KJO
pISSN: 1011-8942 eISSN: 2092-9382

Korean J Ophthalmol 2024;38(6):471-479
https://doi.org/10.3341/kjo.2024.0032

Original Article

Predictive Factors for Submacular Hemorrhage in Age-related Macular Degeneration: A Retrospective Study

Hanwool Moon, Hyun Goo Kang, Junwon Lee, Christopher Seungkyu Lee, Min Kim, Suk Ho Byeon, Sung Soo Kim

Department of Ophthalmology, Institute of Vision Research, Severance Eye Hospital, Yonsei University College of Medicine, Seoul, Korea

Purpose: Little is known about the major risk factors for submacular hemorrhage (SMH). This study aimed to evaluate the factors associated with SMH in patients with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy receiving three consecutive loading doses of intravitreal aflibercept or ranibizumab injections.

Methods: This retrospective cross-sectional study included 48 patients diagnosed with nAMD and polypoidal choroidal vasculopathy who completed three loading doses under a treat-and-extend regimen. Patients were divided into the SMH group and the non-SMH group (age- and sex-matched without SMH), with 24 patients in each group. Intravitreal injections, agents, and optical coherence tomography (OCT) features were compared.

Results: In the SMH group, SMH occurred approximately 3.29 years after post-nAMD diagnosis. The non-SMH group received more intravitreal injections of aflibercept and brolucizumab during the follow-up period after the initial loading phase. The SMH group exhibited a higher prevalence of serous/hemorrhagic pigment epithelial detachments (PEDs) at the last visit before SMH occurrence compared to the non-SMH group. Patients with a PED increase in the past two visits showed a higher tendency in the SMH group. No other OCT features significantly correlated with SMH development.

Conclusions: The presence of serous/hemorrhagic PEDs may indicate a higher risk of SMH, and eyes with these features should be closely monitored to prevent sudden and devastating visual loss caused by SMH.

Key Words: Neovascular age-related macular degeneration, Pigment epithelial detachment, Polypoidal choroidal vasculopathy, Submacular hemorrhage

Submacular hemorrhage (SMH) is a term commonly used in neovascular age-related macular degeneration (nAMD), which refers to the accumulation of blood between the neurosensory retina and retinal pigment epithelium (RPE), particularly in the macular region [1]. SMH can also occur due to conditions such as polypoidal choroidal vasculopathy (PCV), retinal macroaneurysm, and high myopia, indicating poor visual prognosis [2]. More than 90% of SMH cases are associated with nAMD and PCV, with PCV having a higher reported incidence (59% vs. 31%) [3].

SMH classification is based on size and thickness. Hem-

Received: March 10, 2024 *Final revision:* July 30, 2024
Accepted: September 26, 2024

Corresponding Author: Hyun Goo Kang, MD. Department of Ophthalmology, Institute of Vision Research, Severance Eye Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: 82-2-2228-3570, Fax: 82-2-312-0541, Email: hgkang08@yuhs.ac

orrhages below one disc diameter (1DD) are generally considered to be within the normal spectrum of nAMD rather than specifically defined as SMH. Therefore, most recent studies define SMH as hemorrhage exceeding 1DD. "Small SMH" refers to sizes between 1DD and 4DD, "medium-sized SMH" refers to those that extend beyond 4DD but does not cross the temporal vascular arcade, and "massive SMH" refers to those that cross the temporal arcade. While most SMH have a thickness of 500 μm or less, those with obvious elevation of the retina exceeding 500 μm are termed "thick SMH" [1].

SMH causes photoreceptor layer damage due to iron-induced toxicity and nutrition supply disruptions. Irreversible retinal injury can occur within 24 hours of bleeding, leading to a poor visual prognosis and necessitating prompt treatment [4]. Chang et al. [5] reported that in cases of SMH in nAMD, there is an average decrease in vision of approximately three lines, and the visual prognosis after 6 months is less favorable than that in groups without SMH. Visual prognosis of SMH can be predicted based on OCT findings such as size or thickness of SMH [6]. However, factors predicting the risk of SMH, including OCT features and intravitreal injection information, are not well-established.

This study aimed to investigate the risk factors of SMH in patients diagnosed with nAMD, including PCV. Given that aflibercept or ranibizumab administered at monthly intervals for three loading doses is an accepted standard treatment for nAMD, we focused on patients who received this loading regimen [7–12].

