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Impact of Macular Neovascularization Architecture in Age-Related Macular Degeneration on Treatment Requirement During the First 5 Years of Treatment

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Abstract

Background: To investigate baseline MNV characteristics in Optical Coherence Tomography Angiography (OCTA) and its impact on therapeutic needs and visual acuity after 5 years in initially therapy-naïve eyes. Methods: A retrospective study of 43 therapy-naïve eyes with neovascular AMD (nAMD). OCTA was performed at baseline and all eyes were observed for 5 years. MNV architecture was characterized by area, total vessel length, flow density and fractal dimension. These variables were tested for correlation with the number of administered intravitreal injections (IVIs) and best-corrected visual outcome (BCVA) after 5 years of treatment. Results: Mean follow-up time was 4.97 ± 0.21 years. Area and total vessel length of MNVs were significantly associated with a higher number of administered IVIs after 5 years ($p < 0.05$), flow density significantly correlated with fewer IVIs ($p < 0.05$). Fractal dimension showed a tendency to more IVIs ($p = 0.056$) after 5 years. Flow density at baseline correlated with a better BCVA ($p < 0.05$). In contrast, MNV area size, total vessel length and fractal dimension did not show any correlation to BCVA after 5 years ($p > 0.05$). Conclusions: Specific features of MNV architecture such as area, total vessel length and flow density can predict long-term treatment requirement and visual outcome. Further studies using deep learning algorithms are necessary to explore the usage of these findings in daily practice.

Keywords: Age-related Macular Degeneration; Optical Coherence Tomography Angiography; Macular Neovascularization; Intravitreal Injection

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1. Introduction

Age-related macular degeneration (AMD) is a chronic, progressive retinal disease that poses a significant risk of vision loss, especially when advancing to late-stage manifestations presenting as neovascular AMD (nAMD) or geographic atrophy (GA). In industrialized nations, advanced age-related macular degeneration is regarded as the primary cause of blindness among the adult population. Due to the progressive nature of the disease with a greater likelihood of AMD in older patients and the demographic shift of societies, the amount of AMD patients is anticipated to grow by 15% until 2050 in the European Union [1]. While the treatment of nAMD with intravitreal injections (IVIs) of anti-VEGF (Vascular Endothelial Growth Factor) formulations has lead to the stabilization of visual acuity in most patients [2], it is accompanied by tremendous costs, time and human resources within

the healthcare system [3]. Moreover, treatment response may vary markedly between patients. This is why multimodal imaging to assess prognosis on long-term disease outcome is crucial at initial diagnosis.

In the past, prognosis assessments have primarily relied on findings in Optical Coherence Tomography (OCT) and guidelines recommend OCT for initial diagnosis as well as monitoring of disease activity [4]. Within this framework, attention is directed toward secondary manifestations, including intraretinal and subretinal fluid accumulation, whereas the primary pathology, macular neovascularization (MNV), remains not directly assessed. Optical Coherence Tomography Angiography (OCTA) is a relatively new, non-invasive imaging modality that detects motions of blood cells and translates it into a grayscale image of vascular morphology more in contrast to its environment [5]. Unlike fluorescein angiography (FA), OCTA works without intravenous injection of fluorescein and the accompanying risks such as anaphylaxis. The introduction of OCTA and scientific studies using this new technology have not only led to a better understanding of the pathophysiology of diseases such as nAMD, but also to a better understanding of physiological processes such as the precise anatomy of the various capillary networks within the retina [6]. In nAMD, OCTA facilitates a more complex view of the MNV architecture with a three-dimensional presentation [7]. Additionally, the scans can be transformed into mathematical descriptions of MNV morphology [8]. Using MNV vascular analyses, differences in vascular architecture between the various MNV types have been identified [8]. In addition, numerous studies have investigated characteristic MNV vascular configurations and their association with disease activity. Features such as well-defined borders from the surrounding tissue, a dense capillary network at the MNV periphery, tightly packed vascular structures, and the presence of vascular loops are indicative of high MNV activity [9,10]. Our hypothesis is that in-depth analysis of variations in vascular architecture may facilitate the discovery of novel biomarkers for assessing disease activity and forecasting disease progression. In previous studies, we were already able to show that distinct OCTA parameters such as MNV size and MNV complexity were associated with a higher therapy burden in short to medium observation periods up to 3 years. However, at the time of initial diagnosis it is particularly interesting whether these parameters retain their prognostic relevance even after a long observation period [11].

