Review of Fibrosis in Neovascular Age-Related Macular Degeneration

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• PURPOSE: To report the diagnosis and definitions, epidemiology, risk factors, and visual outcomes of fibrosis in neovascular age-related macular degeneration (nAMD).
• DESIGN: Systematic review and meta-analysis.
• METHODS: The review was performed using the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Observational studies and randomized controlled trials were included.
• RESULTS: Identification of fibrosis is challenging. Optical coherence tomography angiography and polarization-sensitive optical coherence tomography represent novel options in multimodal imaging. The prevalence of fibrosis at baseline, 12, 24, and 60 months was 13%, 32%, 36%, and 56%, respectively. Approximately 60% of the fibrosis burden in nAMD at 5 years was present in the first year of treatment. Fibrosis development was highest in the first 12 months and slowed down over time. The risk factors of fibrosis included classic choroidal neovascularization (CNV), intra-retinal fluid, hemorrhage, hyperreflective material, CNV lesion size, and retinal thickness. Sub-retinal fluid and pigment epithelial detachment may be protective. Treatment-associated factors included disease activity and time to diagnosis. At baseline, the best corrected visual acuity in eyes with fibrosis was poorer than in eyes without fibrosis (–18.50 letters); this difference became larger at 12 months despite treatment (–26.86 letters).
• CONCLUSIONS: There is a need to identify effective treatment strategies for fibrosis and to closely monitor at-risk patients. More studies involving multimodal imaging are required to clarify the definitions and grading criteria for fibrosis. (Am J Ophthalmol 2023;246: 192–222.

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INTRODUCTION

Fibrosis is one of the end-stage sequelae of neovascular age-related macular degeneration (nAMD) and is associated with poor long-term visual outcomes.[1–21] In the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), the best corrected visual acuity (BCVA) in eyes with fibrotic scar decreased by a mean of 13 letters between years 1 and 5.[22,23] In real-world studies (RWS), fibrosis resulted in up to a 30-letter drop in BCVA.[24–28] This is despite the prevalent use of anti-vascular endothelial growth factor (anti-VEGF) drugs, which have been developed to prevent severe visual loss in patients with nAMD.

Previous studies have estimated the incidence and prevalence of fibrosis: the 2-year analysis of CATT described that fibrotic scar occurred in about 25% of eyes and RWS have described the incidence of fibrosis to be up to 40% after 2 years of treatment.[23] The prevalence of fibrosis has been described to be up to 70% at 10 years.[29] One of the reasons for the wide variation in the incidence and prevalence estimates of fibrosis may be due to the lack of standardized imaging modality for its diagnosis. While early studies have mainly relied on color fundus photography (CFP) and fluorescein angiography (FA),[22,30,31] newer studies have mostly relied on optical coherence tomography (OCT) with or without CFP and FA.[24,28,32–34]

In addition to diagnosis, many groups have attempted to identify risk factors for fibrosis development based on imaging features. Features that have been associated with fibrosis include classic choroidal neovascularization (CNV),[22,23,26,28,35–37] intra-retinal fluid (IRF),[24–26,28,37] hyperreflective material,[22–24,37–40] hemorrhage,[22,23] CNV lesion size,[27,28,36] and retinal thickness.[22–24] In contrast, sub-retinal fluid (SRF) and pigment epithelial detachment (PED) may be protective.[25,28,38] Treatment-related factors such as disease activity[28,30,34] and time to diagnosis[36,41,42] have also been reported

This systematic review and meta-analysis aimed to report the diagnosis, epidemiology, risk factors, and visual outcomes of fibrosis. These findings will be important for future research aimed at preventing visual loss from fibrosis in nAMD.

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METHODS

This systematic review and meta-analysis were performed using the Cochrane Handbook[43] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[44]

• **ELIGIBILITY CRITERIA:** Eligible studies must have described at least 1 of the following: imaging modalities used to detect fibrosis; incidence and/or prevalence of fibrosis; associated imaging risk factors; treatment-related associations; and/or the visual outcomes in nAMD eyes undergoing anti-VEGF treatment. Randomized controlled trials (RCTs) and their post hoc analyses, and observational studies were included. These studies must have represented original data. If there were serial publications from the same study, multiple publications may have been cited to include all the information; however, only the most comprehensive article from such groups was used for incidence or prevalence calculations to avoid data duplication, as this would have created bias with inappropriate weights accorded to the duplicate data. All articles that were published up to end May 2022 were searched. This review was not registered.

• **SEARCH STRATEGY:** The articles were retrieved from PubMed using a combination of keywords and Boolean operators: (age-related macular degeneration OR age-related maculopathy) AND (fibrosis OR scar OR scarring OR fibrovascular OR fibrotic). The titles and abstracts of all articles were reviewed for relevance. The full text was reviewed if the abstract indicated that the article was relevant.

• **QUALITY ASSESSMENT:** The quality of the included studies was assessed using the Study Quality Assessment Tools by the National Heart, Lung, and Blood Institute of the National Institutes of Health[45] (see Supplementary Tables S1 and S2). Two authors (KXC and KYCT) independently reviewed the quality of the studies. Discrepancies were resolved by an expert senior author (CMC).

• **DATA EXTRACTION:** A standardized form was used to gather the following information: study design, first author's name, year of publication, country of study, sample size, imaging modality, fibrosis definition, and findings (incidence and prevalence, imaging, treatment-related associations, and BCVA).

• **STATISTICAL ANALYSIS:** Cumulative incidence was calculated by dividing the total number of new (incident) fibrosis cases by the total number of eyes at risk. The incidence rate was calculated by dividing the number of incident fibrosis cases by the total number of eye-months of follow-up. When the total number of eye-months of follow-up was unreported, this was calculated by multiplying the number of eyes under follow-up by the mean duration of follow-up. The prevalence for a particular time point was calculated by dividing the number of existing fibrosis cases at a time point by the total number of eyes on follow-up. The difference in BCVA was represented in letters.

Statistical analyses were performed using R statistical software version 4.1.1 (R Foundation for Statistical Computing). The *metarate* function was used to perform meta-analyses of single incidence rates, which were pooled using a random effects model with inverse variance meta-analysis. Log transformation of the incidence rates was performed. The heterogeneity variance parameter used was the DerSimonian–Laird estimator. The incidence rate was represented in events per 1000 eye-months as a weighted average with 95% confidence interval (CI).

The *metaprop* function was used to perform meta-analyses of cumulative incidence and prevalence. Cumulative incidence and prevalence were pooled using random effects models with random intercept logistic regression analyses. Logit transformation of the data was performed. The heterogeneity variance parameter used was the maximum-likelihood estimator. The cumulative incidence and prevalence were represented in proportions as weighted averages with 95% CI.

The *metacont* function was used to perform meta-analyses of difference in BCVA between eyes with fibrosis compared with those without. Study-specific data were pooled using a random effects model with random intercept logistic regression analysis. The heterogeneity variance parameter used was the maximum-likelihood estimator. Hedges' g was used.

A P value $< .05$ was considered statistically significant. The I^2 statistic was used to determine the proportion of variation in the study due to heterogeneity. The τ^2 statistic was used to assess the between-study variation of underlying effects among studies.

RESULTS

A total of 1235 articles were identified, of which 1176 articles were excluded after a review of the abstracts and titles. The full texts of the remaining 59 articles were reviewed and 22 articles were excluded. Therefore, 37 studies were included into this review, of which 29 were RWS,[24–29,32–34,36,38–42,46–59] and the remaining 8 were RCTs[22,23,30,31,35,37,61,62] (see Figure 1).

• **DIAGNOSIS AND DEFINITIONS OF FIBROSIS:** There is currently no gold standard for diagnosing fibrosis. Most studies used multimodal imaging, including CFP, FA, fundus auto-fluorescence, OCT, OCT angiography (OCTA), and polarization-sensitive OCT (PS-OCT) (see Table 1).

• **TRADITIONAL MODALITIES:** Color fundus photography and FA were used in the CATT and IVAN studies.[22,23,30,31]

TABLE 1. Summary of Studies That Stated Diagnostic Modalities and Definitions of Fibrosis

Author, Year	Study (Origin)	Sample Size (Eyes)	Imaging Modality									Definition
			Slit Lamp Biomicroscopy	CFP	FA	OCT	FAF	PS-OCT	OCTA	Multicolor	Red Free	
RWS												
Teo, 2021[34] Teo, 2020[28] Nyugen, 2018[23]	FRB! (Australia, New Zealand, Switzerland, and Singapore)	2109 1950532		√		√						Mixed fibrovascular structure identified as obvious white or yellow mounds of fibrous-appearing tissue well-defined in shape and appears solid on CFP alone or in combination with presence of well-defined SHRM on OCT
Wolff, 2018[29]	FRB! (France)	116	√			√	√					–
Cheung, 2019[24]	Phenotyping Asian Macular Diseases Study, Singapore (Singapore)	78		√	√	√						SHRM on OCT and whitish well-circumscribed lesions on CFP or well-circumscribed lesion with late staining was observed on FA
Llorente-Gonzalez, 2021[25] Saenz-de-Viteri, 2021[38]	Ambispective cohort study (Spain)	354 270		√		√						Presence of yellow-whitish lesion area in CFP and/or a hyperreflective lesion at RPE level in OCT
Roberts, 2022[26]	Prospective cohort study (Austria)	45		√	√			√				Presence of whitish or yellowish material unrelated to drusen, hard exudate, fibrin, or dehemoglobinised blood on CFP associated with hyperreflective material on SD-OCT On FA, fibrosis characterized by early hypofluorescence and late staining Detected automatically by proprietary algorithm based on tissue birefringence on PS-OCT
Motschi, 2021[53]	Prospective cohort study (Austria)	57		√				√				Presence of whitish or yellowish material unrelated to drusen, hard exudate, fibrin, or dehemoglobinised blood on CFP associated with hyperreflective material on SD-OCTDetected automatically by proprietary algorithm based on tissue birefringence on PS-OCT
Roberts, 2021[27]	Prospective cohort study (Austria)	60		√				√				Presence of whitish or yellowish material unrelated to drusen, hard exudate, fibrin, or dehemoglobinised blood on CFP associated with hyperreflective material on SD-OCT Automatically detected by proprietary algorithm based on tissue birefringence on PS-OCT

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TABLE 1. (*continued*)

Author, Year	Study (Origin)	Sample Size (Eyes)	Imaging Modality									Definition
			Slit Lamp Biomicroscopy	CFP	FA	OCT	FAF	PS-OCT	OCTA	Multicolor	Red Free	
Roberts, 2019[40]	Prospective cohort study (Austria)	50	√	√	√	√						Presence of whitish or yellowish material unrelated to drusen, hard exudate, fibrin, or dehemoglobinised blood on CFP associated with hyperreflective material on SD-OCT On FA, fibrosis characterized by early hypofluorescence and late staining
Roberts, 2016[56]	Prospective cohort study (Austria)	15	√	√	√							Whitish or yellowish sub-retinal tissue in fundoscopy unrelated to drusen, hard exudates, fibrin, or dehemoglobinised blood and associated with early hypofluorescence and late staining in FA
Kim, 2021[50]	Cross-sectional study (South Korea)	68	√			√						Well-demarcated, elevated mound of yellowish-white tissue, with variable location in macular area on CFP Corresponding OCT demonstrating fibrosis resembled a sub-retinal hyperreflective lesion with possible loss of adjacent RPE and EZ.
Querques, 2020[55]	Cross-sectional study (Italy)	41							√	√		Well-demarcated bright lime-green or yellowish region on multicolor photographs
Souied, 2020[58]	Cross-sectional study and separate retrospective longitudinal analysis (France)	47	√		√	√						Well demarcated, elevated mound of yellowish-white tissue on CFP On FA, fibrosis caused by late AMD displayed staining, with minimal or no leakage in late phase of the angiographic sequence On SD-OCT, defined as fibrotic if $>$ 50% of its area was occupied by compact, sheet-like hyperreflective material, situated either above or underneath RPE
Gräfe, 2019[49]	Cross-sectional study (Netherlands)	29	√	√				√				Yellow-whitish lesion on fundoscopy and CFP and as hyperreflective lesion on OCT at level of RPE combined with low BCVA when the lesion was sub foveal
Balaskas, 2018[32]	Retrospective cohort study (United Kingdom)	39		√		√			√			White/yellow material in macula on CFP associated with of SHRM on OCT
Küçük, 2018[51]	Retrospective cohort study (Turkey)	74		√	√	√						–

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TABLE 1. (*continued*)