Materials and Methods

Ethics statement

This study was approved by the Institutional Review Board of Severance Eye Hospital (No. 4-2023-1472). The requirement for informed consent was waived, due to the retrospective nature of the study. The study adhered to the principles outlined in the Declaration of Helsinki.

Study design and setting

This retrospective observational case study was conducted at Severance Eye Hospital (Seoul, Korea), a high-volume tertiary referral hospital affiliated with Yonsei University College of Medicine (Seoul, Korea). We retrospectively reviewed the electronic medical records of 108 patients (108 eyes) diagnosed with SMH secondary to exudative AMD or PCV, who visited the hospital between January 2014 and August 2023. Among them, 84 patients (84 eyes) were excluded based on the exclusion criteria: already received anti–vascular endothelial growth factor (anti-VEGF) injections at other hospitals or did not undergo three loading doses (including patients diagnosed with SMH at the first visit). Subsequently, a group of 24 patients with SMH occurring after the third loading was established. The non-SMH group consisted of 24 patients matched for age and sex with the SMH group, all diagnosed with nAMD or PCV, having undergone three loading doses, and experiencing no SMH events during the follow-up period. Due to the small sample size, the study did not differentiate between typical AMD and PCV, categorizing them collectively as nAMD. SMH was defined as a subretinal hemorrhage involving at least 1DD of the fovea without further classification based on size or thickness.

All patients were diagnosed with nAMD after choroidal neovascularization was confirmed using fluorescein and indocyanine green angiography at the initial visit. Anti-VEGF loading treatment with aflibercept or ranibizumab was initiated and administered three times at monthly intervals. The patients had mainly undergone treat-and-extend treatment protocols after three loading treatments. Patients with other retinal abnormalities (e.g., those with diabetic retinopathy or pathological myopia) were excluded. Of the 48 patients, 24 received aflibercept, and the remaining 24 received ranibizumab loading injections.

At each visit, every patient underwent a comprehensive ophthalmologic assessment, including measurement of best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy, indirect ophthalmoscopy, ultrawide-field fundus photography, and optical coherence tomography (OCT). Various measurements were obtained, including the size and thickness of the SMH and the greatest height of pigment epithelial detachment (PED) if present.

To investigate the relationship between SMH and OCT features, we analyzed the choroidal thickness and the presence of serous/hemorrhagic PED, corrugated PED margin, subretinal fluid, and intraretinal fluid on the OCT images. The study focused on analyzing OCT images immediately

before SMH occurrence in the SMH group and OCT images from a recent visit in the non-SMH group. Serous or hemorrhagic PED was defined as well-demarcated, abrupt elevations of RPE with homogenous and hyporeflective sub-RPE space on OCT. Additionally, to examine PED size changes, the greatest height of PED was measured in um units in all groups with the presence of PED. "PED increase" was defined as a more than 10% increase in the greatest heights of PED during the two latest visits before the occurrence of SMH (before the last visit in the non-SMH group).

Furthermore, we analyzed the use and frequency of four types of anti-VEGF injections (bevacizumab, aflibercept, ranibizumab, brolucizumab) in all patients. The follow-up interval before SMH occurrence and the interval from the last intravitreal injection to SMH were calculated in weeks. The interval in the non-SMH group was analyzed based on the last visit.

To understand the changes in visual acuity, we compared the differences in BCVA between the two groups and investigated the changes in BCVA before and after SMH occurrence in the SMH group. BCVA values were converted to the logarithm of the minimal angle of resolution (logMAR) values, with assigned values of 2.0, 2.3, and 2.7 for finger counts, hand motion, and light perception, respectively. None of the patients had visual acuity of light perception.

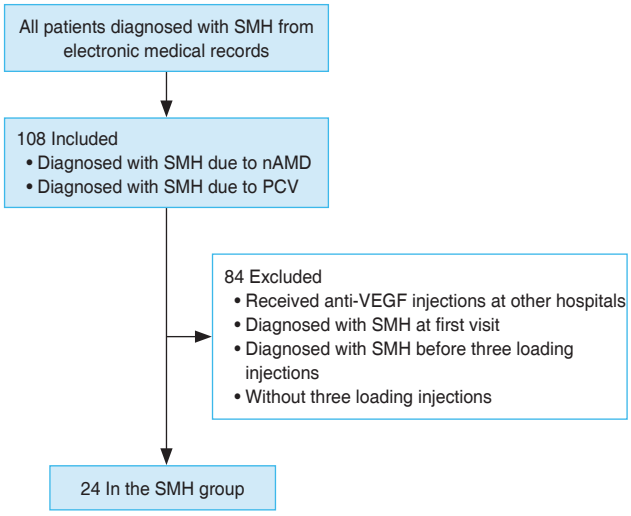

Fig. 1. Flowchart of inclusion and exclusion criteria of the submacular hemorrhage (SMH) group. nAMD = neovascular age-related macular degeneration; PCV = polypoidal choroidal vasculopathy; VEGF = vascular endothelial growth factor.

