yr_beva_cnt$Freq),2)
  table4[6,4] <- round(sqrt(sum((period3_2yr_beva_cnt$Freq)^2)/
length(period3_1yr_beva_cnt$Freq)-(sum(period3_2yr_beva_cnt$Freq)/
length(period3_1yr_beva_cnt$Freq))^2),2)

  ###rani
  #1yr
  period3_1yr_rani <- period3_1yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period3_1yr_rani_cnt <-
data.frame(table(period3_1yr_rani$PERSON_ID))
  table4[5,5] <- round(sum(period3_1yr_rani_cnt$Freq)/
length(period3_1yr_rani_cnt$Freq),2)
  table4[5,6] <- round(sqrt(sum((period3_1yr_rani_cnt$Freq)^2)/
length(period3_1yr_rani_cnt$Freq)-(sum(period3_1yr_rani_cnt$Freq)/
length(period3_1yr_rani_cnt$Freq))^2),2)
  #2yr
  period3_2yr_rani <- period3_2yr %>% filter(FIRST_TREATMENT %in%
drug_rani)
  period3_2yr_rani_cnt <-
data.frame(table(period3_2yr_rani$PERSON_ID))
  table4[6,5] <- round(sum(period3_2yr_rani_cnt$Freq)/
length(period3_1yr_rani_cnt$Freq),2)
  table4[6,6] <- round(sqrt(sum((period3_2yr_rani_cnt$Freq)^2)/
length(period3_1yr_rani_cnt$Freq)-(sum(period3_2yr_rani_cnt$Freq)/
length(period3_1yr_rani_cnt$Freq))^2),2)

  ###afli
  #1yr
```

```
  period3_1yr_afli <- period3_1yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period3_1yr_afli_cnt <-
data.frame(table(period3_1yr_afli$PERSON_ID))
  table4[5,7] <- round(sum(period3_1yr_afli_cnt$Freq)/
length(period3_1yr_afli_cnt$Freq),2)
  table4[5,8] <- round(sqrt(sum((period3_1yr_afli_cnt$Freq)^2)/
length(period3_1yr_afli_cnt$Freq)-(sum(period3_1yr_afli_cnt$Freq)/
length(period3_1yr_afli_cnt$Freq))^2),2)
  #2yr
  period3_2yr_afli <- period3_2yr %>% filter(FIRST_TREATMENT %in%
drug_afli)
  period3_2yr_afli_cnt <-
data.frame(table(period3_2yr_afli$PERSON_ID))
  table4[6,7] <- round(sum(period3_2yr_afli_cnt$Freq)/
length(period3_1yr_afli_cnt$Freq),2)
  table4[6,8] <- round(sqrt(sum((period3_2yr_afli_cnt$Freq)^2)/
length(period3_1yr_afli_cnt$Freq)-(sum(period3_2yr_afli_cnt$Freq)/
length(period3_1yr_afli_cnt$Freq))^2),2)

  ###ptcg
  #1yr
  period3_1yr_ptcg <- period3_1yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period3_1yr_ptcg_cnt <-
data.frame(table(period3_1yr_ptcg$PERSON_ID))
  table4[5,9] <- round(sum(period3_1yr_ptcg_cnt$Freq)/
length(period3_1yr_ptcg_cnt$Freq),2)
  table4[5,10] <- round(sqrt(sum((period3_1yr_ptcg_cnt$Freq)^2)/
length(period3_1yr_ptcg_cnt$Freq)-(sum(period3_1yr_ptcg_cnt$Freq)/
length(period3_1yr_ptcg_cnt$Freq))^2),2)
  #2yr
  period3_2yr_ptcg <- period3_2yr %>% filter(FIRST_TREATMENT %in%
drug_ptcg)
  period3_2yr_ptcg_cnt <-
data.frame(table(period3_2yr_ptcg$PERSON_ID))
  table4[6,9] <- round(sum(period3_2yr_ptcg_cnt$Freq)/
length(period3_1yr_ptcg_cnt$Freq),2)
  table4[6,10] <- round(sqrt(sum((period3_2yr_ptcg_cnt$Freq)^2)/
length(period3_1yr_ptcg_cnt$Freq)-(sum(period3_2yr_ptcg_cnt$Freq)/
length(period3_1yr_ptcg_cnt$Freq))^2),2)

  ###vert
  #1yr
  period3_1yr_vert <- period3_1yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period3_1yr_vert_cnt <-
data.frame(table(period3_1yr_vert$PERSON_ID))
  table4[5,11] <- round(sum(period3_1yr_vert_cnt$Freq)/
length(period3_1yr_vert_cnt$Freq),2)
  table4[5,12] <- round(sqrt(sum((period3_1yr_vert_cnt$Freq)^2)/
length(period3_1yr_vert_cnt$Freq)-(sum(period3_1yr_vert_cnt$Freq)/
length(period3_1yr_vert_cnt$Freq))^2),2)
  #2yr
```