Author, Year	Study (Origin)	Sample Size (Eyes)	Imaging Modality									Definition
			Slit Lamp Biomicroscopy	CFP	FA	OCT	FAF	PS-OCT	OCTA	Multicolor	Red Free	
Casalino, 2017[39]	Retrospective cohort study (United Kingdom)	150		√	√							Well-delineated areas of yellow-white tissue with corresponding initial hypofluorescence, with late hyperfluorescence and staining on FA Lesions further categorized using CATT study fibrotic scar definition
Sagiv, 2017[57]	Retrospective case series	42	√			√						Combination of gray-white elevated sub-retinal tissue on funduscopic examination and thickened homogeneous hyperreflective signal in sub-retinal or sub-RPE space on OCT
Fajnkuchen, 2016[48]	Retrospective, non-comparative case series (France)	22		√		√						Fibrotic scar characterized by the presence of a white, thick sharp-edged sub-retinal lesion
Souied, 2016[59] Miere, 2015[52]	Retrospective, non-comparative case series (France)	49 49		√	√	√			√			On CFP, fibrosis demonstrated by well delineated mound of white-yellowish tissue, corresponding to late staining and no leakage on FA On SD-OCT, fibrosis appears as compact, sub-retinal hyperreflective lesion, with variable degrees of loss of both RPE and EZ
Bloch, 2013[36]	Retrospective cohort study (Denmark)	197		√		√						Based on OCT, subfoveal fibrous tissue was categorized, with reference to standard photographs as minimal fibrosis with or without SRF (stage I), as prominent fibrosis with or without cystoid edema (stage II), and fibrosis with overlying neurosensory retinal atrophy (stage III)

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TABLE 1. (*continued*)

Author, Year	Study (Origin)	Sample Size (Eyes)	Imaging Modality									Definition
			Slit Lamp Biomicroscopy	CFP	FA	OCT	FAF	PS-OCT	OCTA	Multicolor	Red Free	
RCT												
Finn, 2022[37] Daniel, 2018[22] Daniel, 2014[23]	CATT	68 1061 1059		√	√							Obvious white or yellow mounds of fibrous-appearing tissue that were well-defined in shape and appeared solid on color stereo images Hyperfluorescence due to tissue staining or blocked fluorescence of the underlying choroid identified from FA
Mehta, 2021[31]	IVAN	413		√	√							Creamy white or yellow material was observed within boundaries of nAMD lesion on CFP Blocked fluorescence in early phase with hyperfluorescence in mid phase which faded in late frames
Evans, 2020[30]	CATT/IVAN	1720		√	√							Obvious white or yellow mounds of fibrous-appearing tissue that were well-defined in shape and appeared solid on color stereo images Hyperfluorescence due to tissue staining or blocked fluorescence of underlying choroid identified from FA
Adrean, 2020[35]	HARBOR	1097			√						√	By using FA, fibrosis considered present if median area of sub-retinal fibrous tissue or disciform scar from 3 readers was greater than 0 (ie, any detectable fibrosis) By using red-free fundus photography, fibrous location defined as absent, subfoveal fibrosis observed alone or with other locations (any subfoveal), extrafoveal but not subfoveal (extrafoveal only), and remote location only or not reported (other)

BCVA = best corrected visual acuity; CFP = color fundus photographs; EZ = ellipsoid zone; FA = fundus fluorescein angiography; FAF = fundus autofluorescence; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; OCTA = optical coherence tomography angiography; PS-OCT = polarization-sensitive OCT; RCT = randomized controlled trial; RPE = retinal pigment epithelium; RWS = real-world studies; SHRM = sub-retinal hyperreflective material; SRF = sub-retinal fluid.

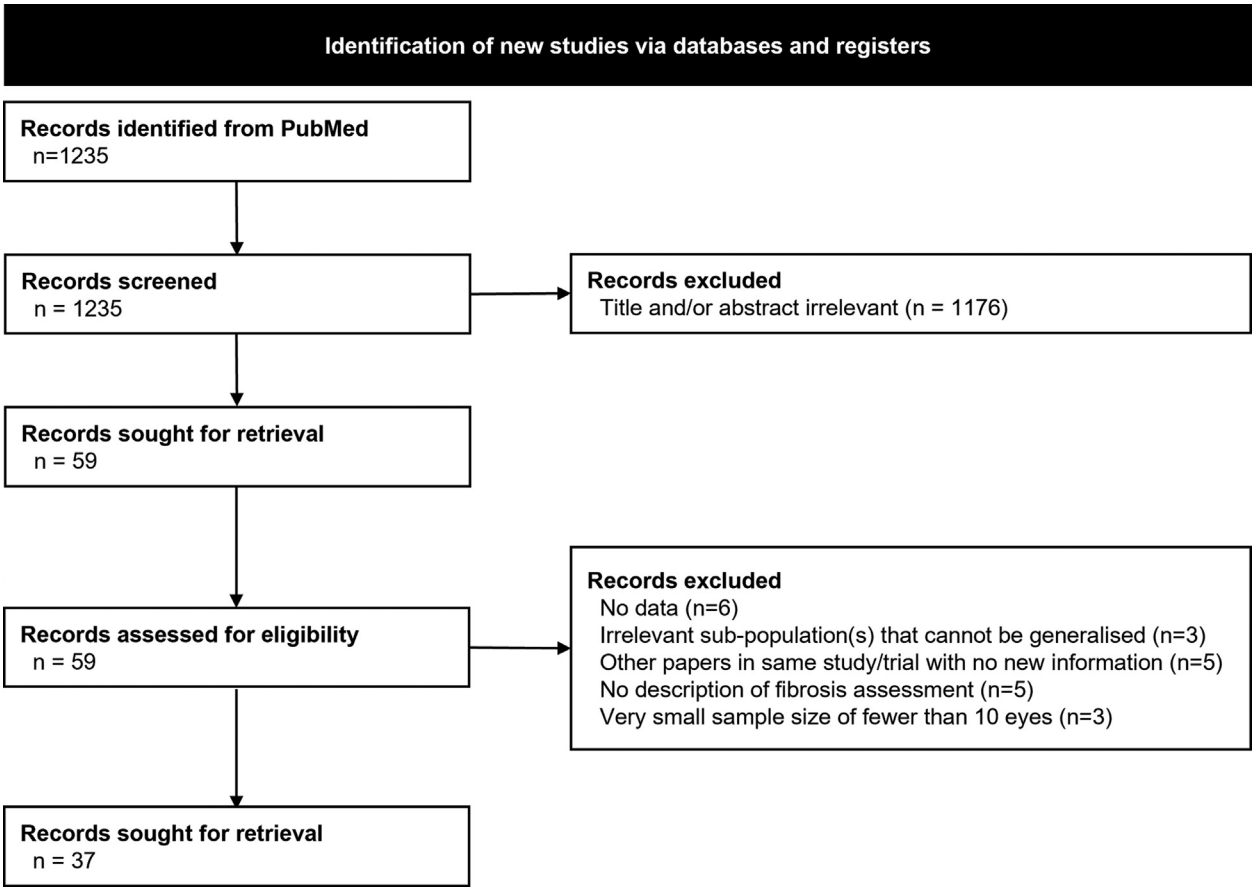

FIGURE 1. Results of the systematic search using key electronic databases. A total of 37 studies were selected for inclusion into this meta-analysis and systematic review.

In the CATT study, fibrotic scars were defined as obvious white or yellow mounds of fibrous-appearing tissue that had a well-defined shape and solid appearance on color stereo images, and displayed hyperfluorescence due to tissue staining or blocked fluorescence of the underlying choroid on FA.[22,23,30] Fluorescein angiography displayed leakage if there was active CNV with the fibrotic scar. The IVAN study used a similar definition:[30,31] fibrosis was graded as present when creamy white or yellow material was observed on color images, and if there was blocked fluorescence in the early phase with hyperfluorescence in the mid-phase that faded in late frames. The CATT study further distinguished between fibrotic scars and nonfibrotic scars, which are usually flat, depigmented lesions with varying amounts of signet-shaped peripheral dark pigmentation that conform to the CNV area.[22,23,30] The CATT study further noted that nonfibrotic scars also manifest as hyperreflective material in a sub-retinal or sub-retinal pigmental epithelium (RPE) location that would be like that of fibrosis.[22,23,30] Furthermore, the foveal retinal thickness of the sub-retinal tissue complex in a nonfibrotic scar was between those with no scar and those with fibrotic scar.

Red-free fundus photography and FA were used in the HARBOR study.[35] Fibrosis was considered present if the median area of sub-retinal fibrous tissue or disciform scar from 3 readers was > 0 (any detectable fibrosis) and was further defined as absent; any subfoveal (subfoveal fibrosis observed alone or with other locations); extrafoveal only (extrafoveal but not subfoveal); or other (remote location only or unreported).[35] In contrast, grading of fibrosis and/or scarring in general was not explained in the SEVEN-UP study.[61,62]

Most of the subsequent studies have incorporated the use of OCT in combination with CFP. Fibrosis is typically defined on OCT as hyperreflective material, either in the sub-retinal or sub-RPE space.[24,28,32–34,36,52,57–59] Different groups have used a variety of terms: most groups have used the term "sub-retinal hyperreflective material" (SHRM) to literally describe the hyperreflective appearance of fibrosis in the sub-retinal compartment on OCT. For example, in the Fight Retina Blindness! (FRB!) studies, fibrosis was defined as a mixed fibrovascular structure that appears as obvious white or yellow mounds of fibrous-appearing tissue that are well-defined in shape and appear solid on CFP alone or

in combination with well-defined SHRM on OCT.[28,33,34] The Phenotyping Asian Macular Diseases Study has similarly defined fibrosis as lesions that manifest as SHRM on OCT and as whitish well-circumscribed lesions on CFP, or as a well-circumscribed lesion with late staining on FA.[24]

Casalino and associates[39] sought to use the term "hyperreflective material" (HRM) instead of SHRM, having noted that the hyperreflective material is found in the sub-retinal space and also other compartments such as the sub-RPE space. Casalino and associates[39] further distinguished well-defined HRM (that with hyperreflectivity whose boundaries could be clearly delineated from the surrounding neural components of the retina) from undefined HRM (that with low reflectivity and whose borders were less well distinguishable from surrounding neural components). Casalino and associates[39] further asserted that eyes with defined HRM had the highest risk of scarring, whereas those with undefined HRM had a lower risk. Lastly, in the Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data by Spaide and associates[62], SHRM does not refer to fibrotic material but represents sub-retinal hyperreflective exudative material and is one of the 4 basic forms of exudation apart from leakage, SRF, and lipid. To avoid confusion this review used the terms that the respective groups originally used.

• **NEWER MODALITIES:** OCTA and PS-OCT are newer imaging modalities that can further characterize fibrosis. Miere and associates[52] characterized the vasculature within fibrosis: blood flow inside the fibrotic scar could be detected in 46 of 49 eyes (93.8%). There were 3 patterns of vascular networks, including the pruned vascular tree, tangled network (14 of 49 eyes; 28.6%), and/or vascular loop.[52] Balaskas and associates[32] reported that a neovascular complex was detectable in 26 of 39 eyes with sub-retinal fibrosis (66.7%). They reported that the edges of the neovascular complex were disrupted and did not appear rounded. The neovascular complexes had a "dead tree" configuration in about half of the eyes; a small vascular loop was detected in avascular and hyporeflective fibrotic tissue in a few other eyes. Furthermore, the presence of a CNV membrane negatively influenced BCVA ($P = .02$).

Ahmed and associates[46] also used OCTA to describe the shape, branching pattern, and termination characteristics of fibrotic lesions in 70 eyes. For shape, the group reported that of 12 eyes with fibrotic MNV, six eyes (50%) had an ill-defined shape, five eyes (41.6%) had long linear vessels, and one eye (8.3%) had a well-defined shape ("medusa" shape). For branching pattern, five eyes (41.6%) had an ill-defined branching pattern, six eyes (50%) were poor in anastomoses, and one eye (8.3%) had dense branching patterns. For termination, five eyes (41.6%) had an ill-defined termination, six eyes (50%) ended in a dead tree aspect, and one eye (8.3%) ended in a peripheral anastomotic arcade.

Optical coherence tomography angiography can yield quantitative information. Roberts and associates[27] analyzed quantitative vasculature biomarkers using OCTA in 60 eyes with sub-retinal fibrosis. Compared with eyes without fibrosis, eyes with fibrosis demonstrated a larger greatest vascular caliber ($P = .001$), greatest linear diameter ($P = .042$), larger CNV area ($P = .026$), larger vessel area ($P = .037$), higher number of vessel junctions ($P = .025$), longer total vessel length ($P = .027$), higher number of vessel endpoints ($P = .007$), and higher endpoint density ($P = .047$). Querques and associates[55] assessed the perfusion density of 41 eyes, which were categorized into the fibrocellular and fibrovascular groups based on the multicolor image appearance. They described that the perfusion density within the neovascular lesion was 28.9% in the fibrocellular group and 44.2% in the fibrovascular group ($P < .0001$).

