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Analysis of prognostic and predictive factors in neovascular age-related macular degeneration Kuopio cohort

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Abstract

Purpose: The aim of the study was to explore factors affecting the progression of neovascular age-related macular degeneration (nAMD) and identify predictive factors that can estimate the duration of intravitreal treatments.

Methods: This retrospective real-world study included 421 nAMD patients treated at the Kuopio University Hospital during years 2007–2021. The collected data included background demographics, treatment history, visual acuity and retinal biomarker analysis. Impact of baseline factors on age at diagnosis, treatment duration, received treatment intensity and visual acuity gains were analysed.

Results: Heavy smoking and high body mass index (BMI) were associated with an earlier onset, while the use of anticoagulation and anti-aggregation medication were associated with a later onset of nAMD. A low number of injections during the first year of treatment and the presence of intraretinal fluid (IRF) at baseline were associated with shorter treatment duration. Interestingly, when IRF only patients were compared to subretinal fluid (SRF) only patients, IRF patients showed higher occurrences of subretinal drusenoid deposits (43.5% vs. 15%, $p=0.04$). In addition, when all patients with IRF were compared to SRF only patients, more hyperreflective foci (HRF) and complete RPE and outer retinal atrophy (cRORA; 20.7% vs. 5%, $p=0.02$) were observed in patients with IRF.

Conclusions: Our results reveal that heavy smoking and high BMI are accelerating factors for earlier emergence of nAMD, while the presence of IRF results in a fast-progressing disease. More intriguingly, the link between IRF and appearance of subretinal drusenoid deposits, HRF, and increased retinal atrophy was observed.

KEYWORDS
ageing, atrophy, degeneration, injection, intravitreal, macula, retina

1 | INTRODUCTION

The introduction of intravitreal antivascular endothelial growth factor (VEGF) therapies has greatly improved visual outcomes for patients with nAMD and are now considered the standard of care (Chakravarthy et al., 2022; Fleckenstein et al., 2021; Mehta et al., 2018). However, vision gains achieved in clinical trials are not always realized in daily clinical practice. This may partially be due to insufficient or suboptimal treatment, as frequent intravitreal injections are often required to maintain clinical benefits but can be burdensome for both patients and clinics (Chakravarthy et al., 2022; Mehta et al., 2018). Thus, increasing patient numbers creates a challenge to the healthcare system and will underline the need to find either novel, longer-acting treatment options or ways to identify patient characteristics to provide even more personalized treatment pathways (Jorstad et al., 2020).

Hanna Heloterä and Leea Siintamo contributed equally to this work.

There is a need to better identify patients whose disease course can be significantly affected by more intense treatment, or alternatively to find out if there is a patient group who can maintain their vision with less injections (Leth-Moller Christensen et al., 2023).

As the rate of disease progression can vary between individuals, previous studies have explored various factors related to nAMD development or progression including both local retinal and systemic molecular regulators, as well as demographic, environmental and genetic factors (Heesterbeek et al., 2020). In contrast, regular exercise, higher education, use of vitamin A, vitamin B6, β-carotene, lutein and zeaxanthin, magnesium, copper, docosahexaenoic acid and omega-3 fatty acid intake seem to have protective effects against nAMD (Ristau et al., 2014; Heesterbeek et al., 2020; Agron et al., 2021). From phenotypic or optical coherence tomography (OCT) biomarkers, intraretinal fluid (IRF), width and height of subretinal hyperreflective material and fibrovascular pigment epithelial detachment have been associated with poor visual outcomes (Nawash et al., 2023). Moreover, high baseline drusen volume, presence of reticular pseudodrusen, subretinal drusenoid deposits (SDDs), irregular choroidal vessels and hyperreflective foci (HRF) are risk factors for disease progression (Heesterbeek et al., 2020; Nawash et al., 2023). HRF also serve as a prognostic marker during anti-VEGF treatment as their number is reduced in patients responsive to treatment. Markers related to higher demand for frequent anti-VEGF injections include the presence of IRF, vitreomacular adhesion and vitreomacular tractions (Nawash et al., 2023). Many genetic markers have been associated with AMD progression, but rs10922109 and rs570618 in *CFH*, rs116503776 in *C2/CFB/SKIV2L*, rs3750846 in *ARMS2/HTRA1* and rs2230199 in *C3* variants are more consistently reported (Heesterbeek et al., 2020). Even though many factors have already been described to be linked with the development and progression of nAMD, more research is needed to clarify current data and understand which of the factors are most relevant. Novel unexplored markers could provide tools to assemble this puzzle together. Finding predictive factors that would enable early intervention to delay nAMD onset would be highly beneficial. In a similar vein, being able to identify patients who are at risk for fast disease progression and need more intensive treatment approaches is much needed.

