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ORIGINAL RESEARCH

The I-OPTA Questionnaire: A National Assessment of Patients with Neovascular Age-Related Macular Degeneration

Benjamin Sommer Thinggaard · Kasper Hansen · Freja Dinesen · Maria Kjøller Pedersen · Lars Morsø · Yousif Subhi · Jakob Grauslund · Lonny Stokholm

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ABSTRACT

***Introduction*:** Neovascular age-related macular degeneration (nAMD) is the leading cause of irreversible vision loss in developed countries. However, a significant gap persists in understanding this population, exacerbated by their advanced age and visual impairments, which can hinder research participation and access to healthcare. The purpose of this study was to describe the content of the questionnaire and the participating patients with nAMD.

***Methods*:** The survey includes patients diagnosed with nAMD who had previously received treatment or were currently undergoing intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. Participants were recruited using various methods, as reaching out to patients who are no longer receiving treatment poses a particular challenge. A patient and public advisory board assisted throughout the study period.

***Results*:** Of the 713 electronic invitations sent out, 494 (69.3%) patients responded to the questionnaire, with an additional 57 responses obtained through e-mail or telephone interviews. Due to the exclusion of 16 responses, there were a total of 535 valid responses, including 176 from patients previously treated and 359 from those currently undergoing treatment for nAMD. The median age of respondents was 79.9 years (interquartile range [IQR] 75.5–84.7), with 59.8% being women. Among them, 53.2% were married, while 43.1% lived alone.

***Conclusions*:** Data from the I-OPTA (Identification of Patient-Reported Barriers in Treatment for nAMD) questionnaire allows future exploration of patients who are no longer receiving treatment, patients' knowledge about preventive measures, and the impact of nAMD on visual

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B. S. Thinggaard (✉) · K. Hansen · F. Dinesen · J. Grauslund
Department of Ophthalmology, Odense University Hospital, Kløvervænget 5, Entrance 132, 1. Floor, 5000 Odense C, Region of Southern Denmark, Denmark
e-mail: benjamin.sommer.thinggaard@rsyd.dk

B. S. Thinggaard · K. Hansen · F. Dinesen · L. Morsø · Y. Subhi · J. Grauslund · L. Stokholm
Department of Clinical Research, University of Southern Denmark, Odense, Denmark

B. S. Thinggaard · L. Morsø · L. Stokholm
OPEN Data Explorative Data Network, Odense University Hospital, Odense, Denmark

M. K. Pedersen
Department of Nursing and Nutrition, University Collage Copenhagen, Copenhagen, Denmark

Y. Subhi
Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark

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function and quality of life. Future research, including studies that integrate data from corresponding retinal images and Danish national registers, has the potential to generate invaluable knowledge, providing benefits to both patients and healthcare professionals.

Keywords: Quality of life; Visual function; Preventive measures; Questionnaire; Neovascular age-related macular degeneration; Retinal disease

Key Summary Points
A significant gap persists in understanding patients with neovascular age-related macular degeneration (nAMD), exacerbated by their advanced age and visual impairments, which can hinder research participation and access to healthcare.
We describe the design, methodology, and cohort characteristics collected in the I-OPTA (Identification of Patient-Reported Barriers in Treatment for nAMD) questionnaire.
A nearly 70% response rate was achieved from electronically distributed questionnaires, supplemented with responses from telephone interviews.
Overall, 535 responses were included, with 176 responses from patients previously treated and 359 responses from patients currently under treatment for nAMD.
Data from the I-OPTA questionnaire allows future exploration of patients who are no longer receiving treatment, patients' knowledge about preventive measures, and the impact of nAMD on visual function and quality of life.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is the primary cause of irreversible vision impairment and blindness among the elderly in developed countries [1]. The disease is characterized by the abnormal growth of choroidal neovascularization beneath the retina, and it results in progressive central vision loss if left untreated. This condition significantly affects the quality of life (QoL) and functional independence of patients with nAMD [2–4]. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy in 2007 has notably improved the prognosis for nAMD, yet aging demographics are projected to escalate the number of intravitreal anti-VEGF injections by 50% from 2022 to 2027 [5].