Polarization-sensitive OCT is an extension of OCT and is currently under evaluation as a research tool so is not yet widely available. Fibrosis is identified based on its birefringence that is caused by the interaction of collagen fibers with the light beam. Roberts and associates[56] described that sub-retinal fibrosis featured birefringent well-defined columns of a uniform axis in all 15 eyes, indicating collagen fiber orientation within scar tissue. The other components within the SHRM or sub-RPE hyperreflective material, such as the CNV complex, drusen, or blood, did not exhibit birefringence. In contrast, spectral-domain OCT was unable to differentiate the components within the SHRM. Polarization-sensitive OCT also demonstrated regions of RPE loss associated with sub-retinal fibrosis, as the RPE exhibited depolarization due to its melanin content on PS-OCT. Similarly, Grafe and associates[49] reported that PS-OCT demonstrated an excellent detection of fibrosis and confirmed the evaluation of retinal specialists regarding the presence of sub-retinal fibrosis in 21 of 22 eyes (95.45%).

Motschi and associates[53] used PS-OCT on 57 eyes to differentiate fibrosis from other structures that also display birefringence, such as the cornea, retinal nerve fiber layer, and Henle fiber layer. The results of fibrosis detection using PS-OCT were compared with clinical diagnosis based on CFP, and there was agreement between PS-OCT and CFP in 48 of 57 eyes (84.21%). The measurement of fibrotic area was precise. The average standard deviation (SD) of the measurements in cases of fibrotic lesion area $> 0.7 mm^2$ was 15%. Discrepancies were only observed in cases of lesion area $< 0.7\ mm^2$.

Apart from reporting qualitative features, Roberts and associates[40] also quantified SHRM volumetric changes of 50 eyes to characterize the angiofibrotic switch. They reported that the SHRM thickness and volume at month 3 ($P = .001$ and $P = .02$, respectively) were significantly larger and the SHRM thickness and volume reduction after anti-VEGF treatment ($P = .002$ and $P = .027$, respectively) were significantly lesser in eyes with fibrosis compared with those without.

• **INCIDENCE AND PREVALENCE OF FIBROSIS:** See Table 2 for the prevalence and incidence.

TABLE 2. Incidence and Prevalence of Fibrosis

Author	Study	Sample Size (Eyes)	Cumulative Incidence					Incidence Rate	Prevalence					
			Month 12	Month 24	Month 36	Month 60	Month 120		Baseline	Month 12	Month 24	Month 36	Month 60	Month 120
RWS														
Teo, 2020[28]	FRB! (Australia, New Zealand, Switzerland, and Singapore)	1950	21.3%	26.3%	–	–	–	137 eyes/ 10,532.6 eye-months (13.0/1000 eye-months)	278/1950 eyes (14.3%)	69/265 eyes (26.0%)	104/371 eyes (28.0%)	155/621 eyes (25.0%)	101/266 eyes (38.0%)	81/162 eyes (50.0%)
Nyugen, 2018[33]	FRB! (Australia, New Zealand, Switzerland)	532	–	–	–	–	–	–	–	–	–	–	196/532 eyes (36.8%)	–
Wolff, 2018[29]	FRB! (France)	116	–	–	–	–	120 months: 52/116 eyes (44.8%)†	52 eyes/ 10320 eye-months (5.0/1000 eye-months)†	30/116 eyes (25.9%)	–	–	–	–	82/116 eyes (70.7%)
Cheung, 2019[24]	Phenotyping Asian Macular Diseases Study, Singapore (Singapore)	78	22/78 eyes (28.2%)	–	–	–	–	22 eyes/ 1104 eye-months (19.9/1000 eye-months)	12/92 eyes (13.0%)	34/90 eyes (37.8%)	–	–	–	–
Llorente-Gonzalez, 2021[25]	Ambispective cohort study (Spain)	354	–	–	–	–	–	–	–	–	–	134/354 eyes (37.9%)	–	
Saenz-de-Viteri, 2021[38]	Ambispective, cohort study (Spain)	270	–	–	–	–	–	–	23/270 eyes (8.5%)	95/270 eyes (35.2%)	–	–	–	–
Roberts, 2022[26]	Prospective cohort study (Austria)	45	–	–	–	–	–	–	8/45 (17.8%)	–	–	–	–	–
Roberts, 2021[27]	Cross-sectional study (Austria)	60	–	–	–	–	–	–	–	20/60 eyes (33.3%)	–	–	–	–
Angermann, 2022[41]	Retrospective cohort study (Austria)	566	–	–	–	–	–	–	–	–	–	–	13/566 eyes (2.3%)	–

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TABLE 2. (*continued*)

Author	Study	Sample Size (Eyes)	Cumulative Incidence					Incidence Rate	Prevalence					
			Month 12	Month 24	Month 36	Month 60	Month 120		Baseline	Month 12	Month 24	Month 36	Month 60	Month 120
Alex, 2021[47]	Cross-sectional study (India)	157	–	–	–	–	–	–	–	50/157 eyes (31.9%)	–	–	–	–
Kim, 2021[50]	Cross-sectional study (South Korea)	68	19/68 eyes (27.9%)†	–	–	–	–	19 eyes/ 816 eye-months (23.3/1000 eye-months)†	–	19/68 eyes (27.9%)	–	–	–	–
Küçük, 2018[51]	Retrospective cohort study (Turkey)	74	–	–	–	47/74 eyes (63.5%)†	–	47 eyes/ 2988 eye-months(15.7/1000 eye-months)†	–	–	–	–	47/74 eyes (63.5%)	–
Casalino, 2017[39]	Retrospective cohort study (United Kingdom)	150	18/127 eyes (14.2%)†	–	–	–	–	18 eyes/ 1524 eye-months (11.8/1000 eye-months)†	23/150 (15.3%)	41/150 (27.3%)	–	–	–	–
Pedrosa, 2017[54]	Retrospective cohort study (Portugal)	117	–	–	–	75/108 eyes (69.4%)	–	75 eyes/ 6480 eye-months (11.6/1000 eye-months)†	9/117 (7.7%)	–	–	–	84/117 (71.79%)	–
Sagiv, 2017[57]	Retrospective case series	42	–	–	–	–	–	–	–	–	–	–	21/42 (50.0%)	–
Bloch, 2013[36]	Retrospective cohort study (Denmark)	197	–	77/197 eyes (39.1%)†	–	–	–	77 eyes/ 4728 eye-months (16.3/1000 eye-months)†	–	71/197 eyes (36.0%)	77/197 eyes (39.1%)	–	–	–
RCT														
Mehta, 2021[31]	IVAN	413	–	158/413 (38.3%)†	–	–	–	158 eyes/ 9420 eye-months (17.1/1000 eye-months)†	55/413 eyes (13.5%)	213/413 eyes (51.8%)	183/372 eyes (49.3%)	–	–	–
Evans, 2020[30]	CATT/IVAN	1720	–	–	–	–	–	–	135/1720 eyes (7.8%)	–	931/1586 eyes (58.7%)	–	–	–

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TABLE 2. (*continued*)

Author	Study	Sample Size (Eyes)	Cumulative Incidence					Incidence Rate	Prevalence					
			Month 12	Month 24	Month 36	Month 60	Month 120		Baseline	Month 12	Month 24	Month 36	Month 60	Month 120
Daniel, 2018[22]	CATT	1061	–	–	–	530/1061 eyes (50.0%)[†§]	–	530 eyes/ 30312 eye-months (17.5/1000 eye-months)[†§]	–	339/1061 eyes (32.0%)[§]	480/1006 eyes (47.7%)[§]	–	530/746 eyes (72.0%)[§]	–
Daniel, 2014[23]	CATT	1059	–	262/1059 eyes (24.7%)	–	–	–	262 eyes/ 25,416 eye-months (10.3/1000 eye-months)	–	205/1059 eyes (19.4%)	262/1059 eyes (24.7%)	–	–	–
Adrean, 2020[35]	HARBOR	1097	–	–	–	–	–	–	–	–	391/904 eyes (43.3%)	–	–	–
Bhisitkul, 2015[60]	SEVEN-UP	65	–	–	–	–	–	–	–	–	–	–	–	84 months: 35/65 eyes (53.9%)
Rofagha, 2013[61]	SEVEN-UP	57	–	–	–	–	–	–	–	–	–	–	–	84 months: 35/57 eyes (61.4%)

RWS = real-world studies; RCT = randomized controlled trial.
[†]Manually calculated, assuming no censorship/loss to follow-up.
[§]Combination of both fibrotic and nonfibrotic scar.

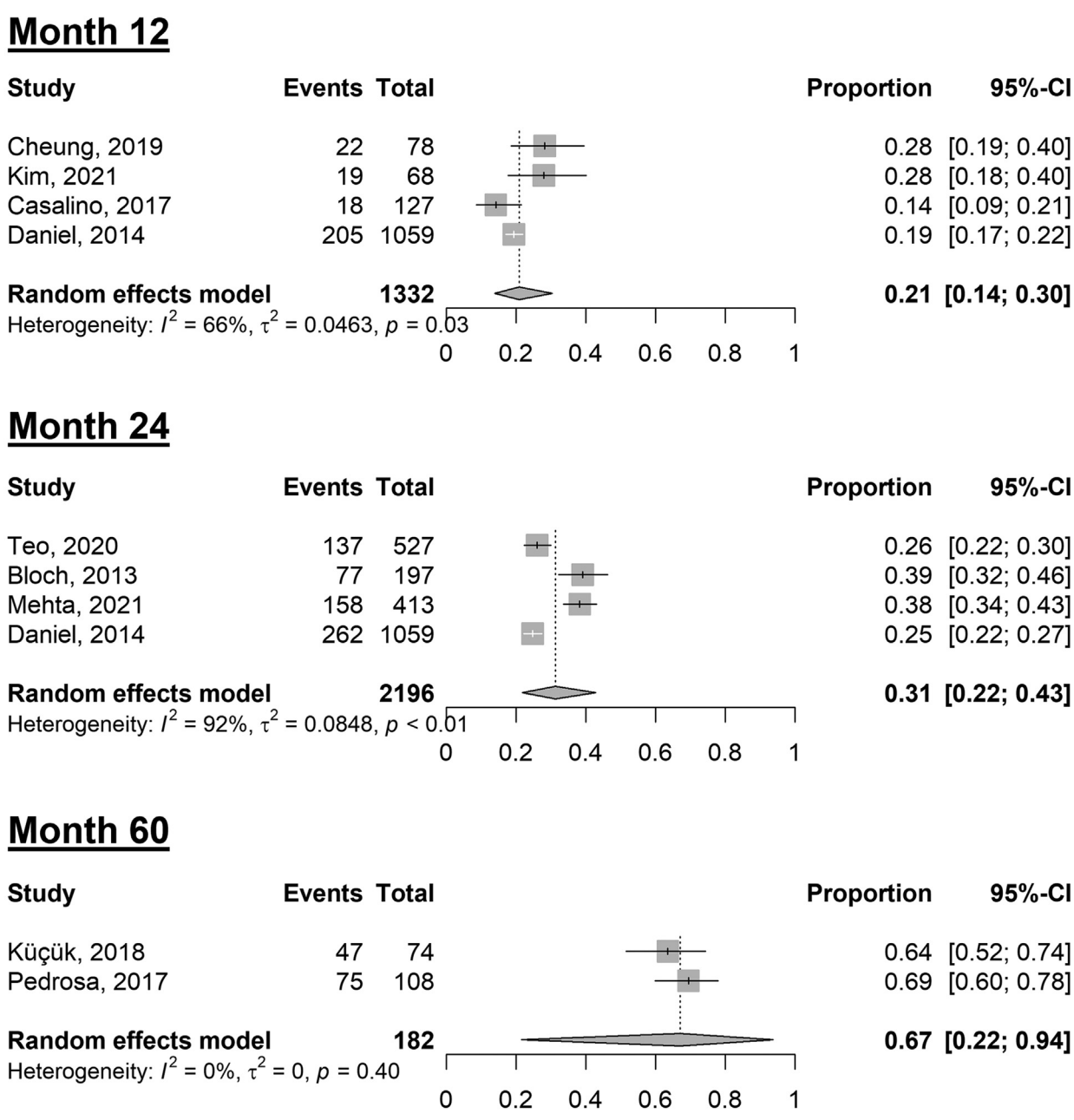

FIGURE 2. Cumulative incidence of fibrosis. The cumulative incidence of fibrosis at 12, 24, and 60 months were 21%, 95% confidence interval (CI) 14% to 30%; 31%, 95% CI 22% to 43%; and 67%, 95% CI 22% to 94%, respectively. There was significant heterogeneity among the studies for the months 12 and 24 analyses, as evidenced by the I^2 of 66% and 92%, respectively, and τ^2 of 0.0463 and 0.0848, respectively.

Cumulative incidence and incidence rate

Meta-analyses were performed for months 12, 24, and 60, which used 4,[23,24,30,39] 4,[23,28,31,36] and 2 studies,[51,54] respectively, representing a total of 7 RWS and 2 RCTs (see Figure 2). The cumulative incidence of fibrosis at 12, 24, and 60 months was 21%, 95% CI 14% to 30%; 31%, 95% CI 22% to 43%; and 67%, 95% CI 22% to 94%, respectively. There was significant heterogeneity among the studies for months 12 and 24, as evidenced by the I^2 of 66% and 92%, respectively, and τ^2 of 0.0463 and 0.0848, respectively.