Statistical analysis

Statistical analyses were performed using the IBM SPSS

Table 1. Clinical information of the patients enrolled in the study (n = 48)

Characteristic	SMH group (n = 24)	Non-SMH group (n = 24)	*p*-value
Sex			>0.999
Male	13 (54.2)	13 (54.2)	
Female	11 (45.8)	11 (45.8)	
Age (yr)	78.67 ± 6.57	78.00 ± 6.26	0.720
At nAMD diagnosis	73.13 ± 7.77	73.71 ± 6.21	0.775
Interval from nAMD to SMH (yr)	3.29 ± 2.68	4.25 ± 1.48	0.132
Hypertension	12 (50.0)	14 (58.3)	0.562
Diabetes mellitus	4 (16.7)	3 (12.5)	0.683
History of cataract surgery	12 (50.0)	13 (54.2)	0.773
History of vitrectomy	1 (4.2)	0 (0)	0.312
BCVA (logMAR)*			
Before SMH	0.71 ± 0.50	0.61 ± 0.50	0.489
At SMH	1.53 ± 0.72	0.75 ± 0.60	<0.001†

Values are presented as number (%) or mean ± standard deviation.
SMH = submacular hemorrhage; nAMD = neovascular age-related macular degeneration; BCVA = best-corrected visual acuity; logMAR = logarithm of minimal angle of resolution.
*BCVA of the non-SMH group was measured at the recent two visits; †Statistically significant ($p < 0.05$).

ver. 26.0 (IBM Corp). Differences between the two groups were analyzed using the Student *t*-test, Mann-Whitney test, or chi-square test. Changes in BCVA before and after SMH in the SMH group were analyzed using paired *t*-tests. Statistical significance was set at $p < 0.05$ and at $p < 0.1$ for indicating tendency.

Results

We recruited 108 patients (108 eyes) diagnosed with submacular hemorrhage secondary to nAMD. Among these patients, 52 (48.1%) were diagnosed with SMH at their initial visit, and 32 (29.6%) were diagnosed before or without the third loading dose. In total, 24 of 108 patients (22.2%) were diagnosed with SMH after completing three loading doses (Fig. 1).

In this study, 24 eyes of 24 patients (13 men and 11 women; mean age, 78.67 ± 6.57 years; range, 65–88 years) with SMH after three loading doses were examined. They were defined as the SMH group, and a non-SMH group matched for age and sex was recruited (13 men and 11 women;

Table 2. Intravitreal injection information of the patients enrolled in the study (n = 48)

Characteristic	SMH group (n = 24)	Non-SMH group (n = 24)	*p*-value
Loading anti-VEGF agent			
Aflibercept	9 (37.5)	15 (62.5)	0.083
Ranibizumab	15 (62.5)	9 (37.5)	0.083
Anti-VEGF agent for nAMD treatment			
Bevacizumab	14 (58.3)	14 (58.3)	>0.999
No. of injections	4.21	4.88	0.721
Aflibercept	13 (54.2)	19 (79.2)	0.066
No. of injections	2.54	6.00	0.031*
Ranibizumab	15 (62.5)	9 (37.5)	0.083
No. of injections	3.54	2.54	0.377
Brolucizumab	1 (4.2)	6 (25.0)	0.097
No. of injections	0.04	1.21	0.045*
No. of total anti-VEGF injections	10.33 ± 7.19	14.63 ± 10.73	0.110

Values are presented as number (%), number only, or mean ± standard deviation.
SMH = submacular hemorrhage; VEGF = vascular endothelial growth factor; nAMD = neovascular age-related macular degeneration.
*Statistically significant ($p < 0.05$).