Long-term treatment with anti-VEGF injections has been deemed safe [6, 7], but the persistently demanding nature of this treatment regimen can present challenges for elderly and visually impaired patients. Consequently, this may lead patients to discontinue treatment prematurely for various reasons [8]. Although efforts have been made to investigate this through an interview study, a broader understanding of whether specific characteristics increase the risk of treatment discontinuation is warranted [9]. However, patients who have previously undergone treatment, particularly those who have discontinued treatment against medical advice, may be challenging to recruit and engage in research. This highlights the need for a diverse recruitment approach.

The outcomes for patients in terms of visual function following the discontinuation of treatment for nAMD, whether due to medical or non-medical reasons, remain inadequately understood. Although vision function has been evaluated in numerous studies, it is important to note that visual function and quality of life (QoL) do not necessarily correlate [10, 11]. QoL is also a crucial aspect to consider when assessing the treatment of eye diseases, given that most eye conditions are not life-threatening but profoundly affect patients' well-being [12]. Studies have evaluated QoL in patients with nAMD [13, 14], but to our knowledge, no studies have explored QoL after ending treatment.

Finally, research indicates that smoking and physical inactivity elevate the risk of nAMD, while the consumption of high doses of vitamins C and E, β-carotene, and zinc (commonly

known as AREDS-2 vitamins) can hinder the progression from intermediate age-related macular degeneration (AMD) to nAMD [15–17]. Patients with nAMD have expressed a desire to know more about preventive measures, enabling them to play an active role in mitigating the progression of the condition [9]. However, uncertainties exist regarding the extent to which patients adhere to these recommendations when adequately informed about them.

The I-OPTA (Identification of Patient-Reported Barriers in Treatment for nAMD) questionnaire collected data on the characteristics, visual function, and QoL of patients with nAMD, as well as their knowledge of preventive measures for nAMD. Future studies will use and analyze this data to focus on patients who are no longer receiving treatment, explore patients' knowledge about preventive measures, and assess the impact of nAMD on visual function and QoL.

In this paper, we describe the design, methodology, and cohort characteristics in the I-OPTA questionnaire.

METHODS

Questionnaire Development

The questionnaire was developed by a consensus group comprising experts in nAMD and questionnaire methodology, drawing on both a priori knowledge and insights gained from 21 semi-structured interviews conducted among patients with nAMD at Odense University Hospital [9].

The validation process of the questionnaire included pilot testing by a total of seven patients undergoing treatment for nAMD. These patients answered the electronic questionnaire either before or after their treatment at the hospital. During the questionnaire completion, they had the option to receive assistance from their relatives. Face-validity assessments were conducted with the primary investigator seated beside the respondents, carefully observing as they answered the questionnaire. Afterwards, the patients and their potential relatives were interviewed regarding the questionnaire, including any interpretational challenges with the questionnaire and if any questions posed difficulties. They were also asked about their general perception of the questionnaire, including its structure and layout and if there were any other relevant questions they would like to see included in the questionnaire. This face-validity assessment was used to explore if the questionnaire was comprehensive and feasible based on subjective judgments.

The questionnaire consisted of five different parts:

Background questions aimed at characterizing patients with nAMD in terms of current treatment status, marital status, family history of AMD, transportation to hospital, occupation, and reasons for eventual discontinuation of treatment.

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) consists of 25 items that assess various aspects of vision function. Scores on the NEI VFQ-25 range from 0 to 100, with higher scores indicating better visual function [18, 19]. Validation studies have highlighted the reliability of the instrument and construct validity in assessing vision-related functioning outcomes among patients with AMD [19–21]. A Danish version of the instrument has been translated and validated among patients with AMD at Roskilde University Hospital by Sorensen et al. in 2011 [11].

The Macular Degeneration on Quality of Life (MacDQoL) questionnaire consists of 22 domains, each comprising a question about the impact on QOL and a question about importance. The impact scores (from − 3 to + 1) are multiplied by the importance scores (from 0 to 3) to give a weighted impact score for each domain of between − 9 and + 3. The use of impact and importance scores enables an estimation of the impact of AMD on an individual's QoL. The MacDQoL demonstrates strong face and content validity, along with evidence of solid internal consistency, reliability, and construct validity [22]. The linguistic validation of the MacDQoL questionnaire from the original language to Danish was conducted by the Mapi Institute in Lyon, France in 2006 [23].