Data of 9 studies (7 RWS and 2 RCTs) were pooled to assess the incidence rate of fibrosis[23,24,28,31,36,39,50,51,54] (see Figure 3). The pooled overall incidence rate was 14.71 events per 1000 eye-months, 95% CI 12.28 to 17.61. There was significant heterogeneity among the studies, as evi-

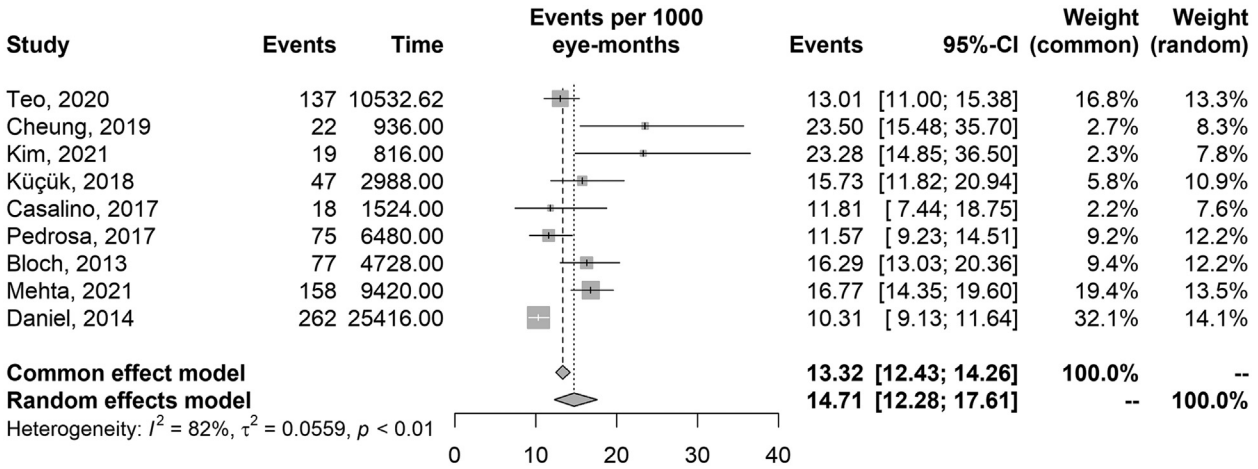

FIGURE 3. Overall incidence rate of fibrosis. The pooled incidence rate of fibrosis was 14.71 events per 1000 eye-months, 95% CI 12.28 to 17.61. There was significant heterogeneity among the studies, as evidenced by the I^2 of 82% and τ^2 of 0.0559.

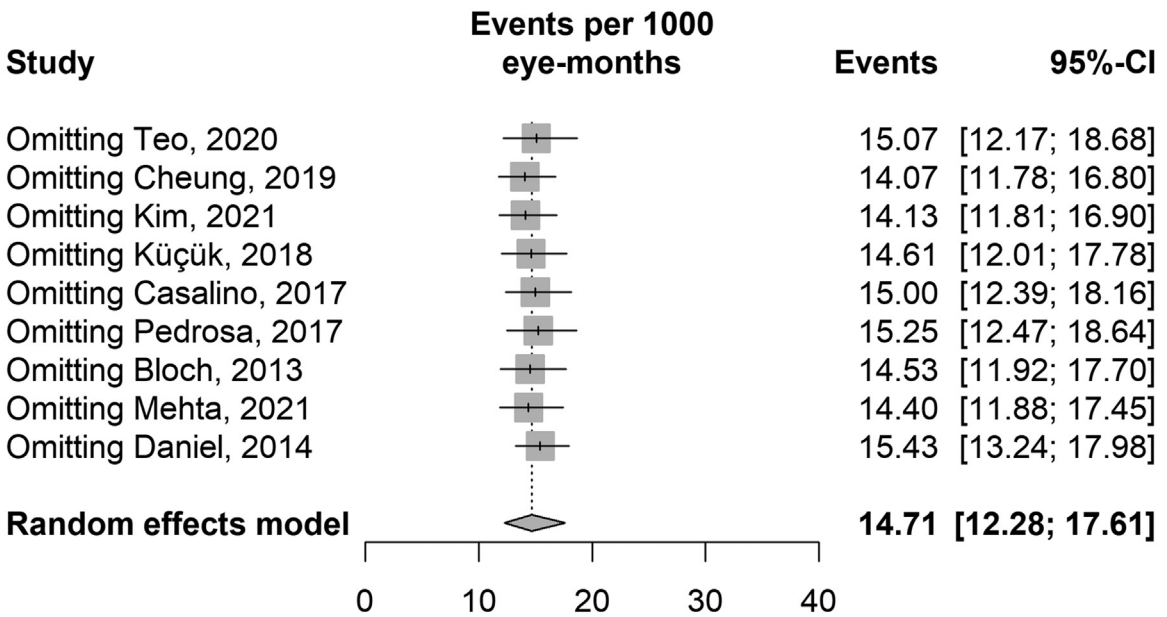

FIGURE 4. Heterogeneity analysis for incidence rate of fibrosis: leave-one-out analysis. A leave-one-out analysis was performed. The pooled incidence rate did not significantly change with the omission of any of the studies.

denced by the I^2 of 82% and τ^2 of 0.0559. A leave-one-out analysis was performed (see Figure 4). The pooled incidence rate did not change significantly with omission of any of the studies. The incidence rate analysis was further categorized into the respective follow-up periods. The 12-month, 24-month, and 60-month incidence rate analyses used 4,[23,24,30,39] 4,[23,28,31,36] and 2 studies,[51,54] respectively, representing a total of 7 RWS and 2 RCTs (see Figure 5). The incidence rate of fibrosis at 12, 24, and 60 months was 17.70 events/1000 eye-months, 95% CI 13.58 to 23.06; 13.74 events/1000 eye-months, 95% CI 10.73 to 17.60; and 13.32 events/1000 eye-months, 95% CI 9.87 to 17.97, respectively. There was significant heterogeneity among the studies for month 12 (I^2 of 89% and τ^2 of 0.0564).

Prevalence

Meta-analyses were performed for baseline, months 12, 24, and 60, which used 7,[24,26,28,31,38,39,54] 10,[23,24,27,28,31,36,38,39,47,50] 5,[23,28,31,35,36] and 4 studies,[28,51,54,57] respectively, representing a total of 12 RWS and 3 RCTs (see Figure 6). The prevalence of fibrosis at baseline, 12, 24, and 60 months was 13%, 95% CI 10% to 16%; 32%, 95% CI 26% to 39%; 36%, 95% CI 25% to 49%; and 56%, 95% CI 34% to 76%, respectively. There

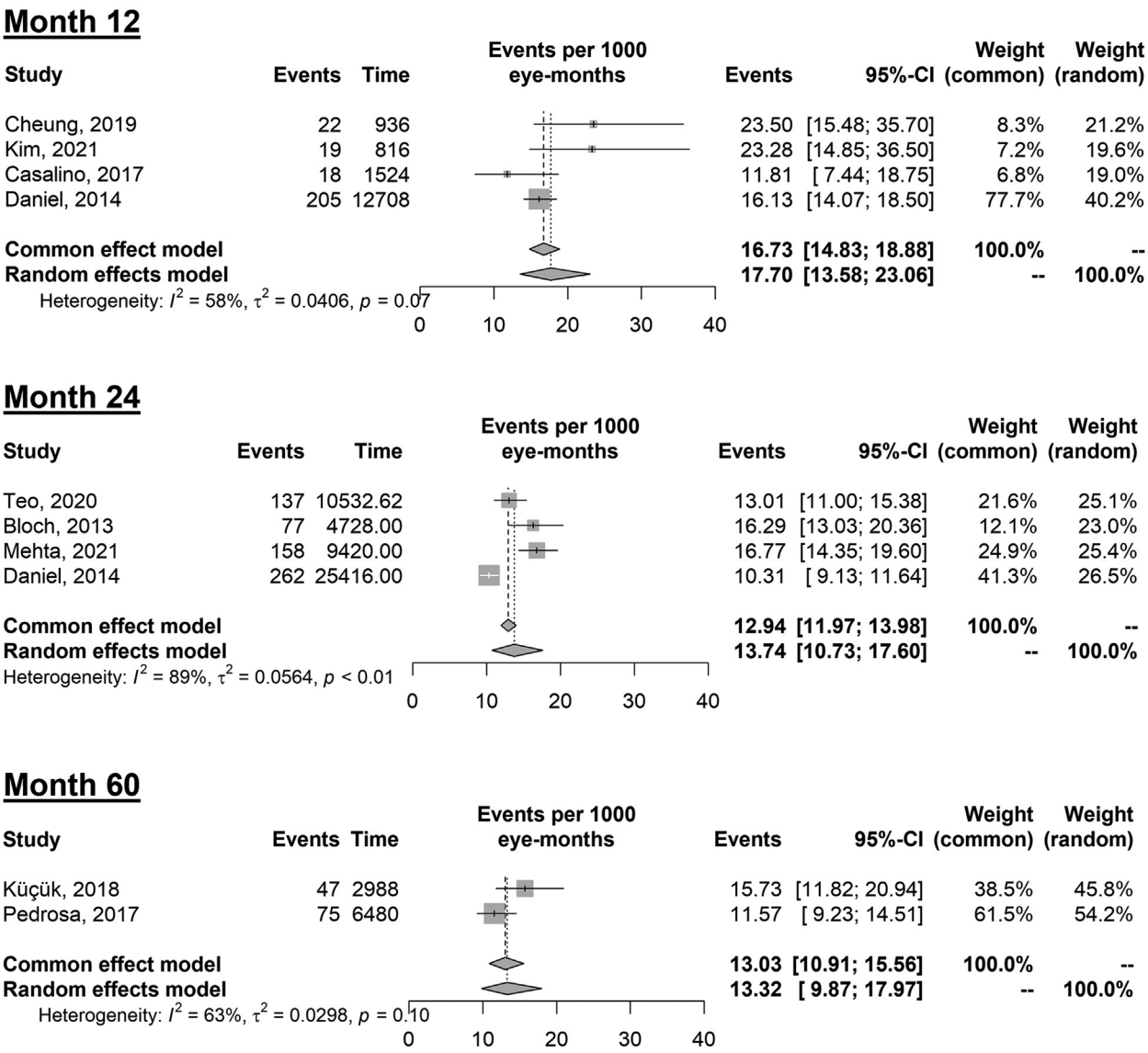

FIGURE 5. Incidence rate of fibrosis (12, 24, and 60 months). The incidence rate of fibrosis at 12, 24, and 60 months were 17.70 events per 1000 eye-months, 95% CI 13.58 to 23.06; 13.74 events per 1000 eye-months, 95% CI 10.73 to 17.60; and 13.32 events per 1000 eye-months, 95% CI 9.87 to 17.97, respectively. There was significant heterogeneity among the studies for the month 12 analysis (I^2 of 89% and τ^2 of 0.0564).

was significant heterogeneity among the studies for months 12, 24, and 60, as evidenced by the I^2 of 94%, 97%, and 93%, respectively, and τ^2 of 0.1456, 0.1596, and 0.2823, respectively.

Heterogeneity

Funnel plots were created to assess the heterogeneity among studies for the pooled overall incidence rate (Supplementary Figure S1) and prevalence at baseline (Supplementary Figure S2) and month 12 (Supplementary Figure S3). The funnel plots looked relatively symmetrical, particularly for prevalence; this was less so for incidence rate, where the asymmetry was greater.

• **RISK FACTORS FOR FIBROSIS:** IMAGING FEATURES: Imaging features associated with fibrosis included classic CNV, IRF, hyperreflective material, hemorrhage, CNV lesion size, and retinal thickness; in contrast, SRF and PED may be protective (see Table 3).