Table 3. Univariate analysis between the two groups on various factors (n = 48)

Variable	SMH group (n = 24)	Non-SMH group (n = 24)	OR (95% CI)	*p*-value
Serous/hemorrhagic PED	10 (41.7)	2 (8.3)	7.86 (1.50–41.30)	0.008*
Subretinal fluid	13 (54.2)	7 (29.2)	2.87 (0.87–9.45)	0.079
Intraretinal fluid	3 (12.5)	4 (16.7)	0.71 (0.14–3.60)	0.683
PED increase	6 (25.0)	1 (4.2)	7.67 (0.85–69.74)	0.097
Corrugated PED margin	10 (41.7)	6 (25.0)	2.14 (0.63–7.33)	0.221
Choroidal thickness (μm)	186.04 ± 44.79	199.04 ± 66.39	-	0.431
Last injection to SMH (wk)	35.85 ± 13.86	55.77 ± 16.80†	-	0.726
Follow-up interval (wk)	9.71 ± 5.06	10.33 ± 5.58	-	0.883

Values are presented as number (%) or mean ± standard deviation.
SMH = submacular hemorrhage; OR = odds ratio; CI = confidence interval; PED = pigment epithelial detachment.
*Statistically significant ($p < 0.05$); †The interval between the last injection and the last follow-up visit.

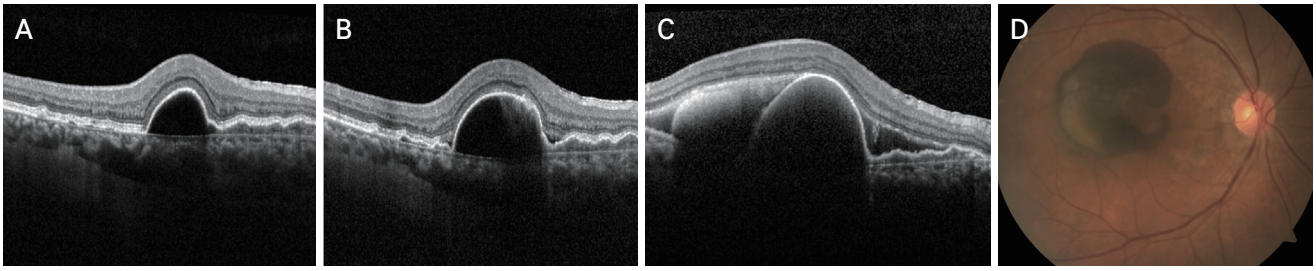

Fig. 2. Images of a 70-year-old male patient who had undergone ranibizumab loading injections three times. (A,B) Optical coherence tomography images of the last two visits prior to submacular hemorrhage (SMH) occurrence. (C) Optical coherence tomography and (D) fundus images at the time of SMH occurrence. SMH occurred after an increase in serous/hemorrhagic pigment epithelial detachment and 9 weeks after the last intravitreal injection.

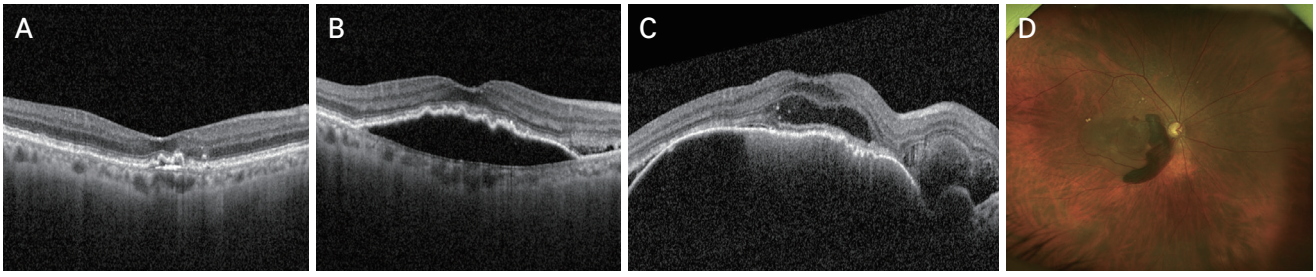

Fig. 3. Images of an 87-year-old male patient who had undergone aflibercept loading injections three times. (A,B) Optical coherence tomography images of the last two visits prior to submacular hemorrhage (SMH) occurrence. (C) Optical coherence tomography and (D) fundus images at the time of SMH occurrence. SMH occurred after the presence of serous/hemorrhagic pigment epithelial detachment and 14 weeks after the last intravitreal injection.