```
  period3_2yr_vert <- period3_2yr %>% filter(FIRST_TREATMENT %in%
drug_vert)
  period3_2yr_vert_cnt <-
data.frame(table(period3_2yr_vert$PERSON_ID))
  table4[6,11] <- round(sum(period3_2yr_vert_cnt$Freq)/
length(period3_1yr_vert_cnt$Freq),2)
  table4[6,12] <- round(sqrt(sum((period3_2yr_vert_cnt$Freq)^2)/
length(period3_1yr_vert_cnt$Freq)-(sum(period3_2yr_vert_cnt$Freq)/
length(period3_1yr_vert_cnt$Freq))^2),2)

}
```

```
{
  ########################################period1
  table4_sup[1,1] <- length(period1_1yr_all$Freq)
  table4_sup[1,2] <- length(period1_2yr_all$Freq)
  table4_sup[1,3] <- length(period1_1yr_all$Freq) -
length(period1_2yr_all$Freq)

  table4_sup[1,4] <- length(period1_1yr_beva_cnt$Freq)
  table4_sup[1,5] <- length(period1_2yr_beva_cnt$Freq)
  table4_sup[1,6] <- length(period1_1yr_beva_cnt$Freq) -
length(period1_2yr_beva_cnt$Freq)

  table4_sup[1,7] <- length(period1_1yr_rani_cnt$Freq)
  table4_sup[1,8] <- length(period1_2yr_rani_cnt$Freq)
  table4_sup[1,9] <- length(period1_1yr_rani_cnt$Freq) -
length(period1_2yr_rani_cnt$Freq)

  table4_sup[1,10] <- length(period1_1yr_afli_cnt$Freq)
  table4_sup[1,11] <- length(period1_2yr_afli_cnt$Freq)
  table4_sup[1,12] <- length(period1_1yr_afli_cnt$Freq) -
length(period1_2yr_afli_cnt$Freq)

  table4_sup[1,13] <- length(period1_1yr_ptcg_cnt$Freq)
  table4_sup[1,14] <- length(period1_2yr_ptcg_cnt$Freq)
  table4_sup[1,15] <- length(period1_1yr_ptcg_cnt$Freq) -
length(period1_2yr_ptcg_cnt$Freq)

  table4_sup[1,16] <- length(period1_1yr_vert_cnt$Freq)
  table4_sup[1,17] <- length(period1_2yr_vert_cnt$Freq)
  table4_sup[1,18] <- length(period1_1yr_vert_cnt$Freq) -
length(period1_2yr_vert_cnt$Freq)

  ########################################period2
  table4_sup[2,1] <- length(period2_1yr_all$Freq)
  table4_sup[2,2] <- length(period2_2yr_all$Freq)
  table4_sup[2,3] <- length(period2_1yr_all$Freq) -
length(period2_2yr_all$Freq)

  table4_sup[2,4] <- length(period2_1yr_beva_cnt$Freq)
  table4_sup[2,5] <- length(period2_2yr_beva_cnt$Freq)
  table4_sup[2,6] <- length(period2_1yr_beva_cnt$Freq) -
length(period2_2yr_beva_cnt$Freq)

  table4_sup[2,7] <- length(period2_1yr_rani_cnt$Freq)
  table4_sup[2,8] <- length(period2_2yr_rani_cnt$Freq)
  table4_sup[2,9] <- length(period2_1yr_rani_cnt$Freq) -
length(period2_2yr_rani_cnt$Freq)

  table4_sup[2,10] <- length(period2_1yr_afli_cnt$Freq)
  table4_sup[2,11] <- length(period2_2yr_afli_cnt$Freq)
  table4_sup[2,12] <- length(period2_1yr_afli_cnt$Freq) -
length(period2_2yr_afli_cnt$Freq)

  table4_sup[2,13] <- length(period2_1yr_ptcg_cnt$Freq)
```

```
  table4_sup[2,14] <- length(period2_2yr_ptcg_cnt$Freq)
  table4_sup[2,15] <- length(period2_1yr_ptcg_cnt$Freq) -
length(period2_2yr_ptcg_cnt$Freq)

  table4_sup[2,16] <- length(period2_1yr_vert_cnt$Freq)
  table4_sup[2,17] <- length(period2_2yr_vert_cnt$Freq)
  table4_sup[2,18] <- length(period2_1yr_vert_cnt$Freq) -
length(period2_2yr_vert_cnt$Freq)