The purpose of this study was therefore to determine MNV morphology parameters in OCTA that have an influence on the therapy requirement and visual outcome after 5 years of treatment to enhance baseline assessment. To that end, we extended the observation period of a cohort that had already been investigated in a previous study [11] to a total of 5 years.

2. Methods

This is a retrospective, single-center study. It was approved by the local ethics committee and all patients consented to participate in the study. Data management was carried out in concurrence with the Declaration of Helsinki and its amendments.

2.1. Study Protocol

Therapy-naive patients diagnosed with nAMD between November of 2016 and May of 2020 were consecutively included in this study. Ophthalmoscopy, fluorescence angiography and SD-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) assured proper diagnosis and exact classification of MNV type. The baseline assessment also included BCVA and OCTA. After a period of 5 years of treatment with anti-VEGF substances including aflibercept, ranibizumab and bevacizumab, patients had a follow-up visit to determine the long-term outcome including a clinical work-up with BCVA, ophthalmoscopy

and OCT scan. The initial diagnosis, clinical work-ups and imaging assessments were verified by a single certified grader at our Reading Center.

In order to carry out OCTA imaging at baseline, OCTA PLEX® Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA) was used. This machine uses the Swept-Source technique with a wavelength of 1060 nm and a scanning rate of 100,000 A-scans per second, capturing two consecutive B-scans of 500 A-scans within a 6 × 6 mm field of view. We selected the automatic artifact suppression feature to present the MVN as realistically and authentically as possible and create more accuracy and reliability [12]. In order to detect the MNV, we selected the ORCC segmentation. This is short for "outer retina to choriocapillaris" and expands from the outer plexiform layer to 49 µm below the Bruch's Membrane. This slab is offered by most manufacturers because it has been established as a suitable layer for rapid yet effective screening for MNV [13]. In cases of segmentation errors, lines were corrected by the grader. Next, the approved OCTA images were transferred to the program Fiji (National Institute of Mental Health, Bethesda, MD, USA) in order to frame and separate MNVs from the rest of the image by a single trained and certified grader at our Reading Center. The MNV network was then obtained with MatLab (Mathworks, Version R2014b; Natick, MA, USA). The vascular structure was skeletonized by multiscale calculation of the gradient field in the en-face image of the OCTA scan, as already described in detail in published studies [14]. A binarized image of the MNV was computed in order to calculate flow density. The imaging modalities used in this study can be seen in Figure 1.