Preventive measures were self-developed questions focusing on clarifying patients'

understanding and utilization of strategies such as smoking cessation, AREDS-2 vitamin supplements, and physical activities. The response categories were primarily yes/no/don't know. Two questions allowed free-text responses, such as "Please specify why you are not taking the recommended dose".

Endophthalmitis and Charles Bonnet syndrome were the final components of the questionnaire assessing patients' knowledge of both conditions. Endophthalmitis is a rare but serious inflammatory condition of the eye that can occur after anti-VEGF injections, while Charles Bonnet syndrome is a condition where individuals with visual impairment experience vivid visual hallucinations. The questions were self-developed with yes/no/don't know as response categories, and they aimed to determine whether patients were familiar with these conditions and if they had ever experienced them firsthand.

The questionnaire is available as supplementary information (see the appendix in the electronic supplementary material).

Cohort Recruitment and Eligibility

We employed different methods to recruit patients who have undergone or are currently undergoing treatment with intravitreal anti-VEGF injections for nAMD (see Figure S1 in the electronic supplementary material).

Patients currently undergoing treatment for nAMD were recruited at the Department of Ophthalmology at Odense University Hospital in September and October 2023. Initially, the treatment regimen involves three anti-VEGF treatments administered at 4-week intervals. Following this, the treatment frequency is adjusted, typically comprising three treatments at a specific interval before undergoing further evaluation and planning. During their anti-VEGF treatment sessions, patients were asked if they would be willing to participate in the study. Those who agreed received written information about the study.

Patients who had previously received anti-VEGF injections for nAMD but were no longer undergoing treatment were recruited through three distinct methods:

1. Patients were recruited at the Department of Ophthalmology at Odense University Hospital from December 2022 to March 2023, where an ophthalmologist invited them to participate in the study upon discharge from the department.
2. Patients were recruited through a central patient registry at Odense University Hospital, which comprised all patients recorded as discharged from the Department of Ophthalmology between January 2019 and December 2021. If these patients subsequently resumed treatment, they were included in the study as patients undergoing current treatment.
3. Efforts were made to recruit patients through postings on various social media platforms and newsletters. Additionally, relatives of patients who had discontinued treatment were encouraged to contact the study group if they came across the postings.

Patients were invited to participate irrespective of the number of injections they had received, whether they underwent unilateral or bilateral treatment, or the intervals between injections, as long as they had received at least one injection of intravitreal anti-VEGF inhibitor for the treatment of nAMD. Patients with severe Alzheimer's disease and individuals who were deaf-blind were not offered the opportunity to participate in the study.

Distribution of the Questionnaire

In Denmark, all citizens are legally required to use and have access to a digital mail solution by the name Digital Post. Digital Post is used for communication between the citizens and public services in Denmark, including hospitals. A link to the online questionnaire was distributed via this Digital Post account. Should a patient fail to respond or provide a complete response within 2 weeks, a reminder containing a new link was sent via Digital Post. A last reminder was sent after an additional 2 weeks, and if the patients still had not responded after another 2 weeks, they were recorded as 'not responding'. Citizens can apply for exemption from Digital Post, e.g., if they have impaired vision or

other health conditions [24]. Patients who were exempt from Digital Post were contacted by phone and given the option to complete the questionnaire via email or through a telephone interview conducted by a scientific assistant. The assistant read out the questions and answer options, allowing the patient to answer the questions during the phone interview. Subsequently, the scientific assistant entered the patient's responses directly into the electronic questionnaire. All patients were informed, either in writing or verbally, that they could enlist the help of a family member to answer the questionnaire, as long as the responses reflected the patient's own perspectives.

Patient and Public Involvement

To ensure the relevance and applicability of the study with patient and public involvement (PPI), a continuous advisory board was established. This board consisted of five individuals currently undergoing treatment for nAMD and three ophthalmologists. Moreover, three out of five patients in the PPI had their close relatives present at the meetings, providing valuable insights from multiple perspectives. Throughout the research process, the PPI offered feedback on various aspects of the study, including the enrollment process of the cohort and the content, format, wording, structure, and length of the questionnaire. Their contributions helped ensure that the research effectively captured the patient's viewpoint and addressed the concerns and needs of both patients and the broader public.