  ######################################period3
  table4_sup[3,1] <- length(period3_1yr_all$Freq)
  table4_sup[3,2] <- length(period3_2yr_all$Freq)
  table4_sup[3,3] <- length(period3_1yr_all$Freq) -
length(period3_2yr_all$Freq)

  table4_sup[3,4] <- length(period3_1yr_beva_cnt$Freq)
  table4_sup[3,5] <- length(period3_2yr_beva_cnt$Freq)
  table4_sup[3,6] <- length(period3_1yr_beva_cnt$Freq) -
length(period3_2yr_beva_cnt$Freq)

  table4_sup[3,7] <- length(period3_1yr_rani_cnt$Freq)
  table4_sup[3,8] <- length(period3_2yr_rani_cnt$Freq)
  table4_sup[3,9] <- length(period3_1yr_rani_cnt$Freq) -
length(period3_2yr_rani_cnt$Freq)

  table4_sup[3,10] <- length(period3_1yr_afli_cnt$Freq)
  table4_sup[3,11] <- length(period3_2yr_afli_cnt$Freq)
  table4_sup[3,12] <- length(period3_1yr_afli_cnt$Freq) -
length(period3_2yr_afli_cnt$Freq)

  table4_sup[3,13] <- length(period3_1yr_ptcg_cnt$Freq)
  table4_sup[3,14] <- length(period3_2yr_ptcg_cnt$Freq)
  table4_sup[3,15] <- length(period3_1yr_ptcg_cnt$Freq) -
length(period3_2yr_ptcg_cnt$Freq)

  table4_sup[3,16] <- length(period3_1yr_vert_cnt$Freq)
  table4_sup[3,17] <- length(period3_2yr_vert_cnt$Freq)
  table4_sup[3,18] <- length(period3_1yr_vert_cnt$Freq) -
length(period3_2yr_vert_cnt$Freq)
}
```

요약(국문초록)

근시 맥락막 신생혈관 환자의 실제임상 치료부담 및 치료양상: 안과 공통데이터모델

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배경: 대규모 데이터 소스를 사용하여 근시 맥락막 신생혈관(mCNV) 치료에서 항혈관내피세포생성인자억제제(anti-vascular endothelial growth factor drugs)의 사용에 대한 실제임상 연구는 거의 실행되지 않았다.

목적: 본 학위논문에서는 mCNV의 치료부담 및 치료양상에 대한 연구를 하고자 한다.

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방법: 본 연구는 공통데이터모델을 이용한 후향적 관찰연구(retrospective observational study)이다. 먼저, 공통데이터모델로 변환된 분당서울대학교병원의 자료원을 이용하였다. 자료원은 18년(2003년-2020년)의 기간동안 200만명 이상의 의료이용기록이 포함되어있었으며, 여기에서 mCNV을 처음 진단받은 환자들로 구성된 환자 코호트를 구성하였다. 치료부담에 대한 연구는 연구기간에 따른 치료횟수의 변화, 치료 후 1차년도 및 이후 년도별 치료횟수, 2차 연도 무치료 환자 비율, 등을 확인하였으며, 치료양상에 대한 연구는 정의된 치료 방법들이 선택되는 순서와 분율등을 확인하였다. 공통데이터모델의 분석소프트웨이어니 ATLAS 및 OHDSI Methods Library, 그리고 R, SQL을 이용하였다.

결과: 본 연구에는 최소 1년의 관찰기간을 가진 94명의 mCNV 환자가 포함되었다. 시간이 지남에 따라 총 치료 횟수는 증가하는 경향이었다. 2년째 환자의 평균 주사 횟수는 치료 시작 후 1년째에 비해 2.14회에서 0.46회로 (2006~2017년), 1.67회에서 0.56회로 (2017년~2020년) 급격히 감소했으며 76.71%의 환자가 두 번째 해에 치료를 받지 않았다. 이런 경향은 약물종류에 상관없이 유사했다. 대부분의 환자에서 약제의 변경이 없었으며, (86.2%)

베바시주맙은 1차 선택 약제 (68.1%) 및 2차 선택 약제 (53.8%) 모두에서 가장 흔하게 사용되었다. 애플리버셉트는 시간이 지남에 따라 1차 치료제로 선택되는 비율이 늘어나는 것이 관찰되었다.

결론: 항혈관내피세포생성인자억제제은 지난 수십 년 동안 mCNV를 1차 및 2차 치료제로 치료하는 데 주로 사용되었다. 항혈관내피세포생성인자억제제의 효과도 입증되었다: 대부분의 경우는 약제의 변경이 없는 것이 충분하고 두 번째 해부터 치료 부담이 크게 줄어든다.

주요어: mCNV, 병리학적 근시, 치료 경로, 항-VEGF 약물, 베바시주맙, 평균 주사, CDM, OHDSI, 관찰 연구

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