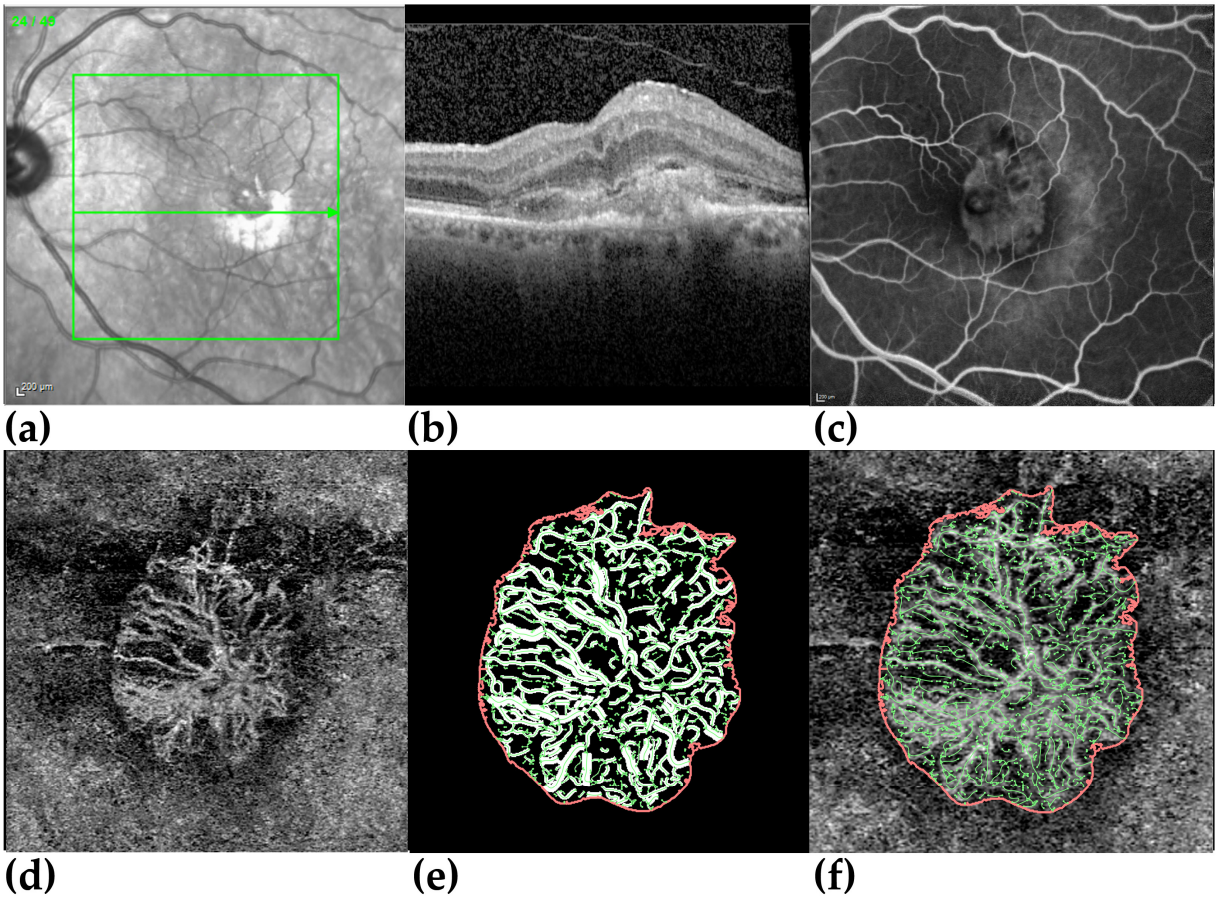


Figure 1. Overview of a case with typical type 2 MNV in IR image (**a**) with a green line referring to the corresponding OCT slice (**b**), FA (**c**), en-face view of the ORCC segmentation in OCTA (**d**), magnified view of the binarized vessels (**e**), and the skeletonized vessels (**f**).

Four variables were used to characterize architecture of the MNV: area, total vessel length (sumL), flow density and fractal dimension (FD). The total vessel length describes the total length obtained when the lengths of all individual vessels are added together. Area portrays the extent of the MNV in the horizontal plane seen in the OCTA en-face view. Flow density is a parameter describing the extent of actual vascularization inside of the MNV area. The complexity of an object is described by the fractal dimension, a parameter identified to be of importance during anti-VEGF treatment [15].

The described parameters assessing the MNV architecture obtained by OCTA and the aforementioned data transformation were then analyzed for correlation to the amount of IVIs administered within the first 5 treatment years and to the BCVA after 5 years.

Eyes presenting with alternative diagnoses to nAMD and/or concurrent retinal pathologies, including diabetic retinopathy or retinal vein occlusion, were excluded. Moreover, eyes with inadequate quality of OCTA imaging or where MNV could not be visualized at baseline were removed from the study. Last but not least, patients who did not have a follow-up visit after 5 years were excluded from further analyses. Due to the long-term follow-up over five years, missed follow-up visits occurred for several reasons, such as patients transitioning to other healthcare providers or passing away.

2.2. Statistical Analysis

Statistical analyses were calculated with software R (Version 4.2.3, R Core Team 2023. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The threshold for a significant result was set at 5%. Mean ± standard deviation are displayed to describe the distribution of numeric data and contingencies to report categorial variables. For correlation tests, we chose weighted linear regression models to measure correlation of the independent variables (IVs) and dependent variables (DVs). Weights were introduced by the geometric mean weights of the involved variables to reduce the influence of far outliers by the 10% and 90% percentiles (p_{10} and p_{90}) as

$$w(x) = \exp -0.5 \cdot \left(\frac{\max\left\{0,\ t_{low} - x,\ x - t_{high}\right\}}{0.5 \cdot \left(t_{high} - t_{low}\right)} \right)^2 \text{ where}$$

$$t_{low} = p_{10} - 1.5 \cdot (p_{90} - p_{10}) \text{ and } t_{high} = p_{90} + 1.5 \cdot (p_{90} - p_{10})$$

This statistical method is a pragmatic approach which helps to lower the impact of markedly differing values without requiring their exclusion. Without adjusting for statistical outliers, there is a risk that the regression model will be distorted, especially in cases of a small sample size. However, removing the outliers would completely disregard valid values from a sample [16]. Additional exploratory multivariable analyses for parameters like baseline BCVA or age were not performed to maintain a simple and robust model.