The goal of the study was to explore factors which could have an effect on the progression of nAMD or which may be a result of an altered need for treatment intensity. Explored factors included patient demographics, baseline medications and anatomical variables.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

All nAMD patients (n=421) were subjected to examination in the Department of Ophthalmology at the Kuopio University Hospital (KUH), including biomicroscopy examination, fundus photographs (Canon CX−1 Retinal Camera, Canon, Tokyo, Japan) and/or optical coherence tomography (OCT) (SPECTRALIS OCT2, Heidelberg Engineering, Heidelberg, Germany) and, when needed, fluorescein angiography (FAG) (Canon CX−1). The Ethics Committee of the Kuopio University Hospital has approved the study (approval number 42/2014) and the tenets of the Declaration of Helsinki were followed. All participants signed an informed consent form. Inclusion criterion for the patients in this study was intravitreal treatment for nAMD at KUH during years 2007–2021. Only patients with enough information for each corresponding analysis were included. If patient had signs of other retinal diseases, the patient was excluded from analyses. As this study includes analysis of retrospective real-world data, there is variance in the recording of the individual variables. Thus, not all data are available from all patients. One eye per patient was selected for the study. In case only one eye had nAMD, it was picked as the study eye. If both eyes had nAMD, the eye with a longer treatment history was picked unless it was found to exhibit signs of fibrotic late-stage nAMDFAG and OCT analysis was carried out by our retina experts LS, NK and KK.

2.2 | Anti-VEGF treatments

The nAMD patients got their first three monthly loading intravitreal bevacizumab injections in 2008. Bevacizumab treatments were continued as long as satisfactory treatment responses were observed. Ranibizumab or pegaptanib was primarily used during 2007–2008. Patient eyes were imaged using OCT on their monthly visits at the early state of nAMD. Follow-up visit intervals were gradually extended to 2–4 weeks once their macula exhibited dry state signals. Anti-VEGF injections were carried out with the modified pro re nata protocol according to the Finnish nAMD guidelines (Tuuminen et al., 2017).

2.3 | Statistical analysis

Statistical analyses were explorative and descriptive; the study did not aim to confirm or reject predefined hypotheses. Continuous variables are described by absolute values and as changes from baseline per analysis time point. All data reported here are only for patients with assessments at each of the indicated time points. Furthermore, only patients receiving treatment each year have participated in calculations on the median number of injections. Significance values were determined using a two-tailed t-test analysis, with a significance value of $p<0.05$ used for all analyses. Correlations were checked using multiple regression analysis.

3 | RESULTS

3.1 | Study population and treatment characteristics

The study population included 421 nAMD patients treated at KUH during years 2007–2021. Due to the nature of real-world data, not all patients had full coverage of relevant information for all analyses. Patients were treated according to the Finnish pro re nata regimen. The median age at the time of treatment initiation was 79.

To understand the basic characteristics of outcomes in our study population, we first analysed treatment patterns and visual outcomes in the whole study population. As shown in Table 1a, 364 patients were included in treatment intensity analyses. Available patient numbers were observed to rapidly decrease as the number of treatment years increased, as only 60.7% and 44.8% of patients were still on treatment during the second and third treatment years. Only 4.9% of patients remained in treatment on the tenth treatment year.

During the first year of treatment, the median injection frequency was 5 (STDEV 2.4, range 1–11) and 16.2% of patients also received treatment in the nonstudy eye (n=59). During the first treatment year, Bevacizumab was the most common treatment (81.0% of patients received, in use from 2008 forwards), followed by 23.6% for ranibizumab (in use during 2007–2020), 10.4% for aflibercept (in use from 2012 onwards) and 4.1% for pegaptanib (in use during 2007–2008). During the one treatment year, one patient may have received multiple treatment options. As this data set includes patients treated at KUH during the years 2007–2021, this study only visualizes the treatment patterns during that period and does not reflect the current treatment practices at the clinic. In recent years, treatment practices including treatment intensity and treatment choices have evolved at KUH.

From the baseline characteristics, we can see that at the time of the treatment initiation, many patients already had severely affected visual function as the median VA at baseline was only 0.25 (range 0–0.8, Table 1b). At baseline, 12.7% of patients (n=47) had VA under the detection limit (counted as 0 in analyses). Median VA improvement varied between 0 and −1 rows during years 1–10 (range+9–(−10)).

3.2 | Association of baseline characteristics to disease course and treatment duration

As treatment duration varied considerably between the patients, our aim was to identify baseline characteristics that could help predict how long a patient would benefit from the treatment. Thus, we compared patients who had received treatment during treatment year 6 (long-treatment duration group) to patients who had not received treatment during years 3–10 (short-treatment duration group).