Classic choroidal neovascularization

Classic (Type 2) CNV is more likely to be associated with fibrosis than occult (Type 1) CNV. The disruption of the RPE monolayer and loss of RPE cell–cell contact is hypothesized to induce the transdifferentiation of epithelial cells to myofibroblasts, which results in fibrosis.[2,9,18]

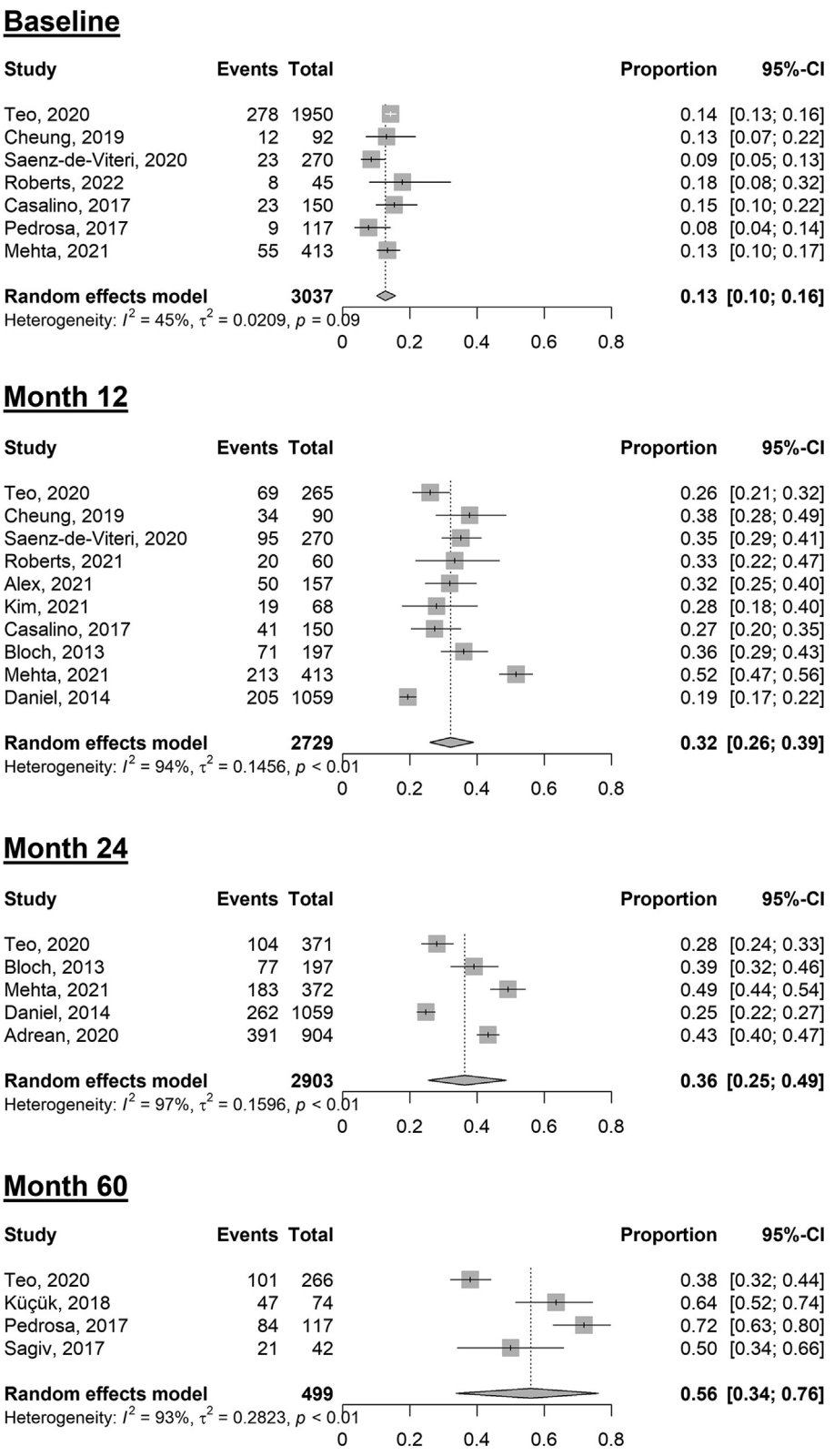

FIGURE 6. Prevalence of fibrosis. The prevalence of fibrosis at baseline, 12, 24, and 60 months was 13%, 95% CI 10% to 16%; 32%, 95% CI 26% to 39%; 36%, 95% CI 25% to 49%; and 56%, 95% CI 34% to 76%, respectively. There was significant heterogeneity among the studies for months 12, 24, and 60 analyses, as evidenced by the I^2 of 94%, 97%, and 93%, respectively, and τ^2 of 0.1456, 0.1596, and 0.2823, respectively.

TABLE 3. Risk Factors and Visual Outcomes of Fibrosis

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
RWS									
Teo, 2021[34]	FRB! (Australia, New Zealand, Switzerland, and Singapore)	2109	–	–	–	–	Proportion of fibrosis in low, moderate, and high activity groups: 130 (27.4%) vs 136 (35.3%) vs 128 (41.8%), respectively, $P < .01$	–	Regression Month 60 VA change: Beta -6.05, 95% CI –8.36 to –3.75, $P < .01$
Teo, 2020[28]	FRB! (Australia, New Zealand, Switzerland, and Singapore)	1950	Baseline lesion size per 1000 μm: adjusted OR 1.08, 95% CI 1.08-1.14, $P = .03$ Lesion type (predominantly classic vs occult: adjusted OR 1.42, 95% CI 1.17-1.72, $P = .02$	PED (presence vs absence): adjusted OR 0.76 95% CI 0.62-0.96)	–	–	Proportion of active visits (high vs low: adjusted OR 1.58, 95% CI 1.25-2.01, $P < .01$	Gender Baseline age Number of injections Initial anti-VEGF agent used	Fibrosis vs no fibrosis (Letters) Baseline: 49.8 ± 21.4 vs 61.8 ± 16.9, $P < .01$
Nyugen, 2018[33]	FRB! (Australia, New Zealand, Switzerland,	532	–	–	–	–	–	–	≥ 15 letter loss (fibrosis presence vs absence): 57.1% (36/63 eyes) vs 42.9% (27/63 eyes) ≥30 letter loss (fibrosis presence vs absence): 72.7% (16/22 eyes) vs 27.3% (6/22 eyes)
Wolff, 2018[29]	FRB! (France)	116	–	–	–	–	Pre-treatment at baseline (yes vs no): 47% vs 3%	–	–
Cheung, 2019[24]	Phenotyping Asian Macular Diseases Study, Singapore (Singapore)	78	Fibrosis vs no fibrosis Thicker CRT at baseline: 568.7 ± 145.3 μm vs 432.4 ± 155.9 μm, $P = .002$ Thicker CRT at month 12: 456.7 ± 193.0 μm vs 305.4 ± 97.7 μm, $P = .014$ SHRM at baseline: 100% (22/22 eyes) vs 60.7% (34/56 eyes), $P < .001$ SHRM at month 12: 100% (22/22 eyes) vs 10.7% (6/56 eyes), $P < .001$ IRF at baseline: 54.5% (12/22 eyes) vs 25.0% (14/56 eyes), $P = .017$	–	–	MA FA pattern	Fibrosis vs no fibrosis Received ≥ 1 PDT: 12 eyes (54.5%) vs 16 eyes (28.6%), $P = .039$	Gender Age Number of injections MA FA pattern	Fibrosis vs no fibrosis (Letters) Baseline: 21.5 vs 54.5, $P < .001$ Month 12: 30.5 vs 62.0, $P < .001$ Regression Baseline: Beta 0.22, 95% CI –0.08-0.52, $P = .151$ Month 12: Beta 0.25, 95% CI 0.02-0.47, $P = .032$
Llorente-Gonzalez, 2021[25]	Ambispective cohort study (Spain)	354	IRF (Baseline): OR 2.23, 95% CI 1.36-3.65, $P = .001$ IRF (Visit 4): OR 2.66, 95% CI 1.59-4.46, $P < .001$ IRF (month 36): OR 2.49, 95% CI 1.53-4.04, $P < .001$	SRF (month 36): OR 0.49, 95% CI 0.29-0.81, $P = .005$)	–	–	–	Gender Age Number of injections	Fibrosis vs no fibrosis (Letters) Baseline: 48.7 ± 19.7 vs 60.5 ± 14.7, $P < .001$ Month 12: 56.1 ± 19.9 vs 67.5 ± 12.4, $P < .0001$ Month 36: 48.3 ± 24.0 vs 64.7 ± 15.5, $P < .001$

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Saenz-de-Viteri, 2021[38]	Ambispective, cohort study (Spain)	270	Classic CNV: OR 1.94, 95% CI 1.11-3.40, $P = .018$ Atrophy at visit 4 or at final visit: OR 2.15, 95% CI 1.067-4.32, $P = .034$; OR 2.65, 95% CI 1.43-4.91, $P = .0022$ IRF (baseline): OR 2.43, 95% CI 1.26-4.66, $P = .006$ IRF (visit 4): OR 1.899, 95% CI 1.02-3.53, $P = .045$	SRF (month 36): OR 0.369, 95% CI 0.185-0.738, $P = .007$)	–	–	–	Gender Age Number of injections Treatment regime	–
Roberts, 2022[26]	Prospective cohort study (Austria)	45	Fibrosis vs no fibrosis IRF, n (%): 8 (100%) vs 19 (51%), $P = .014$ SHRM, n (%): 8 (100%) vs 20 (54%), $P = .017$ Type 2/mixed MNV: 7 (88%) vs 3 (8%), $P < .001$	–	–	SRF PCV	–	Gender Age Number of injections	Fibrosis vs no fibrosis (Letters) Baseline: 54, range (30-74) vs 74, range (36-84), $P = .001$
Motschi, 2021[53]	Prospective cohort study (Austria)	57	–	–	Fibrosis detection by CFP and PS-OCT agreed in 48 cases Discrepancies only observed in cases of lesion area < 0.7mm^2	–	–	–	–
Roberts, 2021[27]	Prospective cohort study (Austria)	60	Fibrosis vs no fibrosis ORT: 17 (85%) vs 4 (10%), $P < .001$ HRF: 7 (35%) vs 30 (75%), $P = .004$ Type 2 MNV: 5 (25%) vs 1 (3%), $P = .013$ Greatest vascular caliber, μM: 109 (median: 30-229) vs 161 (median: 67-268), $P = .001$ Greatest linear diameter, μM: 2366 (median: 415-4190) vs 3010 (median: 1594-5518), $P = .042$ Lesion area, mm^2: 3.62 (median: 0.10-9.80) vs 4.89 (median: 1.33-17.42), $P = .026$ Vessel area, mm^2: 1.57 (median: 0.07-4.82) vs 2.16 (median: 0.87-7.35), $P = .037$ Number of junctions: 156 (median: 4-514) vs 242 (median: 74-866) 0.025* Total vessel length, mm: 32.88 (median: 1.23-94.11) vs 43.83 (median: 14.47 to161.05), $P = .027$ Total number of endpoints: 51 (median: 2-215) vs 96 (median: 9-370), $P = .007$ Endpoint density, n/mm: 1.41 (median: 0.66-3.27) vs 1.76 (median: 0.62 to3.10), $P = .047$	–	–	–	–	Gender Age Number of injections Time since first injection	Fibrosis vs no fibrosis (Letters) Month 12: 39, range 6-79 vs 78, range 25-90, $P < .001$ (LogMAR) Month 12: 0.9, range 0.1-1.6) vs 0.2, range –0.1 to 1.1), $P < .001$

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Roberts, 2019[40]	Prospective cohort study (Austria)	50	Fibrosis vs no fibrosis SHRM volume 3 months, mm^3: 0.28, range 0.03-0.37 vs 0.03, range 0-0.49, $P = .020$ SHRM volume change, %: –48%, range –92% to –2% vs –82%, range –100% to –17%, $P = .027$ SHRM max. thickness 3 months, μM: 146, range 79-233 vs 87, range 0-222, $P = .001$ SHRM max. thickness change, %: –19%, range –38% to 17% vs –52%, range –100% to –6%, $P = .002$	–	–	SHRM area SHRM intensity	–	–	Fibrosis vs no fibrosis (logMAR) Month 3: 0.8, range 0.3-1.5 vs 0.3, range 0.0-1.8), $P = .090$ Month 3 BCVA change: 0.0, range –0.1 to 0.5 vs –0.1, range –0.5 to 0.8, $P = .249$
Roberts, 2016[56]	Prospective cohort study (Austria)	15	Fibrosis vs no fibrosis Thinning/loss of in areas of sub-retinal scarring Disseminated depolarizing particles present within sub-retinal scar complex, presumably remnants of dissociated RPE cells. Intact RPE-layer not detected in any region where sub-retinal fibrosis had occurred Averaged axis orientation B-scan images: distinct pattern of well-defined regions (columns) of uniform axis orientation (similarly colored blocks) observed in areas of fibrosis, indicating orientation of collagenous fibers within scar tissue	–	–	–	–	–	–
Angermann, 2022[41]	Retrospective cohort study (Austria)	566	–	–	–	–	Higher proportion of eyes developed foveal fibrosis in nonpersistent group (appointment >6 months) (8 eyes; 5.0%) compared to persistent group (5 eyes; 1.2%; $P = .013$ (four-fold risk)	–	–