3. Results

After all of the aforementioned exclusion criteria were applied, from the initial 107 eyes, a total of 43 eyes remained for further analyses. Out of these, 11 eyes were of male patients (25.6%) while 32 eyes were of female patients (74.4%). Mean age was 77.84 ± 6.99 years. The majority of MNV were type 1 (41.9%), followed by type 2 MNV (27.9%) and type 3 MNV (30.2%). At baseline, BCVA was 0.63 ± 0.35 logMAR, and 0.57 ± 0.37 logMAR at 5 years. An average of 32.98 ± 11.92 IVIs were given during this period. Mean follow-up time was 4.97 ± 0.21 years.

The mean area of the MNV was 1.12 ± 1.09 mm^2, whereas the mean flow density was 41.54 ± 6.26%. The medial fractal dimension amounted to 1.26 ± 0.15 and the mean total vessel length was 13.00 ± 12.89 mm.

Three of the MNV parameters showed a significant correlation with the number of administered IVIs after 5 years. A greater MNV size and a greater total vessel length were both associated with a greater amount of IVIs ($p < 0.05$). Meanwhile, a higher flow density was correlated with a smaller amount of IVIs ($p < 0.05$). A higher fractal dimension showed the tendency to a higher need of IVIs; however, this correlation did not reach statistical significance ($p = 0.056$). In terms of visual outcome, only one parameter showed a correlation with the BCVA after 5 years of treatment. Greater flow density at initial diagnosis was correlated with improved visual acuity ($p < 0.05$), while the area, the total vessel length and the fractal dimension of the MNV did not show any correlation to BCVA after 5 years ($p > 0.05$). Table 1 shows all assessed OCTA variables and their associations with the amount of IVIs and BCVA outcome.

Table 1. OCTA variables and their impact on IVIs and BCVA after 5 years. Significant values are marked with *.

	Unit	**beta (β)**	***p* Value**
Influence on IVIs			
MNV area	1 mm	3.617	<0.05 *
MNV total vessel length	20 mm	6.254	<0.05 *
MNV flow density	10%	−6.550	<0.05 *
MNV fractal dimension		23.418	0.055
Influence on BCVA			
MNV area	1 mm	0.0029	0.495
MNV total vessel length	20 mm	0.0360	0.622
MNV flow density	10%	−0.150	<0.05 *
MNV fractal dimension		0.379	0.222

4. Discussion

Beyond its non-invasive nature, OCTA demonstrates specific advantages over both OCT and fluorescein angiography (FA), thereby enhancing its diagnostic utility. Thanks to the 3-dimensional view of OCTA imaging, a more complex visualization of MNV is possible [17]. Today, even MNVs which have not led to exudation with subretinal and/or intraretinal fluid or visual deterioration can be detected. These "sub-clinical" or "non-exudative" MNVs are at great risk of transforming into exudative MNVs and therefore need to be carefully monitored [18,19]. OCTA has also led to the potential to mathematically describe MNV. Told et al. have pointed out the dynamic pattern of some MNV morphology parameters in OCTA, showing a reaction to the initial therapy and a subsequent deterioration as the therapy effect wears off. The MNV size, for example, decreases initially and then expands above the size at baseline right after the first uploading phase with an anti-VEGF substance [20]. Apart from the depiction of these changes to initial therapy, parameters describing MNV architecture have also gained interest in terms of possibly serving as predictors of the development of the disease on the long-term.

There are studies which have previously reported a correlation of specific parameters describing the morphology of MNV in OCTA on the one hand and important outcome variables like therapy burden and visual acuity on the other. Faghihi et al. described the mean vessel percentage area and the fractal dimension to be significantly associated with a

better visual outcome after 3 months and 12 months [21]. Other publications have shown an influence of the initial area size, the total vessel length and the flow value on BCVA after 1 year, and a significant influence of the flow value and the vessel caliber on the therapy burden during the first year of treatment [22]. MNV area, total vessel length and fractal dimension were associated with a higher amount of administered IVIs during the first 3 years of therapy [11].