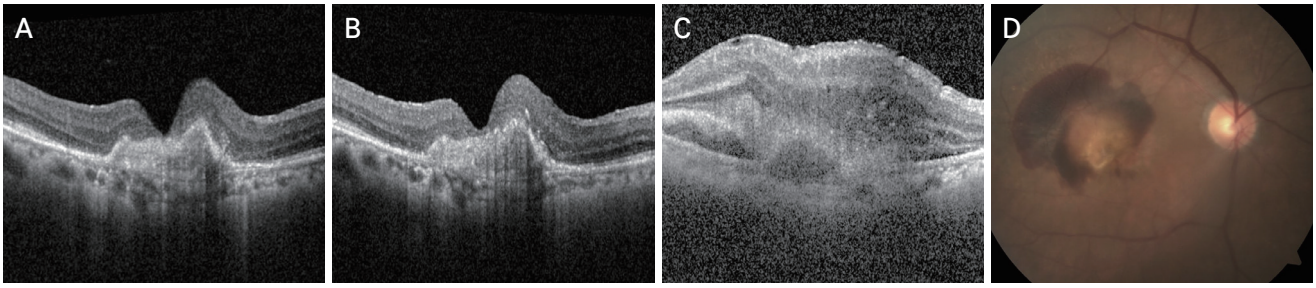

Fig. 4. Images of an 86-year-old female patient who had undergone aflibercept loading injections three times. (A,B) Optical coherence tomography images of the last two visits prior to submacular hemorrhage (SMH) occurrence. (C) Optical coherence tomography and (D) fundus images at the time of SMH occurrence. SMH occurred without serous/hemorrhagic pigment epithelial detachment and 33 weeks after the last intravitreal injection.

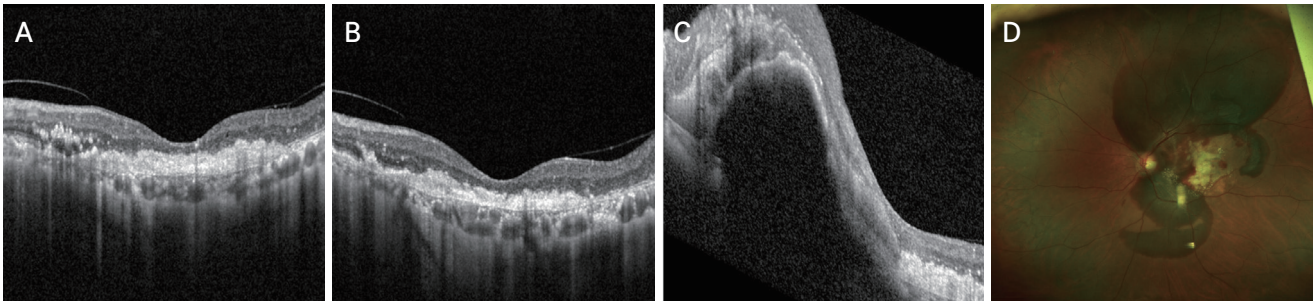

Fig. 5. Images of an 81-year-old male patient who had undergone ranibizumab loading injections three times. (A,B) Optical coherence tomography images of the last two visits prior to submacular hemorrhage (SMH) occurrence. (C) Optical coherence tomography and (D) fundus images at the time of SMH occurrence. SMH occurred without serous/hemorrhagic pigment epithelial detachment and 15 weeks after the last intravitreal injection.

mean age, 78.00 ± 6.26 years; range, 64–85 years).

Table 1 presents the basic characteristics of the SMH and non-SMH patients. The time from nAMD diagnosis to the occurrence of SMH in the SMH group was approximately 3.29 years, whereas the non-SMH group had a mean follow-up period of 4.25 years. There were no significant differences between the two groups in terms of systemic disease or history of ocular surgery (cataract or vitrectomy).

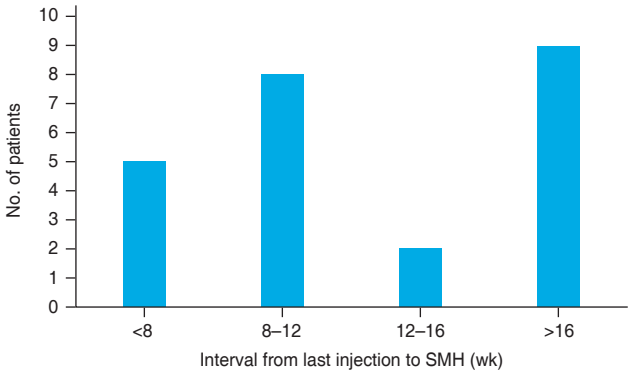

Fig. 6. Classification of the "interval from last injection to submacular hemorrhage (SMH)" in the SMH group (n = 24).