We did not observe statistically significant differences in baseline characteristics, which might have been caused by the small number of patients in the respective groups. On the other hand, patients who were in the short-treatment duration group had less intravitreal injections (IVTs) during the first (4 vs. 6, p=0.009; n=41/65 short/long resp.) and second year of treatment (0 vs. 4, p=0.001; n=41/64 short/long resp.) compared to the patients in the long-treatment duration group. Baseline VA was comparable between the groups (p=0.2, VA 0.32/0.25 short/long resp.), but the short-treatment duration group gained less rows than the long-treatment duration group during both first (0 vs. 1, p<0.001, short vs. long resp.) and second (−1 vs 1, p<0.001, short vs. long resp.) year

TABLE 1 Injection frequency and visual acuity outcomes in the selected study eye. (a) Injection frequency per treatment year; (b) Change in Snellen equivalent visual acuity per treatment year.

(a)

	Treatment year									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Injection frequency									
Median	5	4	5	5	5	5	5	4	4	4
STDEV	2.4	2.3	2.5	2.7	2.6	2.4	2.1	2	1.1	1.9
Range	1–11	1–11	1–12	1–12	1–12	1–13	1–9	1–9	3–6	1–7
Patients, *n*	364	221	163	117	83	65	46	35	21	18
Males, %	32.5	30.3	28.2	25.6	28.9	27.7	23.9	25.7	23.8	11.1

(b)

		Treatment year									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Baseline VA	**Change in VA, rows**									
Median	0.25	0	0	0	0	−1	0	0	−1	-1	-1
Mean	0.3	0.5	−0.1	−0.3	−0.5	−0.7	−0.4	−0.2	−1	−0.5	−2
STDEV	0.2	2.7	3	3.2	3.2	3.2	3.4	3.6	3.9	3.8	3.3
Range	0–0.8	(−7)–9	(−8)–9	(−10)–9	(−10)–8	(−8)–8	(−8)–7	(−7)–7	(−8)–7	(−7)–8	(−6)–7
Patients, *n*	364	363	271	163	164	122	91	65	51	32	24

Abbreviations: STDEV, standard deviation; VA, visual acuity.

of treatment. Interestingly, fewer deaths were observed in the short-treatment duration group, as 0% of patients in the short-treatment duration group and 12.3% of patients in the long-treatment duration group died during the anti-VEGF treatment period ($p=0.004$). No difference was observed in median age at treatment initiation ($p=0.2$, 78/77 short/long resp.).

To further establish whether the baseline factors were linked with disease progression, we analysed the association of baseline medication, smoking status and BMI to patient age at the time of nAMD diagnosis (age at first anti-VEGF injection), median number of injections administered during the first four treatment years and the percentage of patients remaining on treatment during years 1–4 (Table 2). In these analyses, two groups in particular were highlighted as they had noticeable changes in all analyses: patients with anticoagulation medication and the heavy smokers, who represented the opposite ends in two of our analyses. In this patient population, anticoagulation medication appeared to delay the emergence of nAMD ($p=0.001$, age 78.1 vs. 81 years, no med. vs. med. resp.) and a high percentage of these patients remained on treatment during the second and third treatment year (2nd year: $p=0.003$, 59.7% vs. 74.2%, no med. vs. med. resp.; 3rd year: $p=0.006$, 45.3% vs. 51.6%, no med. vs. med. resp.). Death was the reason for anti-VEGF treatment discontinuation in 25.8% of anticoagulation medication users and 7.6% of patients with no anticoagulation medication ($p=0.003$). On the other hand, the median age for nAMD diagnosis was 76 years among heavy smokers and 80 years among nonsmokers ($p<0.001$). During the second year of treatment, 44.8% of heavy smokers and 62.5% of nonsmokers remained on treatment, but this difference was not statistically significant ($p=0.07$).

Later onset of nAMD was also found to occur in patients on anti-aggregation ($p=0.024$, 78 vs. 79.7 years no med. vs. med. resp.) and blood pressure medication ($p=0.032$, 76.9 vs. 79.2 years no med. vs. med. resp.), whereas high BMI was linked to earlier onset of nAMD ($p=0.006$, 76.5 years vs. 79.4 years BMI ≥30 vs. BMI <25 resp.). The relationship of diagnosis age of nAMD with smoking status, anticoagulation medication, BMI, anti-aggregation medication and blood pressure medication was further analysed using multiple regression analysis. In this study, 310 patients had data from all these variables and were thus included in the analysis. In multiple regression analysis, 15.7% of the variation in the age of nAMD diagnosis could be explained by these factors (Table 2d). All the chosen factors were highly statistically significant except the data on blood pressure medication.