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Ahmed, 2021[46]	Cross-sectional study (Tunisia)	70	–	–	Shape: 50% of fibrotic MNV had ill-defined shape, 41.6% had long linear vessels), and 8.3% had a well-defined shape ("medusa" shape). Branching pattern: 41.6% had ill-defined branching pattern, 50% were poor in anastomoses, and 8.3% had dense branching patterns. Termination: 41.6% had ill-defined termination, 50% ended in dead tree aspect, and 8.3% ended in peripheral anastomotic arcade. Perilesional dark halo present around a single unclassified fibrotic lesion (8.3%)	–	–	–	–
Alex, 2021[47]	Cross-sectional study (India)	157	SHRM (with vs without): 50 eyes (31.8%) vs without (9.4%), $P = .003$ Hyperreflective SHRM: $P = .004$ Well–defined anterior and posterior borders at baseline, $P = .001$	–	–	–	–	–	–
Kim, 2021[50]	Cross-sectional study (South Korea)	68	Presence of layer 2 (homogenous strong hyper-reflective band in multi-layered PED) at baseline: beta: 0.632, $P = .026$; presence vs absence: 36.8% vs 16.7%; $P = .026$)	–	–	–	–	Age Number of injections	–
Zhao, 2021[42]	Cross-sectional study (China)	155	–	–	–	–	Delayed treatment (vs no delay): $P < .05$)	–	–
Querques, 2020[55]	Cross-sectional study (Italy)	41	–	–	Fibrocellular group: perfusion density of 28.9% ± 9.9% Fibrovascular group: perfusion density of 44.2% ± 5.9%	–	–	–	–

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Souied, 2020[58]	Cross-sectional study and separate retrospective longitudinal analysis (France)	47	–	–	Types Type A: well-defined sub-RPE lesions, with or without intralesional abnormalities (43/44, 98% of eyes) Type B: well-defined hyperreflective lesions in sub-retinal and sub-RPE space with intact RPE band(8/44, 18% of eyes) Type C: prominent, elevated fibrotic lesions, with a complex pattern and RPE atrophy and loss of identifiable RPE band (6/44, 14% of eyes) Longitudinal Progression Progression to type A, followed by RPE erosion and SHRM, then type B and type C fibroglial lesion (FGL; 17/47 eyes) Progression to type B then type C FGL (17/47 eyes) Persistence of type A with development of flat, fibroatrophic lesion (13/47 eyes)	–	–	–	–
Gräfe, 2019[49]	Cross-sectional study (Netherlands)	29	–	–	PS-OCT confirmed evaluation of retinal specialists regarding fibrosis in 21 oof 22 eyes	–	–	–	–
Balaskas, 2018[32]	Retrospective cohort study (United Kingdom)	39	–	–	Out of 26 cases of detectable CNV, the complex did not conform to a specific pattern in 15 cases "Dead tree" configuration in 7 cases Small vascular loop detected in otherwise avascular, hyporeflective fibrotic tissue	–	–	–	Poorer BCVA in fibrosis associated with detectable neovascular membrane on OCTA ($P = .02$) and SHRM thickness ($P = .034$)

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Küçük, 2018[51]	Retrospective cohort study (Turkey)	74	–	–	–	–	–	–	–
Casalino, 2017[39]	Retrospective cohort study (United Kingdom)	150	HRM thickness: beta 0.0027, 95% CI 0.0011-0.0042, $P < .001$ HRM width: beta 0.0008, 95% CI 0.0003-0.0012, $P = .002$	–	–	–	–	–	Fibrosis vs no fibrosis (Letters) Month 12: Mild: 65.0, 95% CI 57.9-72.2 Moderate: 58.3, 95% CI 53.7-63.0 Severe: 43.4, 95% CI 34.3-52.4, vs None: 62.5, 95% CI 60.3-64.6
Pedrosa, 2017[54]	Retrospective cohort study (Portugal)	117	–	–	–	–	–	–	Fibrosis vs no fibrosis (Letters) Month 12: $P \geq .05$ Month 60: $P = .012$
Sagiv, 2017[57]	Retrospective case series	42	–	–	–	–	–	Number of injections	Worse VA with fibrosis
Fajnkuchen, 2016[48]	Retrospective, non-comparative case series (France)	22	Bridge arch-shaped SRD: Fibrotic tissue observed in 18/22 eyes (81.8%) Fibrotic scar developed during follow-up (in 2 cases after submacular hemorrhage), and in remaining case, bridge arch-shaped SRD preceded development of fibrotic tissue.	–	–	–	–	–	–
Souied, 2016[59]	Retrospective, non-comparative case series (France)	49	–	–	Vascular networks: pruned vascular tree, tangled network, and vascular loop patterns. Two types of low-flow structures: large flow void and dark halo	–	–	–	–
Miere, 2015[52]	Retrospective, non-comparative case series (France)	49	–	–	Vascular networks Pruned vascular tree (26 of 49 eyes: 53.1%) Tangled network (14 of 49; 28.6%) Vascular loop (25 of 49; 51.0%) Hyporeflective structures Large flow void (63%) Dark halo (65%) Others Blood flow inside fibrotic scar could be detected in 46 of 49 cases (93.8%). Patterns did not differ between active or inactive lesions	–	–	–	–

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Bloch, 2013[36]	Retrospective cohort study (Denmark)	197	Lesion type (classic vs occult CNV): HR 5.95, 95% CI 3.25-10.90, $P <$ .0001 Area of CNV (5.0-12.0 vs <1.5DA): HR 4.49, 95% CI 1.33-15.14, $P = .0155$	–	–	–	Interval to first diagnosis (>14 days vs ≤14 days: HR 2.24, 95% CI 1.28-3.94, $P = .0050$	–	Fibrotic or fibroatrophic lesions (stages II and III) lost 8.5 more ETDRS letters (95% CI –1.0 to –15.9, P < .0242), and 10.3 more ETDRS letters (95% CI –4.0 to –16.5, P = .0012), respectively, compared with eyes with no fibrosis
RCT									
Finn, 2022[37]	CATT	68	Year 2 Photoreceptor loss: OR 0.04, 95% CI 0.01-0.32, $P = .002$ SHRM: OR 4.04, 95% CI 1.81-9.01, $P < .001$ PED: OR 3.46, 95% CI 1.32-9.06, $P = .01$ MNV/sub-retinal lesion: OR 6.15, 95% CI 3.02-12.53, $P < .001$ IRF: OR 3.20, 95% CI 1.64-6.24, $P < .001$ Thin retina: OR 1.70, 95% CI 0.60-4.80, $P = .003$ Thick retina: OR 3.28, 95% CI 1.57-6.86, $P = .003$ Thin RPE, drusen, and lesion complex: OR 0.58, 95% CI 0.33-1.05, $P = .009$ Thick RPE, drusen, and lesion complex: OR 3.91, 95% CI 1.62-9.43, $P = .009$ Year 5 RPE atrophy without lesion: OR 0.03, 95% CI 0.00-0.28, $P = .002$ PED: OR 5.81, 95% CI 1.82-18.53, $P = .003$ MNV/sub-retinal lesion: OR 7.72, 95% 3.08-19.34, $P < .001$ Sub-RPE fluid: OR 8.82, 95% CI 2.20-35.33, $P = .002$ Thin retina: OR 3.03, 95% CI 1.71-5.35, $P < .001$ Thick retina: OR 3.48, 95% CI 1.25-9.70, $P < .001$ Thin RPE, drusen, and lesion complex: OR 1.68, 95% CI 0.78-3.64, $P = .006$ Thick RPE, drusen, and lesion complex: OR 5.98, 95% CI 1.76-20.28, $P = .006$	–	–	SRF	–	–	–

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Mehta, 2021[31]	IVAN	413	–	–		Baseline submacular hemorrhage	–	–	–
Evans, 2020[30]	CATT/IVAN	1720	–	–	–	–	Fluctuations in retinal thickness: OR for fibrosis increased from 1.40, 95% CI 1.03-1.91 for quartile 2-1.95, 95% CI 1.42-2.68 for quartile 4	–	–
Daniel, 2018[22]	CATT	1061	Lesion type (classic vs occult CNV) (adjusted HR 4.49, 95% CI 3.34-6.04, $P < .001$) Hemorrhage >1 DA vs no hemorrhage (adjusted HR 2.28, 95% CI 1.49-3.47, $P < .001$) Retinal thickness >212 µm vs <120 µm (adjusted HR 2.58, 95% CI 1.69-3.94, $P < .001$) Sub-retinal tissue complex thickness >27 5µm vs ≤75 µm (adjusted HR 2.64, 95% CI 1.81-3.84, $P < .001$) SRF thickness >25 µm vs no fluid (adjusted HR 1.31, 95% CI 0.97-1.75, $P = .01$) VA in fellow eye 20/20 vs 20/50 or worse (adjusted HR 1.34, 95% CI 1.00-1.79) RPE elevation absence (adjusted HR 1.7, 95% CI 1.21-2.41, $P = .002$) SHRM (adjusted HR 1.72, 95% CI 1.25-2.36, $P < .001$)	–	–	–	–	Drug group (Ranibizumab vs Bevacizumab) Dosing regimen (PRN vs switch from monthly to PRN vs monthly) Baseline VA	BCVA by year (letters) Year 1: 61.1 ± 21.0 Year 2: 63.2 ± 18.3 Year 5: 48.1 ± 26.5

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TABLE 3. (*continued*)

Author	Study	Sample Size (Eyes)	Imaging Factors Risk	Protective	Other Associations	Non-Significant	Treatment-Related Associations Risk	Non-Significant	Visual Outcomes
Daniel, 2014[23]	CATT	1059	Fibrotic and Nonfibrotic Scars Lesion type (classic vs occult CNV): adjusted HR 4.14, 95% CI 2.84-6.03, $P < .0001$) Blocked fluorescence: adjusted HR 1.84, 95% CI 1.32-2.58, $P = .0004$) Retinal thickness >212 μm vs <120 μm: adjusted HR 2.73, 95% CI 1.60-4.66, $P < .0001$) Sub-retinal tissue complex thickness >275 μm vs ≤75 μm: adjusted HR 3.11, 95% CI 1.96-4.94, $P < .0001$) SRF at foveal center: adjusted HR 1.60, 95% CI 1.04-2.46, $P = .012$ RPE elevation: adjusted HR 0.50, 95% CI 0.36-0.70, $P < .0001$) SHRM (adjusted HR 1.82, 95% CI 1.17-2.83, $P = .008$)	–	–	–	–	Drug group (Ranibizumab vs Bevacizumab) Dosing regimen (PRN vs switch from monthly to PRN vs monthly) Baseline VA	Fibrosis vs no fibrosis (Letters) Month 24: 57.6 ± 1.34 vs 71.8 ± 0.63, $P < .0001$) Regression Baseline BCVA: 20/50-80: adjusted HR 1.61, 95% CI 1.10-2.35; 20/100-160: adjusted HR 2.14, 95% CI 1.42-3.22; 20/200-320: adjusted HR 1.52, 95% CI 0.86-2.68
Adrean, 2020[35]	HARBOR	1097	CNV lesion subtype at month 24: predominantly classic 78.2% (111/142 eyes) vs minimally classic: 50.7% (212/418 eyes) vs occult CNV 19.8% (68/344 eyes), $P < .001$	–	–	–	–	–	Subfoveal vs extrafoveal vs no fibrosis (Letters) Month 12: 8.5 ± 15.82 vs 16.7 ± 13.35 vs 9.2 ± 11.71, $P < .0001$ Month 24: 8.3 ± 17.35 vs 14.5 ± 15.84 vs 8.2 ± 13.87, $P = .0012$
Bhisitkul, 2015[60]	SEVEN-UP	65	–	–	–	–	–	–	Fibrosis vs no fibrosis (Letters) Month 84: 42.3 ± 29.3 vs 50.9 ± 20.7, $P < .0001$ Regression Month 84: Beta –1.84, 95% CI –13.39-9.71, $P = .75$ No effect on BCVA
Rofagha, 2013[61]	SEVEN-UP	57	–	–	–	–	–	–	No effect on BCVA

anti-VEGF = anti-vascular endothelial growth factor; BCVA = best corrected visual acuity; CFP = color fundus photographs; CI = confidence interval; CNV = choroidal neovascularization; DA = disc area; ETDRS = Early Treatment of Diabetic Retinopathy Study; EZ = ellipsoid zone; FA = fundus fluorescein angiography; HR = hazard ratio; HRF = hyperreflective foci; HRM = hyperreflective material; IRF = intra-retinal fluid; MA = macular atrophy; MNV = macular neovascularization; nAMD = neovascular age-related macular degeneration; OCTA = optical coherence tomography angiography; OR = odds ratio; ORT = outer retinal tubulation; PCV = polypoidal choroidal vascularization; PED = pigment epithelial detachment; PRN = *pro re nata*; PS-OCT = polarization-sensitive OCT; RCT = randomized controlled trials; RPE = retinal pigment epithelium; RWS = real-world studies; SHRM = sub-retinal hyperreflective material; SRD = sub-retinal detachment; SRF = sub-retinal fluid.