The mean BCVA with SMH (BCVA at the time of SMH occurrence) was 1.53 ± 0.72 logMAR, significantly worse than that without SMH (BCVA at the latest visit in the non-SMH group) at 0.75 ± 0.60 logMAR ($p < 0.001$). Additionally, a comparison of the BCVA immediately before and after SMH in the SMH group showed a significant decrease after the occurrence of SMH ($p < 0.001$) (Table 1).

The types and frequencies of anti-VEGF injections were compared between the two groups. In the SMH group, nine patients (37.5%) had aflibercept loading, while 15 (62.5%) in the non-SMH group had aflibercept loading. The difference had a relative significance ($p = 0.083$). The total number of injections showed no significant differences between the two groups ($p = 0.110$). Significant differences were observed in the number of aflibercept injections ($p = 0.031$) and brolucizumab injections ($p = 0.045$), with a higher frequency in the non-SMH group (independent *t*-test) (Table 2).

Table 3 presents the results of the univariate analysis of the OCT features and follow-up intervals. The proportion

Table 4. Subgroup analysis based on the "interval from last injection to SMH" of 12 weeks (n = 24)

Variable	Interval from last injection to SMH		*p*-value
	≤12 wk (n = 13)	>12 wk (n = 11)	
Loading anti-VEGF agent			
Aflibercept	3 (21.1)	6 (54.5)	0.206
Ranibizumab	10 (76.9)	5 (45.5)	0.206
Anti-VEGF agent for nAMD treatment			
Bevacizumab	8 (61.5)	6 (54.5)	>0.999
No. of injections	4.69 ± 5.85	3.64 ± 6.65	0.531
Aflibercept	7 (53.8)	6 (54.5)	0.973
No. of injections	2.23 ± 2.49	2.91 ± 3.56	0.776
Ranibizumab	10 (76.9)	5 (45.5)	0.206
No. of injections	4.77 ± 3.86	2.09 ± 2.55	0.082
Brolucizumab	1 (7.7)	0 (0)	>0.999
No. of injections	0.08 ± 0.28	0 (0)	0.776
No. of total anti-VEGF injections	11.77 ± 7.18	8.64 ± 7.15	0.303
Serous/hemorrhagic PED	5 (38.5)	5 (45.5)	>0.999
Subretinal fluid	8 (61.5)	5 (45.5)	0.431
Intraretinal fluid	3 (23.1)	0 (0)	0.223
PED increase	3 (23.1)	4 (36.4)	0.659

Values are presented as number (%) or mean ± standard deviation.
SMH = submacular hemorrhage; VEGF = vascular endothelial growth factor; nAMD = neovascular age-related macular degeneration; PED = pigment epithelial detachment.

of patients with PED that increased in the last two visits before SMH occurrence tended to be higher in the SMH group, although the difference was not statistically significant ($p = 0.097$; $p < 0.1$, which may indicate a trend, though not reaching statistically significant difference). However, the number of patients with serous/hemorrhagic PED in the preceding visit was significantly higher in the SMH group than in the non-SMH group (10 patients [41.7%] vs. 2 patients [8.3%], $p = 0.008$) (Fig. 2A–2D, 3A–3D, 4A–4D, 5A–5D). There were no significant differences in the presence of intraretinal fluid and choroidal thickness between the two groups; however, there was a higher tendency for subretinal fluid in the SMH group ($p = 0.079$). In the SMH group, SMH occurred 35.85 weeks after the last intravitreal injection (median, 11.3 weeks), with no differences compared to the control group (Fig. 6). We conducted a subgroup analysis based on the 12-week interval between the last injection and the SMH, and no significant differences were found (Table 4).