As the relationship between retinal fluid characteristics and vision outcomes during anti-VEGF treatment has been under discussion during recent years, we also explored these factors from our data set. Information about IRF, SRF and Sub-RPEF could be found at baseline from 107 patients, of whom 87 (81.3%) had IRF, 84 (78.5%) had SRF and 92 (86%) had sub-RPEF. When patients with ($n=87$) and without ($n=20$, SRF only) baseline IRF were analysed, we observed that baseline VA differed significantly between these patients ($p=0.0001$, VA 0.26 vs. 0.5 IRF vs. no IRF resp.). In addition, patients who had only IRF at baseline were older than the SRF only patients at the time of nAMD diagnosis ($p=0.001$, median 87 vs. 73.5 years IRF only vs. SFR only resp.). Furthermore, patients with baseline IRF seemed to have discontinued treatment sooner, as 51.7% of patients with IRF remained on treatment during the third year of treatment compared to 75% of patients without baseline IRF ($p=0.047$). However, patients with IRF at baseline showed better VA development during the first treatment year (baseline IRF +1 row, no IRF 0 rows, $p=0.015$), but it is important to recognize that VA level of IRF only patients was lower at the beginning than in the SRF only group (Figure 1c).

Interestingly, when IRF only patients were compared to SRF only patients, the difference in patients who remained on treatment was even more pronounced. For example, during the third year of treatment just 30.4% of IRF only patients remained on treatment, whereas 75% of SRF only patients remained on treatment ($p=0.003$). Death was the reason for the discontinuation of anti-VEGF treatment in 30.4% of IRF only patients and 10% of SRF only patients, but the difference was not statistically significant ($p=0.1$). In addition, IRF only patients who stopped treatment during years 1–3 had numerically lower baseline VA than patients who continued treatment over 3 years, but the difference was not statistically significant (median 0.25 vs. 0.41, $p=0.2$).

As we have described above, a lower number of injections during the first treatment year is associated with shorter treatment duration. We analysed the treatment intensity among the IRF only and SRF only subgroups. Fluctuations in treatment patterns were observed in IRF only patients during the first 5 years of treatment (Figure 1b). A significant difference between IRF only and SRF only patients in median injection number was observed in year 2 (4 vs. 6, IRF only vs. SRF only, $p=0.03$), which was the year preceding the most prominent difference in the patients on treatment observations. Curiously, VA gain development trend in IRF only patients followed the trend of administered IVTs (Figure 1b,c). The age of the patients at treatment initiation varied significantly depending on the fluid status, which may have affected the intensity of the treatment. The median age at treatment initiation was 82 for all IRF patients, 87 for IRF only patients, 81 for IRF + SRF patients, 79 for all SRF patients and 73.5 for SRF only patients. Difference in median ages at treatment initiation was statistically significant when IRF only and SRF only ($p=0.0001$) as well as IRF all and SRF only ($p=0.001$) patients were compared.

As a clear effect of IRF on treatment duration was observed, we wanted to look more deeply at how the presence of IRF affects the disease severity on an anatomical level. Thus, we compared the presence of sub-RPEF, HRF, drusen, SDDs and the level of atrophy at baseline (before treatment initiation) between the SRF only and IRF only or IRF all patients.

Interestingly, more sub-RPEF was observed in SRF only patients than IRF only patients (100% vs. 56.5%, $p=0.0005$). Conversely, more HRF, an increased number of drusen and SDDs as well as more severe atrophy level

TABLE 2 Association of baseline medication, body mass index and smoking to treatment initiation, intensity and duration. (a) Age at treatment initiation, (b) median number of injections per treatment year, (c) percentage of patients remaining on treatment per treatment year, (d) multiple regression analysis on the age at nAMD diagnosis and the variables of interest.

(a)

	Age at the anti-VEGF initiation			
	Patients. *n*	**Mean**	**STDEV**	***p*-Value**
Anticoagulation medication				
No medication	262	78.1	7.5	**0.001**
Mediation in use	62	81.0	5.5	
Anti-aggregation medication				
No medication	184	78.0	7.9	**0.024**
Mediation in use	139	79.7	6.3	
Anticholesterol medication				
No medication	164	78.3	8.0	0.322
Mediation in use	157	79.1	6.4	
Blood pressure medication				
No medication	70	76.9	8.0	**0.032**
Mediation in use	257	79.2	7.0	
BMI				
<25	136	79.4	7.3	<25 vs. ≥30. ***p*** **= 0.006**
25 to <30	80	79.3	7.2	
≥30	66	76.5	7.1	
Smoking				
Non-smoker	253	80.0	7.0	Non vs. Random ***p*** **= 0.016**; non vs. heavy ***p*** **< 0.001**
Random smoking	56	77.3	7.5	
Heavy smoking	58	76.0	7.0	

(b)