Data Management

We employed an electronic data capture system, REDCap, to create and distribute the questionnaire via Digital Post. REDCap is a software solution specifically crafted to facilitate clinical and translational research [25]. The responses from participating patients were directly entered into the REDCap database for storage.

Data were securely stored and managed on a secure server at Open Patient Data Explorative Network (OPEN), located at Odense University Hospital and the University of Southern Denmark, Odense, Denmark. All participating patients provided written or verbal informed consent before completing the questionnaire. Data management and descriptive statistics were carried out using STATA 18 (StataCorp LP, College Station, TX, USA).

Statement of Ethics

The study adhered to the ethical principles outlined in the Declaration of Helsinki. Prior to participating in the study, all participants provided written informed consent. Confidentiality of the participants' data was strictly maintained, following established guidelines for data handling and protection, including the use of electronically secured databases with log files and access limited to only two of the authors. The study was assigned the record number 22/10138 in the register of the Region of Southern Denmark, indicating its official registration. Although the study was reviewed by The Regional Committees on Health Research Ethics for Southern Denmark, it did not require explicit permission to be conducted.

RESULTS

Development and Recruitment

During the pilot test, two questions were incorporated into the questionnaire based on respondents' feedback. One addressed insecurity while driving, and the other inquired about conditions like lung or heart disease that might cause increased breathlessness during physical activity. Overall, respondents in the pilot test were satisfied with the layout and content of the questionnaire, and none of the questions posed persistent issues for them. Thus, the questionnaire held 129 items, with an additional 23

items pertaining to preventive measures for patients currently under treatment.

We sent out 713 participation invitations via Digital post, from which we received 494 (69.3%) responses. Patients who were exempt from Digital Post ($n = 316$) were contacted by telephone, resulting in 52 patients completing the questionnaire via telephone interview and five patients completing it through a link sent by e-mail. The remaining patients either had invalid phone numbers, did not answer calls, had poor hearing, declined participation, or had passed away. Overall, we had to exclude responses from 16 patients either because they stated they had not received treatment for nAMD, or because they failed to indicate whether they were currently undergoing treatment or not (Fig. 1).

Cohort Characteristics

Between September 29, 2023, and February 19, 2024, a total of 535 patients with nAMD responded to the questionnaire either fully or partially. The NEI-VFQ-25 questionnaire and the MacDQoL questionnaire were completed by 528 (98.7%) and 508 (95.0%), respectively. Among patients currently undergoing treatment, 346 patients (96.4%) responded to the questions about preventive measures (Fig. 2).

The median age of respondents was 79.9 years (interquartile range 75.5–84.7), with 59.8% being women. Among them, 53.2% were married, while 43.1% lived alone. Most of the patients were retired and 31.9% received assistance with completing the questionnaire. Among the respondents, 359 were currently undergoing treatment, while 176 had previously been treated for nAMD (Table 1).

DISCUSSION

To gain a better understanding of patients with nAMD, we conducted a questionnaire to evaluate these patients on various parameters. We observed a notable achievement with a response rate of almost 70% from the patients to whom we electronically administered the questionnaire. This response rate is significantly higher than previous studies using electronic questionnaires, and studies have highlighted the potential obstacle of time commitments in research participation [26, 27]. With this survey, we aimed to overcome this barrier by simplifying the participation process, requiring patients to complete just one questionnaire, conveniently done in their own homes. Engaging PPI, as we did, has been acknowledged as an effective approach to enhance the relevance of the study to individual patients, thus potentially increasing their willingness to participate [26]. Correspondingly, we allowed patients to seek assistance from relatives in answering the questions, as long as they provided their own perspectives. This approach intended to encourage more patients with potentially severe vision impairment to complete the questionnaire, although it may introduce some information bias when answers were discussed or even mediated by a friend or relative. Nonetheless, this method, along with telephone interviews, was implemented to counteract the risk of selection bias, wherein patients with good vision and the ability to complete an electronic questionnaire independently might be overrepresented. Using this approach, we obtained responses from a population that closely resembles both the distribution of sex and treatment duration of the entire cohort of patients with nAMD undergoing treatment in Denmark, as outlined in a recently published nationwide register-based cohort study [7]. However, the median age in this study was higher, potentially reflecting challenges in recruiting younger participants, especially those involved in full-time employment—a well-documented difficulty in engaging young adults in research endeavors [28].