The aim of this study was to investigative the significance of these MNV characteristics on long-term disease development. We found that parameters describing the size of an MNV, namely the area and the total vessel length, were significantly associated with a higher number of given IVIs after 5 years ($p < 0.05$), whereas the flow density was significantly correlated with fewer IVIs ($p < 0.05$). The fractal dimension showed a tendency to more IVIs ($p = 0.056$) after 5 years. The flow density at initial diagnosis was also correlated with a better visual acuity ($p < 0.05$). However, MNV area size, total vessel length and fractal dimension did not show any correlation to BCVA after 5 years ($p > 0.05$).

The area and total vessel length are two variables characterizing the size of a vessel network. In the present study, both of them correlated with a higher therapy burden during the first 5 years of treatment, both in line with previous research with shorter observation periods [11]. Some of the parameters assessing the MNV morphology like the vascular density as well as the fractal dimension were described as suitable variables to evaluate MNV activity [23]. Fractal dimension serves as a tool to illustrate the complexity of vessels. In our study, it showed the tendency to a higher number of administered IVIs within the first 5 years of treatment but just missed the threshold of significance. This is likely due to the smaller sample size in contrast to previous studies that have pointed out this correlation in shorter observation periods [11]. This observation is consistent with a study published by Song et al. They investigated which morphological characteristics in OCTA are associated with residual retinal fluid after an initial anti-VEGF loading dose. They were able to show that the presence of loops (anastomoses between small vessels) and peripheral arcades (connections between small capillaries with tangled morphology in the peripheral aspect of the MNV) at baseline correlated with residual fluid after loading dose, with only the peripheral arcades remaining significant in a multivariate analysis. This study therefore also showed that more complex MNVs appear to respond less well to therapy, which could result in an increased need for treatment [24].

The flow density represents the proportion of pixels where a flow signal was detected, compared to the total quantity of pixels within the MNV area. In this study, we found that flow density was associated with lower therapy requirements and a better visual outcome after 5 years, meaning that this parameter had the greatest importance on the long-term outcome in this study. We hypothesize that a higher flow density may serve as an indicator of a relatively younger MNV which is more susceptible to anti-VEGF treatment. However, this is only one possible interpretation of the data, and there is currently no certain basis for this in the existing literature. Previous findings have shown that a lower flow density is associated with retinal atrophy, a clinical finding seen in late-stage forms of AMD, which supports our thesis [25]. On the other hand, our result differs from the observations of Schranz et al. They found an increased probability of persistent IRF after loading dose in larger, more densely packed MNVs and concluded that higher density indicates more active MNV, which is likely to have a greater need for therapy [26]. Since we did not examine fluid volumes in our study, it is difficult to directly compare these two studies. However, our long-term observation shows that increased flow density at baseline is associated with a lower long-term need for therapy. Another retrospective study by Jaggi et al. examined eyes that had been treated with a treat-and-extend regimen and in which therapy could be discontinued due to lack of disease activity. These eyes were monitored further, and part of

the cohort required renewed therapy due to renewed activity. They found that a higher vessel density in OCTA at the time of discontinuation of therapy was associated with an increased risk of recurrence of disease activity over time. However, these results are not readily comparable with the results of the present study because the cohort of Jaggi et al. is a very specific population of eyes in which therapy could initially be paused due to a lack of signs of activity. In addition, the OCTAs were performed at a completely different time than in our study, in which the OCTA parameters were measured at the time of initial diagnosis, i.e., before the start of therapy [27].

MNV area size, total vessel length and fractal dimension did not show any correlation with the visual outcome after 5 years. In previous studies with shorter observation periods, several MNV morphology parameters were associated with the visual outcome in nAMD, such as mean vessels percentage area, fractal dimension, total vessel length and MNV area size [21,22]. The deficiency of finding more variables associated with BCVA in our study may be due to the long observation period of 5 years. As we know from the natural course of the disease, most nAMD patients experience a slow but steady decline of visual acuity despite intensive treatment [28]. This might complicate the differentiation between BCVA outcomes within the cohort when long observation periods like 5 years are chosen, thus making it unlikely to find relevant baseline predictors. Hence, these parameters might be helpful to predict visual outcome of shorter observation periods, but not to predict long-term visual outcomes.