	Median number of injections			
	Year 1	**Year 2**	**Year 3**	**Year 4**
Anticoagulation medication				
No medication	5	4	5	5
Mediation in use	6	4	3.5	4
p-value	0.975	0.257	**0.025**	**0.009**
Anti-aggregation medication				
No medication	5	4	5	5
Mediation in use	5	4	4	4
p-value	0.909	0.967	0.360	0.890
Anticholesterol medication				
No medication	5	4	5	5
Mediation in use	5	4	4	5
p-value	0.488	0.977	0.718	0.336
Blood pressure medication				
No medication	5	4	5	5
Mediation in use	6	4	4.5	5
p-value	0.225	0.806	0.235	0.849
BMI				
<25	5	5	5	4
25 to <30	5	4	4	6
≥30	5	4	5	4
p-value <25 vs. ≥30	0.789	0.639	0.680	0.421
Smoking				

(Continues)

TABLE 2 (Continued)

(b)	Median number of injections			
	Year 1	**Year 2**	**Year 3**	**Year 4**
Non-smoker	5	4	4	5
Random smoking	6	4	6	5
Heavy smoking	4	4	3	4
p-value non vs. heavy	**0.001**	0.499	0.252	0.130

(c)	**Year 1**	**Year 2**	**Year 3**	**Year 4**
Anticoagulation medication				
Patients, *n*				
No medication	258	154	117	85
Mediation in use	62	46	32	19
% Remaining on treatment				
No medication	100	**59.7**	**45.3**	32.9
Mediation in use	100	**74.2**	**51.6**	30.6
Anti-aggregation medication				
Patients, *n*				
No medication	181	117	88	64
Mediation in use	138	84	62	41
% Remaining on treatment				
No medication	100	64.6	48.6	35.4
Mediation in use	100	60.9	44.9	29.7
Anticholesterol medication				
Patients, *n*				
No medication	163	94	76	55
Mediation in use	154	105	73	49
% Remaining on treatment				
No medication	100	57.7	46.6	33.7
Mediation in use	100	68.2	47.4	31.8
Blood pressure medication				
Patients, *n*				
No medication	67	41	28	23
Mediation in use	256	162	124	83
% Remaining on treatment				
No medication	100	61.2	41.8	34.3
Mediation in use	100	63.3	48.4	32.4
BMI				
Patients, *n*				
<25	133	79	62	44
25 to <30	154	92	66	43
30 or higher	65	44	32	28
% Remaining on treatment				
<25	100	**59.4**	46.6	33.1
25 to <30	100	59.7	42.9	27.9
30 or higher	100	**67.7**	49.2	43.1
Smoking				
Patients, *n*				
Non-smoker	248	155	117	86
Random smoking	55	39	26	15

TABLE 2 (Continued)

(c)	Year 1	Year 2	Year 3	Year 4
Heavy smoking	58	26	20	16
% Remaining on treatment				
Non-smoker	100	62.5	47.2	34.7
Random smoking	100	70.9	47.3	27.3
Heavy smoking	100	44.8	34.5	27.6

(d) Regression statistics	
Multiple *R*	0.396
R^2	0.157
Adjusted R^2	0.143
Standard error	6.813
Observations	310

	Coefficients	Standard error	*t* Stat	*p*-Value
Intercept	88 922	2596	34 249	2.3E-106
BMI	−0.384	0.095	−4058	6.3E-05
Smoking	−2208	0.524	−4216	3.3E-05
Blood pressure med.	1620	1013	1598	0.111
Anticoagulation med.	3583	1057	3389	0.001
Anti-aggregation med.	2584	0.848	3046	0.003

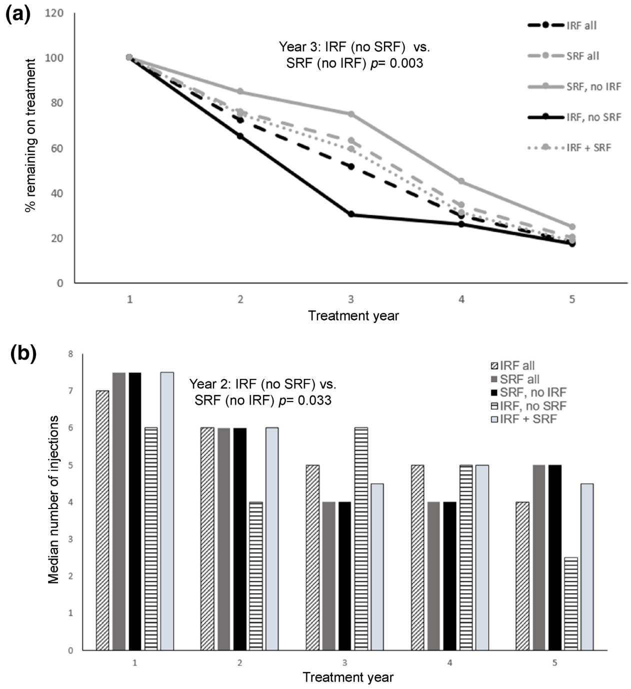
Note: Significant changes in bold.
Abbreviations: BMI, body mass index; STDEV, standard deviation; VEGF, vascular endothelial growth factor.

was observed in patients with IRF (Table 3). Intriguingly, significantly more HRF were observed when all IRF patients were compared to SRF only patients (Table 3b). However, only numerically more HRF were observed when IRF only and SRF only patients were compared, but this may be due to the limited number of patients in these subgroups (Table 3a). Furthermore, our sample size was not large enough to statistically confirm whether IRF and SRF patients had differences in the number of drusen.