The questionnaire was comprehensive and might have posed challenges for older, vulnerable patients. It could have impacted the completion rate, given previous research indicating a link between questionnaire length and dropout rates [29]. Nonetheless, the dropout rate in this study was eight percent, falling within the expected range for a questionnaire of this scale [29]. Additionally, the face validity of the

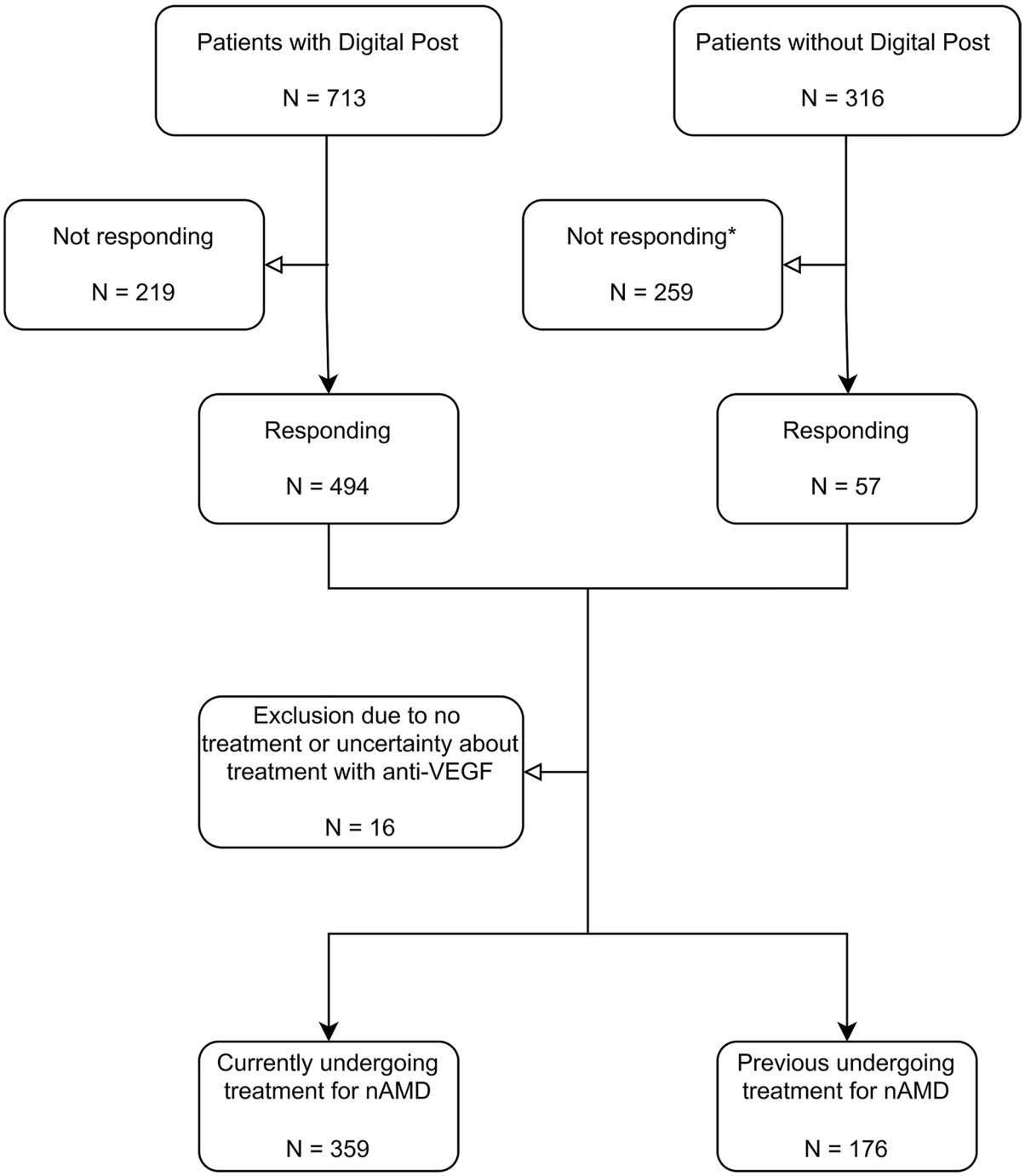

Fig. 1 The recruitment process for patients with nAMD. *When contacted by phone, the patients had invalid phone numbers, did not answer calls, had poor hearing, declined participation, or had unfortunately passed away in the meantime. *anti-VEGF* anti-vascular endothelial growth factor, *nAMD* neovascular age-related macular degeneration