Discussion

In patients with nAMD, SMH primarily occurs due to choroidal neovascularization (CNV) that grows through the Bruch membrane. However, SMH can also arise without evidence of CNV; in these cases, it is caused by choriocapillaris hemorrhage through discontinuities in Bruch membrane. The natural course of SMH varies depending on its cause [2]. With some cases may spontaneously resolve, and there is a recent trend towards active treatments, such as pneumatic displacement, tissue plasminogen activator, anti-VEGF injections, and surgical removal [1,4,13,14]. Despite these treatments, the visual prognosis of SMH remains poor. Chang et al. [5] compared BCVA in patients with nAMD with and without SMH after 6 months and found a significantly lower BCVA in the hemorrhage group.

This poor outcome can be explained by the mechanism through which SMH induces irreversible retinal damage. Iron generated during hemorrhage absorption can cause direct toxicity to the photoreceptor layer. Additionally, the contracting fibrin meshwork can lead to retinal traction, and the barrier effect of hemorrhage can disrupt the proper transfer of nutrients and metabolites. Experimental studies emphasize the need for prompt treatment as tissue damage can progress within 24 hours [1].

Based on these mechanisms, studies have explored the impact of SMH duration, size, and thickness on prognosis. Scupola et al. [6] reported that the size and thickness of the SMH negatively influenced the natural prognosis of nAMD. The presence of CNV is also a crucial prognostic factor, with SMH occurring in patients with nAMD and CNV that show poor outcomes. By contrast, patients with conditions without CNV, such as AMD without CNV, retinal macroaneurysms, high myopia, or trauma, tend to recover good vision [2].

While many studies have focused on predicting future outcomes in patients with SMH, research on the risk factors for SMH is limited, and much remains unknown. Gabrielle et al. [15] reported in a study focusing on nAMD that male sex and disciform scars were associated with the risk of SMH, while age, baseline visual acuity, and type of anti-VEGF were not related. In a study on PCV, the cluster type of polyps was identified as a risk factor for massive SMH, and hypertension was recognized as a risk factor for recurrent SMH [16,17]. A previous study examined the correlation between OCT features and SMH; however, it did not predict the risk of SMH in patients with nAMD but the prognosis after the occurrence of SMH. SMH can occur in patients with hemorrhagic PED due to an RPE break [2]. This study demonstrated that serous/hemorrhagic PED is a statistically significant risk factor for SMH in patients with nAMD. According to the treat-and-extend regimen of nAMD, disease activity is determined not by PED but by subretinal and intraretinal fluids [18,19]. However, it suggests the importance of considering PED in the treatment of nAMD, which can increase the risk of SMH occurrence.

Mehta et al. [20] conducted a secondary analysis of patients from the IVAN (Inhibit VEGF in Age-related Choroidal Neovascularization) trial, and found baseline SMH in approximately 53% of patients. Interestingly, their analysis reported no significant differences in BCVA between the SMH and non-SMH groups at the 12- and 24-month follow-up, contrary to findings from other studies. This may be due to the inclusion of SMH less than 1DD in addition to sub-RPE and intraretinal hemorrhages in the SMH group, which led to a higher prevalence of SMH in their study. Moreover, as approximately 90% of the patients in the SMH group had sizes below 1DD, which is within the normal spectrum of nAMD, there might be no significant differences in BCVA outcomes between the two groups. In

addition, there is a need for classification based on the area and thickness of the SMH, as there may be differences in treatment approaches and visual outcomes between SMH sizes <1DD and massive SMH.

In the present study, significant differences were observed in the number of aflibercept and rollizumab injections between the two groups, with the non-SMH group receiving more injections of each type. Additionally, there was a trend towards a higher proportion of ranibizumab loading in the SMH group, although this trend was not statistically significant. This implies the potential influence of anti-VEGF therapy on SMH, although no other studies have shown significant results with intravitreal injections. Among the 24 individuals in the SMH group, one (4.2%) experienced massive SMH 2 days after ranibizumab injection. There have been case reports of SMH occurring shortly after anti-VEGF treatment (bevacizumab, ranibizumab, and aflibercept), indicating complications following intravitreal injections [21–23]. More research with a larger sample size is needed to establish the association between anti-VEGF therapy and SMH.

The strengths of this study include its appropriate comparison with a control group and the analysis of OCT findings, which were not present in previous research. However, the study was limited by its retrospective nature, small sample size, and the possibility that other factors influencing SMH were not adequately tested owing to the insufficient sample size. Due to a lack of information on anticoagulants, an analysis of this issue was not performed. Furthermore, the natural course and outcome of SMH occurrence in nAMD and PCV may differ; however, the small sample size did not allow differentiation between the two diseases.