There are several strengths and limitations to this study. The greatest strength of this study is its long observation period of 5 years. Finding relevant baseline parameters to improve the understanding of different courses of the diseases at first diagnosis is not only important to identify patients who might need special attention during treatment, but also to improve the dialog between patient and practitioner. However, long observation periods bring the disadvantage of greater percentages of patients being lost to follow-up, a problem we also experienced in this study. Another strength of this study is the relatively new technique used, namely OCTA imaging and data processing allowing for a more detailed description of MNV architecture. The findings may be able to improve the characterization of different baseline disease conditions, which in the past primarily relied on ophthalmoscopy and OCT findings. However, we have yet to figure out how we can implement these techniques into our daily clinical routine. The data transformation following the OCTA imaging described above is still a time-consuming process and would need to be automatized to use this technique in a daily routine. The data could probably be best used in the context of deep learning algorithms, which could additionally use data assessed by OCT and other clinical findings to create a better idea about the long-term outcome. Further limitations include the retrospective character of the study as well as the single-center design.

Moreover, a major limitation is the restricted resolution power of the OCTA technology, a factor which has to particularly be considered when fine vascular structures are analyzed. Also, only the perfused portion of the MNV in a given two-dimensional segmentation is described by the tested variables area, total vessel length, FD and flow density. Furthermore, we manually outlined the MNV, which is a process susceptible to subjectivity to some extent. Vessels may also be incorrectly identified by the process of automated vessel skeletonization.

5. Conclusions

We investigated baseline MNV characteristics in OCTA and its impact on the therapy requirements during the first 5 years of treating nAMD, as well as the visual outcome after 5 years. We were able to demonstrate that morphology variables describing the MNV

size were correlated with a higher therapy need. Flow density, potentially serving as an indicator of a younger MNV which is more susceptible to treatment, seemed to be the most important parameter at baseline as it was associated with both fewer IVIs and a better visual outcome after 5 years. Nevertheless, the methodology used in this study is time-consuming and an OCTA assessment of every MNV is not yet feasible in clinical practice. In addition, a lack of standardization between different OCTA devices makes it difficult to compare images and transfer study results. Future studies are therefore needed to address the issue of OCTA comparability across different devices. Processes that automate the time-consuming process of data extraction and evaluation would also be helpful, as is already being implemented, at least in part, in individual studies [29]. In order to enable the most accurate prediction of long-term progression possible, a combination of different imaging modalities consisting of OCT, OCTA, and clinical parameters would probably be most effective. The use of deep learning algorithms may help to achieve this goal.

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Data Availability Statement: The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author HF upon request.

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References

1. Li, J.Q.; Welchowski, T.; Schmid, M.; Mauschitz, M.M.; Holz, F.G.; Finger, R.P. Prevalence and incidence of age-related macular degeneration in Europe: A systematic review and meta-analysis. *Br. J. Ophthalmol.* **2020**, *104*, 1077. [CrossRef]
2. Lim, L.S.; Mitchell, P.; Seddon, J.M.; Holz, F.G.; Wong, T.Y. Age-related macular degeneration. *Lancet* **2012**, *379*, 1728–1738. [CrossRef] [PubMed]
3. Almony, A.; Keyloun, K.R.; Shah-Manek, B.; Multani, J.K.; McGuiness, C.B.; Chen, C.-C.; Campbell, J.H. Clinical and economic burden of neovascular age-related macular degeneration by disease status: A US claims-based analysis. *J. Manag. Care Spéc. Pharm.* **2021**, *27*, 1260–1272. [CrossRef] [PubMed]
4. Schmidt-Erfurth, U.; Chong, V.; Loewenstein, A.; Larsen, M.; Souied, E.; Schlingemann, R.; Eldem, B.; Monés, J.; Richard, G.; Bandello, F. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br. J. Ophthalmol.* **2014**, *98*, 1144. [CrossRef]
5. Coscas, G.; Lupidi, M.; Coscas, F. Image Analysis of Optical Coherence Tomography Angiography. *Dev. Ophthalmol.* **2016**, *56*, 30–36.
6. Tombolini, B.; Crincoli, E.; Sacconi, R.; Battista, M.; Fantaguzzi, F.; Servillo, A.; Bandello, F.; Querques, G. Optical Coherence Tomography Angiography: A 2023 Focused Update on Age-Related Macular Degeneration. *Ophthalmol. Ther.* **2024**, *13*, 449–467. [CrossRef] [PubMed]
7. Spaide, R.F.; Fujimoto, J.G.; Waheed, N.K.; Sadda, S.R.; Staurenghi, G. Optical coherence tomography angiography. *Prog. Retin. Eye Res.* **2018**, *64*, 1–55. [CrossRef] [PubMed]
8. Nakano, Y.; Kataoka, K.; Takeuchi, J.; Fujita, A.; Kaneko, H.; Shimizu, H.; Ito, Y.; Terasaki, H. Vascular maturity of type 1 and type 2 choroidal neovascularization evaluated by optical coherence tomography angiography. *PLoS ONE* **2019**, *14*, e0216304. [CrossRef]