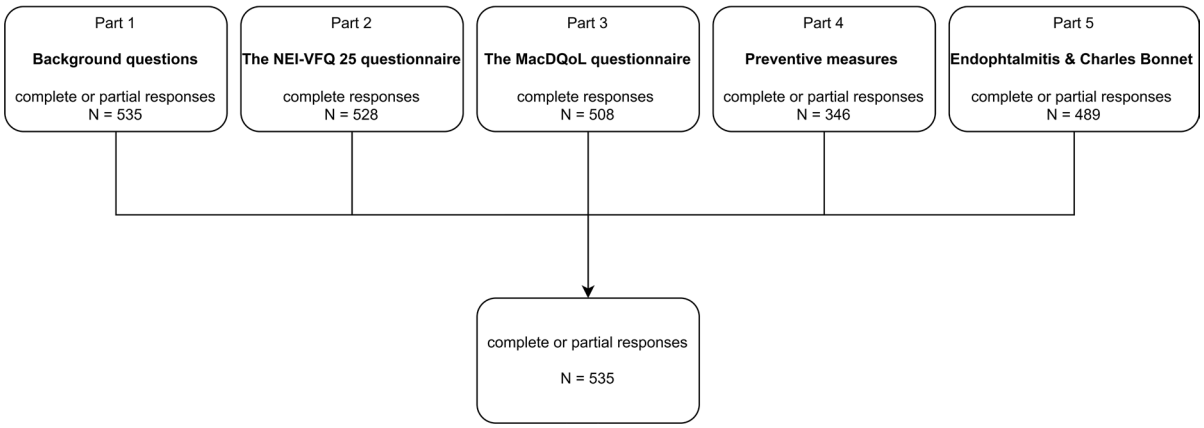

Fig. 2 Number of responses for every part of the questionnaire. Only complete responses were included for parts 2 and 3, and only patients currently undergoing treatment were asked to answer part 4 about preventive measures. *NEI-VFQ 25* National Eye Institute Visual Function Questionnaire-25, *MacDQoL* macular degeneration on quality of life

Table 1 Descriptive characteristics of patients with neovascular age-related macular degeneration previously or currently in treatment with intravitreal anti-vascular endothelial growth factor

	N **= 535**
Sex, *n* (%)	
Women	320 (59.8)
Men	215 (40.2)
Age, years (IQR)	79.9 (75.5–84.7)
Treatment initiation, year (IQR)	2019 (2016–2021)
Duration of treatment, years (IQR)	3.5 (2.0–7.0)
Marital status, *n* (%)	
Married	284 (53.2)
Widow/widower	177 (33.1)
Separated or divorced	41 (7.7)
Never married	22 (4.1)
Other	10 (1.9)
Living alone, *n* (%)	230 (43.1)
Retired, *n* (%)	516 (96.6)
Assistance in completing questionnaire, *n* (%)	170 (31.9)
Currently in treatment for nAMD	359 (66.6)

IQR interquartile range, *nAMD* neovascular age-related macular degeneration

questionnaire appeared to be sufficient based on pilot test respondents, and they did not indicate that the questionnaire was overly lengthy.

In 2019, Solomon et al. concluded in a comprehensive literature review that patient perspectives are underrepresented in published nAMD studies [30]. Since then, several studies have explored the relationship between nAMD and QoL, with varying outcomes [3]. Finger et al. found that QoL, as measured by the NEI VFQ-25, improved early in patients treated with anti-VEGF agents, with better visual acuity linked to higher QoL scores [31]. A Norwegian study reported a significant QoL increase when the better-seeing eye was treated, but no change when the worse-seeing eye was treated, despite improved BCVA [32]. Kubin et al. observed that while visual function-related QoL improved, overall health-related QoL decreased in older patients with nAMD within the first 12 months of anti-VEGF treatment, particularly in those with good baseline visual acuity or multiple comorbidities [33]. Changes in QoL thus depend on numerous factors including BCVA, age, whether one or both eyes are treated, comorbidities and treatment duration. Future studies identifying the specific factors that affect different domains QoL are essential for tailoring treatment to individual patients and making it more patient-centered.