More SDDs were observed in patients with IRF only than in patients with only SRF (IRF only vs. SRF only: 43.5% vs. 15%, $p=0.039$; IRF all vs. SRF only: 31% vs. 15%, $p=0.104$). Thus, it was intriguing to also observe more severe atrophic changes in patients with IRF. When all patients with IRF were compared to SRF only patients, significantly more complete RPE and outer retinal atrophy (cRORA) were observed (20.7% vs. 5%, $p=0.020$, Table 3b). Our sample size was not large enough to statistically confirm differences in atrophic changes between IRF only and SRF only patients (26.1% vs. 5%, $p=0.060$, Table 3a).

4 | DISCUSSION

In this study, we observed that heavy smoking and high BMI were associated with earlier diagnosis of nAMD in a Kuopio nAMD cohort. The use of anticoagulation and anti-aggregation medication were associated with later onset of nAMD. Surprisingly, analysis of age at diagnosis revealed that patients who had IRF (IRF all and IRF only) at baseline were older than patients who had only SRF at baseline. Heavy smoking and high BMI are already previously linked to an increased risk of nAMD, but the role of anticoagulation and anti-aggregation medication as factors which could delay onset of nAMD is less discussed (Heesterbeek et al., 2020). Studies done with anticoagulation and anti-aggregation medication have mainly focused on safety and, by current understanding, these agents may increase the risk for intraocular haemorrhage and increase submacular haemorrhage area in nAMD patients (Kiernan et al., 2010; Weber et al., 2023). Interestingly, controversial results have been obtained from the link between nAMD and aspirin use (Yan et al., 2022). Our observations reveal that even though cardiovascular diseases can increase the risk of nAMD, the proper medication of these diseases and thus better vascular health could be able to delay the onset of nAMD. As far as we are aware, this is the first study which describes how anticoagulation and anti-aggregation medication could affect nAMD age of onset. A bigger data set is needed to understand why anticoagulation and anti-aggregation medication use could modify the disease course. In our study, high BMI and smoking had opposite effects on nAMD diagnosis age than anticoagulation and anti-aggregation medication. This observation is intriguing as altered vascular health is associated with both smoking and high BMI (Faber et al., 2009). Additionally, obesity and smoking have been shown to be linked with hypercoagulability (Barua & Ambrose, 2013; Faber



(c)

		End of treatment year			
		1	2	3	4
	VA baseline	VA change from baseline, rows			
IRF all	0.25	1	0	0	0
SRF all	0.25	1	0	0	0
SRF, no IRF	0.5	0	-1	-1.5	-1
IRF, no SRF	0.32	1	-0.5	0.5	-0.5
IRF + SRF	0.25	1	1	0	0.5

FIGURE 1 Fluid status and treatment outcomes. (a) Percentage of patients remaining on treatment per treatment year and fluid status; (b) median number of injections per treatment year and fluid status; (c) Snellen equivalent visual acuity outcomes per fluid status. 'IRF all' includes all patients who had IRF at baseline, 'SRF all' includes all patients who had SRF at baseline, 'IRF, no SRF' includes patients who had only IRF at baseline, 'SRF, no IRF' includes patients who had only SRF at baseline and 'IRF + SRF' includes patients who had both IRF and SRF at baseline. IRF, intraretinal fluid; SRF, subretinal fluid; VA, visual acuity.

et al., 2009; Kornblith et al., 2015). Hypercoagulability associated with obesity may be due to chronic low-grade inflammation, altered hepatic synthesis of coagulation factors or adipose tissue-derived coagulation mediators (Faber et al., 2009; Kornblith et al., 2015). Also, smoking has been shown to alter the balance of coagulation factors (Barua & Ambrose, 2013). We believe that this study provides a reason to explore the relationship between the previously mentioned baseline factors and the development of nAMD in more detail. This study shows that there is at least an association between these findings, but confirming causality would require studies that are more detailed and done with a bigger patient population (Seidell & Visscher, 2000).