9. Sulzbacher, F.; Pollreisz, A.; Kaider, A.; Kickinger, S.; Sacu, S.; Schmidt-Erfurth, U.; The Vienna Eye Study Center. Identification and clinical role of choroidal neovascularization characteristics based on optical coherence tomography angiography. *Acta Ophthalmol.* **2017**, *95*, 414–420. [CrossRef]
10. Coscas, G.J.; Lupidi, M.; Coscas, F.; Cagini, C.; Souied, E.H. Optical coherence tomography angiography versus traditional multimodal imaging in assessing the activity of exudative age-related macular degeneration: A New Diagnostic Challenge. *Retina* **2015**, *35*, 2219–2228. [CrossRef]
11. Grün, M.; Rothaus, K.; Ziegler, M.; Lange, C.; Lommatzsch, A.; Faatz, H. The Vascular Architecture of Macular Neovascularization in Age-Related Macular Degeneration as a Predictor of Therapy Requirements: A 3-Year Longitudinal Analysis. *Diagnostics* **2025**, *15*, 982. [CrossRef]
12. Zhang, Q.; Zhang, A.; Lee, C.S.; Lee, A.Y.; Rezaei, K.A.; Roisman, L.; Miller, A.; Zheng, F.; Gregori, G.; Durbin, M.K.; et al. Projection Artifact Removal Improves Visualization and Quantitation of Macular Neovascularization Imaged by Optical Coherence Tomography Angiography. *Ophthalmol. Retin.* **2016**, *1*, 124–136. [CrossRef]
13. Greig, E.C.; Duker, J.S.; Waheed, N.K. A practical guide to optical coherence tomography angiography interpretation. *Int. J. Retin. Vitr.* **2020**, *6*, 55. [CrossRef]
14. Faatz, H.; Farecki, M.-L.; Rothaus, K.; Gunnemann, F.; Gutfleisch, M.; Lommatzsch, A.; Pauleikhoff, D. Optical coherence tomography angiography of types 1 and 2 choroidal neovascularization in age-related macular degeneration during anti-VEGF therapy: Evaluation of a new quantitative method. *Eye* **2019**, *33*, 1466–1471. [CrossRef] [PubMed]
15. Al-Sheikh, M.; Iafe, N.A.; Phasukkijwatana, N.; Sadda, S.R.; Sarraf, D. Biomarkers of neovascular activity in age-related macular degeneration using optical coherence tomography angiography. *Retina* **2018**, *38*, 220–230. [CrossRef] [PubMed]
16. Fox, J. *Applied Regression Analysis and Generalized Linear Models*; Sage Publications: Thousand Oaks, CA, USA, 2008.
17. El Ameen, A.; Cohen, S.Y.; Semoun, O.; Miere, A.; Srour, M.; Maftouhi, M.Q.-E.; Oubraham, H.; Blanco-Garavito, R.; Querques, G.; Souied, E.H. Type 2 neovascularization secondary to age-related macular degeneration imaged by optical coherence tomography angiography. *Retina* **2015**, *35*, 2212–2218. [CrossRef]
18. Laiginhas, R.; Yang, J.; Rosenfeld, P.J.; Falcão, M. Nonexudative Macular Neovascularization—A Systematic Review of Prevalence, Natural History, and Recent Insights from OCT Angiography. *Ophthalmol. Retin.* **2020**, *4*, 651–661. [CrossRef] [PubMed]
19. Wang, Y.; Sun, J.; Wu, J.; Jia, H.; Feng, J.; Chen, J.; Yan, Q.; Huang, P.; Wang, F.; Bo, Q.; et al. Growth of nonexudative macular neovascularization in age-related macular degeneration: An indicator of biological lesion activity. *Eye* **2023**, *37*, 2048–2054. [CrossRef]