A strength of this study was the execution of telephone interviews where two scientific assistants took on the role of the interviewer was the best feasible option, even though this method may introduce a certain degree of interview bias, as the patient needs to disclose their responses to a person associated with the treatment facility. The high response rate, which enhanced data validity and reliability, thereby reducing non-response biases was a strength as well. Furthermore, it improved data completeness and the credibility of the study findings. Finally, the use of two validated questionnaires specifically targeting nAMD is also a strength of this questionnaire. QoL encompasses various dimensions, sometimes divided into health-related QoL and visual function-related QoL [33]. Therefore, it might be important to assess patients using multiple questionnaires to capture the full range of QoL aspects, as demonstrated in this study. Acknowledging the limitations of this study is crucial. While the MacDQoL questionnaire has been validated in the native language, there has not been a cross-cultural adaptation or validation of the Danish translation among patients with nAMD in Denmark. However, we adapted the questionnaire items to be culturally appropriate and relevant through a collaboration between the expert group, PPI, and based on the results of the pilot test. Furthermore, in studies involving older individuals, recall bias is prone to occur, e.g., regarding the cessation and start of treatment. However, efforts were made to mitigate recall bias by limiting historical questions and excluding patients no longer undergoing treatment from questions about preventive measures.

CONCLUSIONS

With data from the I-OPTA questionnaire, we can explore the potential correlations between patient characteristics, their QoL and visual function outcomes, and their awareness and adoption of preventive measures. Understanding these connections may provide valuable insights into, for example, the types of patients who are more likely to engage in preventive measures and those who experience better outcomes in terms of QoL post anti-VEGF treatment.

We plan to enrich these data with follow-up questionnaires, information from Danish national registers, and details from patients' medical records, including visual acuity. Additionally, we intend to link data to better understand the relationship between QoL, visual function, and retinal markers measured by optical coherence tomography. This endeavor will benefit both patients and healthcare providers by optimizing future healthcare resource allocation.

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Author Contributions. Benjamin Sommer Thinggaard contributed to the study design and the enrollment of patients in the cohort and wrote the manuscript. Kasper Hansen and Freja Dinesen conducted phone interviews with patients. Maria Kjøller Pedersen, Lars Morsø, Yousif Subhi, Jakob Grauslund, and Lonny Stokholm contributed to the study design and writing of the manuscript. All authors critically reviewed and approved the final version of the manuscript and committed to being accountable for addressing any concerns related to the work's accuracy or integrity. Benjamin Sommer Thinggaard is acting as guarantor for this study.

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Data Availability. Data are available upon reasonable request. Data will be presented as flat text files (CSV) formatted for compatibility with other research units. The authors will electronically provide a deidentified Excel sheet including patient characteristics, NEI-VFQ-25, and/or MacDQoL answers.

Declarations

Conflict of Interest. Benjamin Sommer Thinggaard has received speaker's fee from Roche. Yousif Subhi have received speaker's fee from Bayer and Roche, and have served as an advisory board member for Apellis, not related to this work. Yousif Subhi is an Editorial Board member of *Ophthalmology and Therapy*, however, was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Jakob Grauslund declares to have received speaker's fee from Allergan, Bayer, Novartis, and Roche, and to have served as an advisory board member for Allergan, Apellis, Bayer, Novartis, and Roche, not related to this work. The authors confirm that only they have contributed to the study, and none of the companies were involved in the research, analysis, or writing of this manuscript. Kasper Hansen, Freja Dinesen, Maria Kjøller Pedersen, Lars Morsø, and Lonny Stokholm declare that no potential conflicts of interest exist in relation to this work.

Ethical Approval. The study adhered to the ethical principles outlined in the Declaration of Helsinki. Prior to participating in the study, all participants provided written informed consent. Confidentiality of the participants' data was strictly maintained, following established guidelines for data handling and protection. The study was assigned the record number 22/10138 in the register of the Region of Southern Denmark, indicating its official registration. Although the study was reviewed by The Regional Committees on Health Research Ethics for Southern Denmark, it did not require explicit permission to be conducted.

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