The relationship between classic CNV and fibrosis is well described in RCTs. The CATT 2-year study reported that classic CNV was associated with fibrosis at 2 years (predominantly classic: adjusted hazard ratio [HR] 4.14, 95% CI 2.84 to 6.03; and minimally classic: adjusted HR 2.76, 95% CI 1.92 to 3.97, respectively) vs occult CNV, $P < .0001$.[23] Similar findings were reported in the 5-year study (classic CNV compared with occult CNV: adjusted HR 4.49, 95% CI 3.34 to 6.04, $P < .001$).[22] Using a longitudinal pixel analysis of OCT examinations in a post hoc analysis of CATT data, Finn and associates[37] reported that > 75% of the pixels of fibrotic scar at years 2 and 5 were preceded by pixels of baseline CNV. Likewise in the HARBOR study, fibrosis development by month 24 was significantly associated with CNV lesion subtype ($P < .001$).[35] Predominantly classic CNV had more fibrosis (78.2%; 111 of 142 eyes) compared with minimally classic (50.7%; 212 of 418 eyes) and occult CNV (19.8%; 68 of 344 eyes) ($P < .001$).

The RWS reported similar findings. Teo and associates[28] reported in the FRB! RWS of 1950 eyes that there were more eyes with fibrosis with predominantly classic CNV compared with eyes without fibrosis at 5 years (25.3% vs 19.9%, respectively; $P < .01$). Saenz-de-Viteri and associates[38] reported in the In-Eye study of 270 eyes that a classic membrane increased the odds of fibrosis (odds ratio [OR] 1.94, 95% CI 95% 1.11 to 3.40, $P = .018$) at 12 months. Bloch and associates[36] described in 197 eyes that the adjusted HR of any fibrosis developing in eyes with predominantly classic CNV by 24 months was 5.95, 95% CI 3.25 to 10.90, compared with minimally classic and occult CNV. Using PS-OCT, Roberts and associates[26] described in 45 eyes that there was a greater proportion of Type 2/mixed CNV in fibrotic eyes (88%; 7 eyes) compared with eyes without fibrosis (8%; 3 eyes) ($P < .001$).

Fluid

In recent years, attention has been paid to the retinal fluid location. Intra-retinal fluid has been described to be associated with fibrosis,[24–26,37,38] whereas SRF and PED are thought to be protective.[25,28,38] While there is general consensus on the association of IRF with fibrosis, the effects of SRF and PED are still equivocal.

Regarding IRF, the CATT 2-year study reported that IRF at the foveal center was more common in eyes with fibrotic scars (65.3%) compared with eyes with nonfibrotic scars or no scar (46.3% and 48.1%, respectively; $P < .0001$).[23] In a post hoc analysis of CATT data, Finn and associates[37] described that the pixels of IRF at baseline became pixels of fibrotic scar at year 2 (OR 3.20, 95% CI 1.64 to 6.24, $P < .001$).

The negative influence of IRF on fibrosis has also been consistently reported in the RWS. Cheung and associates[24] described that IRF at baseline (54.5%; 12 of 22 eyes), compared with its absence (25.0%; 14 of 56 eyes), was associated with incident fibrosis ($P = .017$). Using PS-OCT on 45 eyes, Roberts and associates[26] described that there was a greater proportion of IRF in fibrotic eyes (100%; 8 eyes) compared with eyes without fibrosis (51%; 19 eyes) ($P = .014$). Similarly, Saenz-de-Viteri and associates[38] reported in the In-Eye study of 45 eyes that baseline IRF was significantly associated with fibrosis development at 12 months (OR 2.43, 95% CI 1.26 to 4.66, $P = .006$). Llorente-Gonzalez and associates[25] also reported in 354 eyes that IRF was associated with fibrosis development (month 36: OR 2.49, 95% CI 1.53 to 4.04, $P < .001$) and fibrosis progression (month 36: OR 2.46, 95% CI 1.54 to 3.92, $P < .001$).

In the CATT 2-year study, RPE elevation was also associated with a lower risk of fibrotic scar (adjusted HR 0.50, 95% CI 0.36 to 0.70, $P < .0001$).[23] There were similar findings in the CATT 5-year study, where the absence of RPE elevation was associated with a higher risk of fibrotic scar (adjusted HR 1.7, 95% CI 1.21 to 2.41, $P = .002$).[22] However, in a post hoc analysis of CATT data, Finn and associates[37] described that pixels of PED at baseline (OR 5.81, 95% CI 1.82 to 18.53, $P = .003$) and pixels of sub-RPE fluid at baseline (OR 8.82, 95% CI 2.20 to 35.33, $P = .002$) became pixels of fibrotic scar at year 5. Real-world studies have reported protective effects of PED against fibrosis. Teo and associates[28] reported in the FRB! RWS that a PED at baseline was protective against fibrosis (adjusted OR 0.76, 95% CI 0.62 to 0.96).

Baseline SRF was associated with fibrotic scar formation at 2 years in the CATT study (fluid at foveal center: adjusted HR 1.60, 95% CI 1.04 to 2.46, $P = .012$).[23] Similar findings were reported in the CATT 5-year study (SRF thickness > 25 μm vs no fluid: adjusted HR 1.31, 95% CI 0.97 to 1.75, $P = .01$).[22] However, Finn and associates[37] co-localized SRF and fibrotic scar pixel data in a post hoc analysis of CATT data, and reported that SRF was not a precursor to fibrotic scar.

Real-world studies have reported protective effects of SRF against fibrosis. Saenz-de-Viteri and associates[38] reported that baseline SRF significantly decreased the risk of developing fibrosis (OR 0.369, 95% CI 0.185 to 0.738, $P = .007$). Llorente-Gonzalez and associates[25] also described that SRF at month 36 was associated with a lower prevalence of fibrosis (OR 0.49, 95% CI 0.29 to 0.81, $P = .005$) and lesser fibrosis progression (OR 0.5, 95% CI 0.31 to 0.81, $P = .005$).

The potential reasons for the contrasting associations of PED and SRF with fibrotic scars among the various studies[22,23,25,28,37,38] may include differences in study designs, treatment regimens, number of injections, and severity of lesions.

Hyperreflective material

The CATT 2-year study described that SHRM was significantly associated with fibrotic scar (adjusted HR 1.82, 95% CI 1.17 to 2.83, $P = .008$).[23] A sub-retinal tissue complex thickness of > 275 μm predicted a 3 times risk of fibrotic scar compared with that which was ≤ 75 μm (adjusted HR

3.11, 95% CI 1.96 to 4.94, $P < .0001$). Similar findings were established in the CATT 5-year study (SHRM: adjusted HR 1.72, 95% CI 1.25 to 2.36, $P < .001$; and sub-retinal tissue complex thickness > 275 μm vs ≤ 75 μm: adjusted HR 2.64, 95% CI 1.81 to 3.84, $P < .001$).[22] In a post hoc analysis of CATT data, Finn and associates[37] reported that SHRM accounted for 58.6% and 45.8% of fibrotic scar at years 2 and 5, respectively.

The RWS reported similar findings. Cheung and associates[24] reported in 78 eyes that SHRM was a risk factor at baseline and month 12 for fibrosis. At baseline, 22 of 22 eyes with fibrosis (100%) had SHRM vs 34 of 56 eyes without fibrosis (60.7%) ($P < .001$). At month 12: 22 of 22 eyes with fibrosis (100%) had SHRM vs 6 of 56 eyes without fibrosis (10.7%) ($P < .001$). Casalino and associates[39] also described with 150 eyes that both thickness (beta 0.0027, 95% CI 0.0011 to 0.0042, $P < .001$) and width (beta 0.0008, 95% CI 0.0003 to 0.0012, $P = .002$) of HRM were significant risk factors for fibrotic scar development but not for nonfibrotic scar. Using PS-OCT, Roberts and associates[40] described that SHRM volume (mm^3) and max thickness (μm) at 3 months were greater in eyes with fibrosis than in those without fibrosis (0.28 vs 0.03, $P = .020$; and 146 vs 87, $P = .001$, respectively). Similarly, the reduction in SHRM volume and thickness in response to treatment were lesser in eyes with fibrosis than in those without fibrosis (–48% vs –82%, $P = .027$; and –19% vs –52%, $P = .002$, respectively).

Hemorrhage

It is thought that the blood components of a hemorrhage may result in fibrin meshwork contraction, fibrosis formation, and photoreceptor toxicity.[22,23] In the CATT 2-year study, while hemorrhage was not associated with scar development, blocked fluorescence was a strong baseline predictor of fibrotic scar at 2 years (adjusted HR 1.84, 95% CI 1.32 to 2.58, $P = .0004$).[23] The authors hypothesized that the blocked fluorescence could have been the result of deep sub-RPE hemorrhage or deep fibrosis that was not visible on CFP. In the CATT 5-year study, relatively large hemorrhages of more than one disc area at baseline doubled the risk of developing a scar at 5 years (adjusted HR 2.28, 95% CI 1.49 to 3.47, $P < .001$).[22] It is important to note that CATT allowed recruitment of nAMD patients with > 50% hemorrhages relative to the total CNV lesion; other major anti-VEGF studies have excluded such patients. The IVAN study did not establish an association between submacular hemorrhage and fibrosis, even after excluding retinal angiomatous proliferation lesions owing to their tendency to result in atrophy over fibrosis;[31] it excluded eyes with > 50% hemorrhage at baseline.

Choroidal neovascularization lesion size

Studies have reported a relationship between the CNV size and fibrosis development.[27,28,36] In the FRB! RWS study by Teo and associates,[28] the baseline lesion size was associated with fibrosis: (per 1000 μm; any fibrosis: adjusted OR 1.08, 95% CI 1.08 to 1.14, $P = .03$; subfoveal fibrosis: adjusted OR 1.06, 95% CI 1.02 to 1.12, $P = .03$; and extrafoveal fibrosis: adjusted OR 1.11, 95% CI 1.00 to 1.11, $P = .05$).[28] Bloch and associates[36] likewise reported that an area of CNV that is between 5.0 to 12.0 disc area, relative to that which is < 1.5 disc area, was associated with a 4.5 times risk of developing fibrosis (HR 4.49, 95% CI 1.33 to 15.14, $P = .0155$). Using PS-OCT, Roberts and associates[27] described that eyes with fibrosis, compared with those without, demonstrated a larger greatest linear diameter (μm) (2366 vs 3010, $P = .042$) and larger lesion area (mm^2) (3.62 vs 4.89, $P = .026$).

Retinal thickness

A thicker retina was associated with fibrotic scarring in the CATT 2-year study (retinal thickness > 212 μm at the foveal center vs < 120 μm: adjusted HR 2.73, 95% CI 1.60 to 4.66; and retinal thickness between 120 and 212 μm vs < 120 μm: adjusted HR 1.67, 95% CI 0.99 to 2.80, $P < .0001$).[23] Similar findings were reported in the CATT 5-year study (retinal thickness > 212 μm vs < 120 μm: adjusted HR 2.58, 95% CI 1.69 to 3.94, $P < .001$).[22] Similarly, Cheung and associates[24] reported in an RWS that eyes with fibrosis had thicker central retinal thickness at baseline and month 12 compared with eyes without fibrosis (baseline: 568.7 ± 145.3 μm vs 432.4 ± 155.9 μm, $P = .002$; and month 12: 456.7 ± 193.0 μm vs 305.4 ± 97.7 μm, $P = .014$).

Other features

Fajnkuchen and associates[48] described in 22 eyes that a bridge arch-shaped serous retinal detachment in nAMD is a marker for fibrosis development. This is SRF accumulation with a steep angle (mean 53.45 ± 12.5°) at the junction between the neurosensory retina and RPE and adhesion areas between the neurosensory retina and a fibrous complex developed from the CNV.

Kim and associates[50] investigated the structure of multilayered PED and its association with fibrotic scar progression at 12 months. The multi-layered PED compartments were categorized into layer 1: neovascular tissue; layer 2: hyperreflective band; and layer 3: prechoroidal cleft. Among 68 eyes, layer 2 at baseline was significantly associated with fibrotic scar formation (beta 0.632, $P = .023$).

- **TREATMENT-RELATED ASSOCIATIONS OF FIBROSIS:** See Table 3 for these associations.

Disease activity

The assessment of disease activity is important in nAMD management and is one of the key features in establishing the need for retreatment in trials. Studies have described the association of high-activity lesions in nAMD and fibrosis development.[28,30,34] In a post hoc analysis of 2-year data from the CATT and IVAN studies, Evans and associates[30]

reported that eyes that demonstrated a greater fluctuation in retinal thickness had worse BCVA and were more likely to develop fibrosis (OR for fibrosis increased from 1.40, 95% CI 1.03 to 1.91 for quartile 2 to 1.95, 95% CI 1.42 to 2.68 for quartile 4, in increasing magnitude of retinal thickness fluctuations). Evens and associates[30] conjectured that retinal thickness fluctuations were a surrogate measure of worsening, and intermittent stretch is known to cause fibrosis by macrophage activation in non-ocular tissues. Likewise, among the RWS, Teo and associates[28] reported in the FRB! study that there was a significant association between nAMD disease activity and fibrosis formation (high vs low activity: adjusted OR 1.58, 95% CI 1.25 to 2.01, $P < .01$; and moderate vs low activity: adjusted OR 1.28, 95% CI 1.02 to 1.62), $P = .03$. In this study, disease activity referred to a drop in BCVA of ≥ 5 logarithm of the minimum angle of resolution (logMAR) letters, new hemorrhage, or the detection of SRF and/or IRF on OCT.