To further evaluate how baseline characteristics and medications affect the disease course, we analysed their association with treatment duration. A shorter treatment duration is expected to be an indicator of faster-progressing disease. In Finland, patients with nAMD are never considered 'cured' even if medication were to stop for some reason. Medication will continue as long as any benefit in the treatment is detected. Based on the Finnish treatment guidelines, recommendations

TABLE 3 Presence of OCT biomarkers in nAMD. (a) OCT biomarkers in IRF only and SRF only patients; (b) OCT biomarkers in IRF (SRF+/−) and SRF only patients.

(a)

	Baseline		
	IRF (no SRF)	SRF (no IRF)	*p*-Value
Number of patients, *n*	23	20	
Sub-RPEF. of patients % (*n*)	56.5 (13)	100 (20)	**<0.001**
Retinal thickness, median µm (STDEV)	338 (158)	380 (137)	0.642
Peak retinal thickness, median µm (STDEV)	437 (166)	435 (163)	0.860
Retinal volume, µm^3 (STDEV)	0.3 (0.1)	0.27 (0.1)	0.608
HRFs, % of patients			
0–3	13.0	5	0.516
4–24	73.9	95	
25–49	8.7	0	
50 or more	4.3	0	
Drusens, % of patients			
Small	13.0	5	0.369
Medium	0.0	5	
Large	0.0	10	
Small and medium	13.0	3.4	
Small and large	17.4	35	
Medium and large	4.3	0	
Small, medium and large	52.2	30	
Cuticular drusen, % of patients	13	5	0.364
Subretinal drusenoid deposit, % of patients	43.5	15	**0.039**
Atrophy, % of patients			
No atrophy	4.3	5	0.920
iORA	30.4	50	0.200
cORA	8.7	20	0.310
iRORA	30.4	15	0.100
cRORA	26.1	5	0.060
RPE tear	0	10	0.160

(b)

	Baseline		
	IRF (±SRF)	SRF (no IRF)	*p*-Value
Number of patients, *n*	87	20	
SRF % (*n*)	73.6 (64)	100 (20)	
Sub-RPEF % (*n*)	82.8 (72)	100 (20)	**<0.001**
Retinal thickness, median µm (STDEV)	412 (162)	380 (137)	0.310
Peak retinal thickness, median µm (STDEV)	506 (166)	435 (163)	0.150
HRFs, % of patients			
0–3	6.9	5	**<0.001**
4–24	66.7	95	
25–49	18.4	0	
50 or more	8.0	0	

TABLE 3 (Continued)

(b)

	Baseline		
	IRF (±SRF)	SRF (no IRF)	*p*-Value
Drusens, % of patients			
Small	12.6	5	0.183
Medium	0	5	
Large	0	10	
Small and medium	12.6	3.4	
Small and large	16.1	35	
Medium and large	2.3	0	
Small, medium and large	56.3	30	
Cuticular drusen, % of patient	6.9	5	0.741
Subretinal drusenoid deposit, % of patients	31.0	15	0.104
Atrophy, % of patients			
No atrophy	1.1	5	0.460
iORA	26.4	50	0.070
cORA	21.8	20	0.880
iRORA	24.1	15	0.100
cRORA	20.7	5	**0.020**
RPE tear	4.6	10	0.570

Note: Bold values indicate statistically significance of *p*-value.

Abbreviations: cORA, complete outer retinal atrophy; cRORA, complete RPE and outer retinal atrophy; HRF, hyperreflective foci; iORA, incomplete outer retinal atrophy; IRF, intraretinal fluid; iRORA, incomplete RPE and outer retinal atrophy; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; SDDs, Subretinal drusenoid deposits; SRF, subretinal fluid; sub-RPEF, subretinal pigment epithelial fluid; VA, visual acuity.

to stop treatment only include: lack of efficacy, no expectations for improvement in the patient's ability to function or their quality of life, the risks exceeding the benefits or the latest Snellen equivalence results dropping below 0.0625 (Tuuminen et al., 2017). In the search for factors which could predict how long a patient will stay on treatment, only patients who used anticoagulation medication and patients who had only SRF on baseline remained on treatment for a longer period of time compared to the other patients. On the other hand, a low number of intravitreal anti-VEGF injections during the first year of treatment and the presence of baseline IRF were associated with a shorter treatment duration. In the short-treatment duration group, patients seemed to be less responsive to treatment and experienced faster vision decline, but also experienced fewer deaths. Therefore, we think that the faster drop-out from the treatment in the short-treatment duration group was due to vision decline. On the other hand, patients with anticoagulation medication maintained better vision during the first 2 years but had higher levels of anti-VEGF treatment discontinuations due to deaths than those without the medication. Thus, anticoagulation medication users may be more committed to treatment or respond better to the treatment regardless of their worse baseline general health.