In conclusion, SMH is a significant complication of nAMD and is associated with a substantial loss of vision. In patients who receive three loading doses, serous/hemorrhagic PED can be considered a risk factor for subsequent submacular hemorrhage. Patients with serous/hemorrhagic PED may benefit from close monitoring and warnings to improve their visual outcomes. Further studies are required to explore the relationship between anti-VEGF therapy and SMH.

Conflicts of Interest: None.
Acknowledgements: None.
Funding: None.

References

1. Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: a synthesis of the literature. *Surv Ophthalmol* 2016;61:18-32.
2. Hochman MA, Seery CM, Zarbin MA. Pathophysiology and management of subretinal hemorrhage. *Surv Ophthalmol* 1997;42:195–213.
3. Kunavisarut P, Thithuan T, Patikulsila D, et al. Submacular hemorrhage: visual outcomes and prognostic factors. *Asia Pac J Ophthalmol (Phila)* 2018;7:109–13.
4. Steel DH, Sandhu SS. Submacular haemorrhages associated with neovascular age-related macular degeneration. *Br J Ophthalmol* 2011;95:1051–7.
5. Chang YS, Kim JH, Kim JW, et al. Development of submacular hemorrhage in neovascular age-related macular degeneration: influence on visual prognosis in a clinical setting. *Korean J Ophthalmol* 2018;32:361–8.
6. Scupola A, Coscas G, Soubrane G, Balestrazzi E. Natural history of macular subretinal hemorrhage in age-related macular degeneration. *Ophthalmologica* 1999;213:97–102.
7. Ugurtay O, Kockar A, Sengul EA. Real life data of treat and extend intravitreal ranibizumab and aflibercept therapy in wet age-related macular degeneration patients: 3-year results. *Korean J Ophthalmol* 2021;35:280-6.
8. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–44.
9. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.
10. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537–48.
11. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121:193–201.
12. Kim J, Lee SJ, Park TK, et al. Short-term efficacy and safety of intravitreal brolucizumab injection for treatment-naïve exudate age-related macular degeneration: a multicenter study. *Korean J Ophthalmol* 2023;37:365–72.
13. Berrocal MH, Lewis ML, Flynn HW. Variations in the clinical course of submacular hemorrhage. *Am J Ophthalmol* 1996;122:486–93.
14. Kang HG, Han JY, Choi EY, et al. Clinical characteristics,

risk factors, and surgical outcomes of secondary macular hole after vitrectomy. *Sci Rep* 2019;9:19535.

15. Gabrielle PH, Maitrias S, Nguyen V, et al. Incidence, risk factors and outcomes of submacular haemorrhage with loss of vision in neovascular age-related macular degeneration in daily clinical practice: data from the FRB! registry. *Acta Ophthalmol* 2022;100:e1569–78.
16. Cho JH, Ryoo NK, Cho KH, et al. Incidence rate of massive submacular hemorrhage and its risk factors in polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2016;169:79–88.
17. Chung YR, Seo EJ, Kim YH, et al. Hypertension as a risk factor for recurrent subretinal hemorrhage in polypoidal choroidal vasculopathy. *Can J Ophthalmol* 2016;51:348–53.
18. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;143:566–83.
19. Gemenetzi M, Patel PJ. A systematic review of the treat and extend treatment regimen with anti-VEGF agents for neovascular age-related macular degeneration. *Ophthalmol Ther* 2017;6:79–92.
20. Mehta A, Steel DH, Muldrew A, et al. Associations and outcomes of patients with submacular hemorrhage secondary to age-related macular degeneration in the IVAN trial. *Am J Ophthalmol* 2022;236:89–98.
21. Krishnan R, Goverdhan S, Lochhead J. Submacular haemorrhage after intravitreal bevacizumab compared with intravitreal ranibizumab in large occult choroidal neovascularization. *Clin Exp Ophthalmol* 2009;37:384–8.
22. Cho HJ, Lee DW, Cho SW, et al. Hemorrhagic complications after intravitreal ranibizumab injection for polypoidal choroidal vasculopathy. *Can J Ophthalmol* 2012;47:170–5.
23. Khoo C, Flynn E, Sohal P, et al. Submacular hemorrhage following aflibercept intravitreal injection: a report of two cases. *Cureus* 2022;14:e27255.