Treatment regime

Studies have evaluated the relationship between the anti-VEGF drug type and dosing regimen with fibrosis development;[22–24] so far, none have identified a conclusive link. In the CATT studies, the drug group (ranibizumab vs bevacizumab) and the dosing regimen (PRN vs switch from monthly to PRN vs monthly) had no significant influence on fibrotic scar development.[22,23] Among the RWS, Cheung and associates[24] described that eyes with incident fibrosis were more likely to have received PDT (54.5%; 12 of 22 eyes) vs eyes without incident fibrosis (28.6% 16 of 56 eyes) ($P = .039$) but had received similar number of anti-VEGF injections compared with eyes without incident fibrosis. None of the remaining RWS had found a significant association between the number of anti-VEGF injections and fibrosis development.

Time interval

Bloch and associates[36] reported that an interval of at least 2 weeks between diagnosis and treatment conferred twice as much risk of fibrosis compared with a shorter interval (HR 2.24, 95% CI 1.28 to 3.94, $P = .0050$). Zhao and associates[42] also reported that the proportion of sub-macular scar increased in the delayed treatment group ($P = .043$), with a concomitant drop in the BCVA. Similarly, in a study that defined treatment non-persistence as a visit-free interval of > 6 months, Angermann and associates[41] reported that there was a higher proportion of eyes that developed foveal fibrosis in the non-persistent group (5.0%; 8 eyes) than the persistent group (1.2%; 5 eyes) ($P = .013$).[41]

• **VISUAL OUTCOMES OF FIBROSIS:** Fibrosis has a negative influence on BCVA (see Table 3). Among the RCTs, the CATT 2-year study reported that the BCVA of eyes with fibrotic scar at the foveal center was significantly worse than those without a fibrotic scar at month 24 (57.6 ± 1.34 vs 71.8 ± 0.63 letters, $P < .0001$).[23] Similar findings were reported in the CATT 5-year study;[22] longitudinal data showed that the BCVA dropped from 61.1 ± 21.0 letters at year 1, to 63.2 ± 18.3 letters at year 2, and then to 48.1 ± 26.5 letters at year 5. In contrast, the HARBOR and SEVEN-UP studies did not report a significant relationship between fibrosis and BCVA.[35,61,62] In the HARBOR study, patients achieved meaningful gains in vision at month 24 regardless of month 24 fibrosis status.[35] Likewise, the SEVEN-UP study reported in the multivariable regression analysis that fibrosis had no significant relationship with BCVA (beta 1.84, 95% CI 13.39 to 9.71, $P = .75$).[61]

The results among the RWS were more consistent. Teo and associates[28] reported that eyes with sub-retinal fibrosis demonstrated a lower baseline BCVA (any fibrosis: 49.8 ± 21.4 letters; subfoveal fibrosis: 47.8 ± .8 letters; and extrafoveal fibrosis: 57.3 ± 18.0 letters) compared with eyes without fibrosis (61.8 ± 16.9 letters), $P < .01$ for all comparisons. Likewise, Cheung and associates[24] reported in the multivariable analysis that incident fibrosis exerted a negative effect on month 12 BCVA (beta 0.25, 95% CI 0.02 to 0.47, $P = .032$). Bloch and associates[36] similarly reported that eyes with fibrosis or fibrosis with foveal atrophy lost 8.5 more letters (95% CI –1.0 to –15.9, $P < .0242$) and 10.3 more letters (95% CI –4.0 to –16.5, $P = .0012$), respectively, compared with eyes without fibrosis at 12 months. Similarly, using PS-OCT, Roberts and associates[27] reported that the BCVA was poorer at month 12 in eyes with fibrosis compared with those without (39 vs 78 letters, $P < .001$).

Longer term BCVA outcomes in fibrosis have been reported. Teo and associates[34] reported that sub-retinal fibrosis exerted a negative influence on month 60 VA change (beta –6.05, 95% CI –8.36 to –3.75) ($P < .01$). Nyugen and associates[33] also reported that at 5 years there was a greater proportion of eyes with fibrosis that experienced significant BCVA loss compared with those without fibrosis (≥ 15 letter loss: 57.1% (36 of 63 eyes) vs 42.9% (27 of 63 eyes); and ≥ 30 letter loss: 72.7% (16 of 22 eyes) vs 27.3% (6 of 22 eyes), respectively; $P = .01$).

There is also a dose response relationship of fibrosis severity with vision. Casalino and associates[39] reported that at month 12, the worse the fibrotic scarring, the poorer the BCVA (mild: 65.0 letters, 95% CI 57.9 to 72.2; moderate: 58.3 letters, 95% CI 53.7 to 63.0; and severe: 43.4 letters, 95% CI 34.3 to 52.4, vs none: 62.5 letters, 95% CI 60.3 to 64.6).

This study performed a meta-analysis to assess the difference in BCVA between eyes with fibrosis vs those without (see Figure 7). Data from 5 studies (all RWS) were pooled.[24–28] At baseline, the BCVA in eyes with fibrosis was poorer than those without fibrosis (–18.50 letters, 95% CI –34.06 to –2.94). This difference became larger at month 12 despite anti-VEGF treatment (–26.86 letters, 95% CI –62.56 to 8.84). Both baseline and month 12 models showed significant heterogeneity (I^2 of 88% and 95%, respectively, and τ^2 of 82.5550 and 196.1418, respectively).

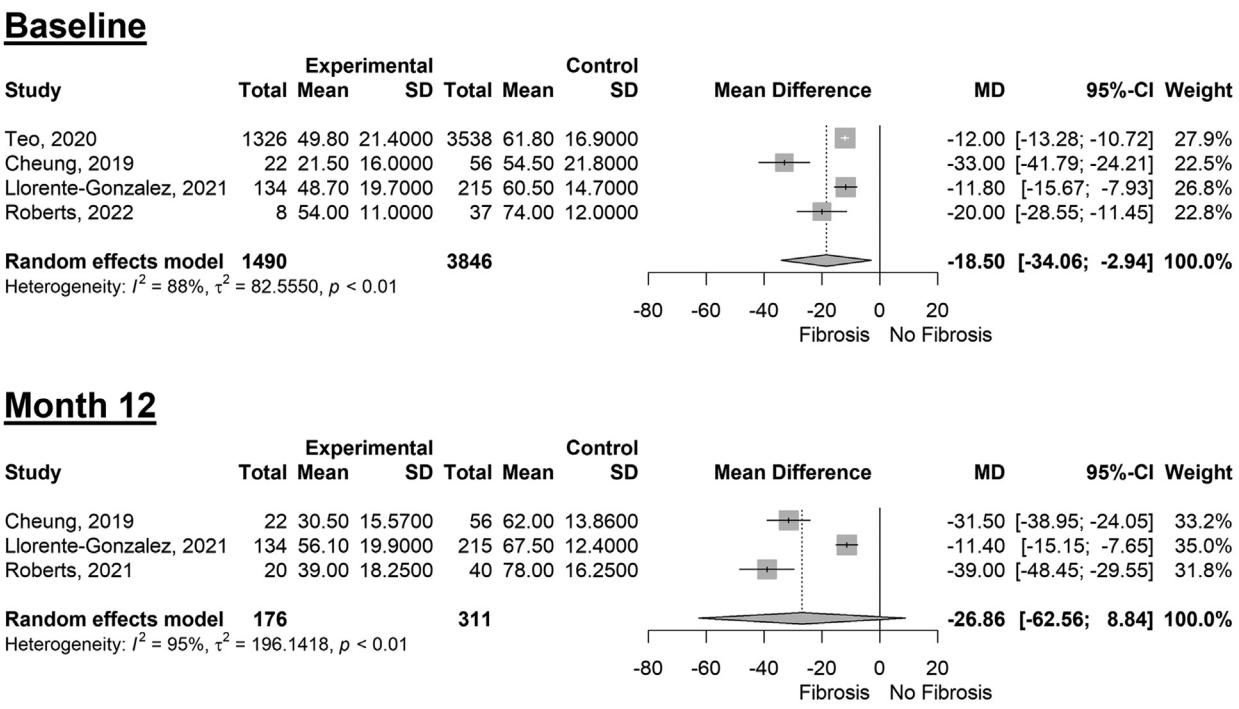

FIGURE 7. Visual outcomes of fibrosis. At baseline, the BCVA in eyes with fibrosis was poorer compared with that in eyes without fibrosis (–18.50 letters, 95% CI –34.06 to –2.94). This difference became larger at month 12 despite anti-VEGF treatment (–26.86 letters, 95% CI –62.56 to 8.84). The random effects models for both baseline and month 12 analyses showed significant heterogeneity (I^2 of 88% and 95%, respectively, and τ^2 of 82.5550 and 196.1418, respectively).

DISCUSSION

Fibrosis is an end-stage sequelae of nAMD that causes significant and irreversible loss of vision. It is important to appreciate the variations in diagnostic methods and definitions of fibrosis, the extent of its occurrence, who is more likely to develop fibrosis, and the magnitude of the associated visual impairment. To these ends, this review reported the following: 1. Evolution of multimodal imaging and the definitions used for fibrosis in nAMD; 2. Incidence and prevalence of fibrosis; 3. Imaging and treatment-related associations of fibrosis; and 4. Visual impact of fibrosis.

Regarding the diagnosis of fibrosis, there has been a shift from CFP and FA to OCT-based techniques. Regarding the OCT description of fibrosis, it is preferred to use the term "well-defined HRM", which in the current authors' opinion more accurately reflects the appearance and location of fibrosis, rather than "SHRM", which can cause confusion. However, regardless, the OCT appearance of HRM has limited specificity. Newer modalities, such as the OCTA and PS-OCT may shed further light into the angiofibrotic switch process.

The current results highlight important information regarding the timing of and risk factors for fibrosis development. The incidence rate data indicate that fibrosis development is the highest in the first 12 months and slows down over time. Based on the prevalence estimates, 60% of the fibrosis burden by 5 years would be present in the first year. This review supports the CATT study, which reported that most of the fibrosis occurred in the first year of anti-VEGF treatment.[22,23] Regarding risk factors, Type 2 CNV, IRF, hemorrhage, hyperreflective material, lesion size, and retinal thickness are all associated with fibrosis development. These characteristics are important in identifying the optimal timing and target groups for evaluating potential new therapies against fibrosis. The review indicates that fibrosis is associated with inadequate disease activity control. Fluctuations in retinal thickness, delayed treatment, and a longer interval between visits, which are probably associated with poor disease control, also adversely influence fibrosis development.

The negative impact of fibrosis on BCVA was confirmed in the meta-analysis, which found that BCVA was worse in eyes with fibrosis compared with that in eyes without fibrosis by 27 letters at month 12 despite anti-VEGF treatment. This finding underscores the need for novel anti-fibrotic therapy to be identified, as BCVA worsened even with anti-VEGF treatment.

The key strength of this study was its comprehensive and systematic review of the literature using a robust and broad

search strategy. A meta-analysis approach was also used to assess the incidence and prevalence of fibrosis and to examine the impact of fibrosis on visual outcomes.

However, the methodological limitations must also be considered. There was significant heterogeneity among the studies, as evidenced by the variations of the pooled estimates. Variations in data may be attributed to the differences in fibrosis definition and grading criteria, study methodology, and in the participants' characteristics. The meta-analyses at various time points were limited by the limited number of studies, and different studies were used for different time points. Many studies did not provide sufficient data that were amenable for meta-analysis. In studies that did not provide censored observations and exact follow-up time, the mean follow-up time was used to estimate the incidence rate, which was not as accurate. Whilst the funnel plots look relatively symmetrical, particularly for prevalence, this was less so for the overall incidence rate, where the asymmetry was greater. This could reflect true heterogeneity, as the incidence rate data were obtained from various studies of different follow-up durations, which would affect the incidence rate estimates, as fibrosis development is not linear. This could be artefactual too, because fibrosis incidence rates in studies that did not report loss to follow-up data were manually calculated with the assumption that no patients were lost to follow-up. Other reasons could include publication bias and chance, as the number of studies was very small.

In addition, many RWS had design limitations, including: a relatively small sample size, absent or inadequate control groups, lack of homogeneity, loss to follow-up, poor quality data that was not purposefully, uniformly, and systematically collected by dedicated teams, missing data, and lack of adjustment for confounding factors. The RCT data regarding fibrosis were from post hoc analyses that were not part of the original protocols of the respective RCTs. There were likely to be biases, unidentified confounders and effect modifiers, misclassifications, and bias in outcomes in these studies. This made comparisons among studies challenging.

In summary, fibrosis poses a significant public health burden and is detrimental to long-term vision gain and maintenance. There is a need to identify effective preventive and therapeutic strategies, including anti-fibrotic agents. Patients who display imaging and treatment risk factors for fibrosis development should be more closely monitored. Lastly, more studies involving multimodal imaging are required to clarify the definitions and grading criteria for fibrosis.

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