Furthermore, patients with only SRF at baseline were younger and had better baseline VA than patients with only IRF at baseline. Patients with only IRF at baseline died numerically more often during the anti-VEGF treatment, but the difference was not statistically significant. As patients with only IRF at baseline were older and had worse VA at baseline, we consider that their anti-VEGF treatments had been discontinued due to previously mentioned guidelines. We do not know how many of the patients discontinued treatment at their own request, as we do not have that data available. From a physicians perspective, nAMD patients are generally well committed to treatment.

As the relationship between retinal fluid characteristics and vision outcomes during anti-VEGF treatment has been under discussion during recent years, we also explored these factors from our data set. We observed that IRF was associated with an increased number of HRF, SDDs as well as a more severe atrophy level. These factors are considered to be associated with disease progression or worse prognosis for a patient. Thus, their enrichment in the IRF-positive population is fascinating especially as we had observed IRF to be linked with faster progression of nAMD. Previously, IRF has been associated with worse VA outcomes (Jaffe et al., 2013; Sharma et al., 2016). Moreover, IRF has recently been reported to be associated with increased atrophy (Llorente-Gonzalez et al., 2022). In contrast to IRF, SRF may protect from macular atrophy or at least is less detrimental (Saenz-de-Viteri et al., 2021; Sanchez-Monroy et al., 2023). Thus, our observation of the relationship between cRORA and IRF builds more evidence that baseline IRF indicates a worse disease case. Furthermore, both HRF and SDDs have previously been suggested to be linked with increased risk of disease progression in nAMD and geographical atrophy (Ferrara et al., 2017; Fragiotta et al., 2018; Marsiglia et al., 2013), which further binds these findings together. IRF have better outcomes when individualized treatment regimens such as pro re nata or treat-and-extend are used (Saenz-de-Viteri et al., 2021).

Pathological fluid accumulation occurs when the leakage exceeds the local capability to remove the fluid. Macular fluids can develop in various ways; they can, for example, result from the breakdown of the blood-retinal barrier, osmotic pressure of accumulated proteins or via dysfunctional fluid transport of the RPE layer. Newly formed incomplete blood vessels can also leak fluid and immune cells to the surrounding tissue microenvironment (Haydinger et al., 2023; Helotera & Kaarniranta, 2022). Accumulating fluid can further damage the tissue microenvironment and may lead to increased inflammatory cytokine release, inflammatory cell infiltration or hypoxia, causing further progression of the disease (Haydinger et al., 2023; Helotera & Kaarniranta, 2022). Development of HRF is not completely understood, but theories of their origin include that HRF may represent anteriorly migrating RPE cells or that HRF may also include lipid-filled immune cells in nAMD (Echols et al., 2020). Observed RPE migration may be driven by hypoxia (Echols et al., 2020). Hypotheses that have been created on SDD development include them stemming from choroidal vascular dysfunction, RPE dysfunction or that SDDs are para-inflammatory phenomena (Monge et al., 2022). Furthermore, the presence of SDDs is linked with AMD severity and photoreceptor disruption, photoreceptor loss, localized Müller cell gliosis and RPE alterations (Monge et al., 2022). Our data reveals a previously undescribed link of IRF to HRF, SDDs and cRORA. We have shown that the presence of IRF is associated with the presence of SDDs and HRF indicating that the developments of these factors share common paths. However, the result of all these changes is an increase in retinal atrophy. As the presence of IRF was also linked to faster disease progression, we think that IRF plays an important role in the escalation of the disease towards non-reversible changes in retinal anatomy.

As the study involved data from real-world patients, the real-world recording practices may have caused limitations to the study. Only patients who had adequate levels of information on their records could be involved in this study and in each corresponding analysis. Therefore, the patient population in this study is smaller than the true patient population in the corresponding clinic and may not fully represent the data from the whole population. In addition, treatment practices have evolved over the years and thus the data does not fully reflect current treatment practices (Purola et al., 2023).

In this study, we were able to show a link between heavy smoking and high BMI to earlier onset of disease. In addition, we found the use of anticoagulation and anti-aggregation to be linked to later onset of nAMD. Furthermore, the use of anticoagulants allowed patients to remain on anti-VEGF treatment for a longer time. We described how patients with IRF tend to be older at the time of diagnosis and how patients with IRF remain on treatment for a shorter time. Importantly, we revealed a previously undescribed link between IRF and the development of SDDs, HRF and increased atrophy. Curiously, all our findings can be linked to the health of vasculature and thus our results underline the importance of keeping in mind the potential role of disturbed vasculature function during the whole disease course of nAMD. Our results may help ophthalmologists judge an individual's risk for disease progression and may draw more attention to early lifestyle intervention to delay nAMD onset as well as help identify patients who are at risk for fast disease progression.

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CONFLICT OF INTEREST STATEMENT

Hanna Heloterä is also an employee of Roche Oy. Otherwise, the authors declare no conflict of interest.

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