20. Told, R.; Reiter, G.S.; Mittermüller, T.J.; Schranz, M.; Reumueller, A.; Schlanitz, F.G.; Weigert, G.; Pollreisz, A.; Sacu, S.; Schmidt-Erfurth, U. Profiling neovascular age-related macular degeneration choroidal neovascularization lesion response to anti-vascular endothelial growth factor therapy using SSOCTA. *Acta Ophthalmol.* **2021**, *99*, e240–e246. [CrossRef]
21. Faghihi, S.; Faghihi, H.; Bazvand, F.; Bahar, M.M.; Torkashvand, A.; Ahmed, A.H.; Rahimi, M.; Akbarzadeh, A.; Khameneh, E.A.; Pour, E.K.; et al. Baseline optical coherence tomography angiography biomarkers predict visual outcomes in treatment-naïve neovascular age-related macular degeneration patients. *Sci. Rep.* **2024**, *14*, 24528. [CrossRef]
22. Faatz, H.; Gunnemann, M.-L.; Rothaus, K.; Book, M.; Gutfleisch, M.; Lommatzsch, A.; Pauleikhoff, D. Einfluss der CNV-Gefäßmorphologie bei exsudativer altersabhängiger Makuladegeneration auf die Visusentwicklung und den Anti-VEGF-Therapiebedarf nach 1 Jahr. *Der Ophthalmol.* **2021**, *118*, 154–161. [CrossRef] [PubMed]
23. Coscas, F.; Cabral, D.; Pereira, T.; Geraldes, C.; Narotamo, H.; Miere, A.; Lupidi, M.; Sellam, A.; Papoila, A.; Coscas, G.; et al. Quantitative optical coherence tomography angiography biomarkers for neovascular age-related macular degeneration in remission. *PLoS ONE* **2018**, *13*, e0205513. [CrossRef]
24. Song, Y.-Y.; Seong, H.-J.; Kim, J.-T.; Lee, S.-C.; Lee, M.-W. Features of optical coherence tomography angiography in age-related macular degeneration with residual fluid after three loading doses of aflibercept. *Eye Vis.* **2024**, *11*, 4. [CrossRef]
25. Faatz, H.; Rothaus, K.; Ziegler, M.; Book, M.; Spital, G.; Heimes-Bussmann, B.; Pauleikhoff, D.; Lommatzsch, A. Correlation of retinal alterations with vascular structure of macular neovascularisation in swept-source optical coherence tomography angiography in age-related macular degeneration. *Int. Ophthalmol.* **2022**, *42*, 1553–1562. [CrossRef] [PubMed]
26. Schranz, M.; Bogunovic, H.; Deak, G.; Sadeghipour, A.; Reiter, G.S.; Schmidt-Erfurth, U. Linking disease activity with optical coherence tomography angiography in neovascular age related macular degeneration using artificial intelligence. *Sci. Rep.* **2024**, *14*, 19278. [CrossRef]
27. Jaggi, D.; Marugg, S.; E Berger, L.; Munk, M.R.; Zinkernagel, M.S.; Heussen, F.M. Evaluating the risk of recurrence in neovascular age-related macular degeneration using OCT-angiography at the time of treatment exit. *Br. J. Ophthalmol.* 2025; *Published Online First*. [CrossRef]

28. Keenan, T.D.; Vitale, S.; Agrón, E.; Domalpally, A.; Antoszyk, A.N.; Elman, M.J.; Clemons, T.E.; Chew, E.Y. Visual Acuity Outcomes after Anti–Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration: Age-Related Eye Disease Study 2 Report Number 19. *Ophthalmol. Retin.* **2020**, *4*, 3–12. [CrossRef] [PubMed]
29. Savastano, M.C.; Fossataro, C.; Carlà, M.M.; Cestrone, V.; Biagini, I.; Rizzo, C.; Kilian, R.; Zweifel, S.A.; Muth, D.R.; Faraldi, F.; et al. OCT Angiography of Type 1 Macular Neovascularization in AMD: A Morphometric Evaluation. *Transl. Vis. Sci. Technol.* **2025**, *14*, 23. [CrossRef]

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