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Review

IMPACT OF FLUID COMPARTMENTS ON FUNCTIONAL OUTCOMES FOR PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

A Systematic Literature Review

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Purpose: Understanding the impact of fluid in different retinal compartments is critical to developing treatment paradigms that optimize visual acuity and reduce treatment burden in neovascular age-related macular degeneration. This systematic review aimed to determine the impact of persistent/new subretinal fluid, intraretinal fluid, and subretinal pigment epithelial fluid on visual acuity over 1 year of treatment.

Methods: Publication eligibility and data extraction were conducted according to Cochrane methods: 27 of the 1,797 screened records were eligible.

Results: Intraretinal fluid negatively affected visual acuity at baseline and throughout treatment, with foveal intraretinal fluid associated with lower visual acuity than extrafoveal intraretinal fluid. Some studies found that subretinal fluid (particularly subfoveal) was associated with higher visual acuity at Year 1 and longer term, and others suggested subretinal fluid did not affect visual acuity at Years 1 and 2. Data on the effects of subretinal pigment epithelial fluid were scarce, and consensus was not reached. Few studies reported numbers of injections associated with fluid status.

Conclusion: To optimally manage neovascular age-related macular degeneration, clinicians should understand the impact of fluid compartments on visual acuity. After initial treatment, antivascular endothelial growth factor regimens that tolerate stable subretinal fluid (if visual acuity is stable/improved) but not intraretinal fluid may enable patients to achieve their best possible visual acuity. Confirmatory studies are required to validate these findings.

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Treatment of neovascular age-related macular degeneration (nAMD) is based on signs of disease activity, including change in visual acuity, new hemorrhage, increased macular thickness, new/persistent fluid, and evidence of membrane leakage/growth. Fluid seen on optical coherence tomography is an important surrogate marker for disease activity, usually mandating aggressive treatment with intravitreal vascular endothelial growth factor (VEGF) inhibitors.[1–5] The introduction of spectral-domain optical coherence tomography and swept-source optical coherence tomography made it possible to detect small anatomic changes within the retina, and thus clinicians can precisely identify fluid within the various retinal compartments.[1]

Emerging evidence suggests disconnection between morphologic features of the macula, and visual acuity outcomes in patients with nAMD.[1,6–12] The presence and location of macular fluid within the intraretinal, subretinal, and subretinal pigment epithelial (sub-RPE) compartments may determine visual acuity outcomes in patients receiving long-term anti-VEGF therapy.[10,13,14] However, the relationship between retinal fluid status and VA outcomes is not well understood.

This systematic review aims to determine the impact of persistent and/or new subretinal fluid (SRF), intraretinal fluid (IRF), and sub-RPE fluid on VA outcomes both at baseline and over a 1-year treatment course.

Methods

This review was conducted in accordance with the Cochrane approach.[15] Methods and results are presented according to PRISMA (http://www.prisma-statement.org).

The primary aim was to determine the impact of SRF, IRF, and sub-RPE fluid on VA at Year 1 in patients with nAMD treated with anti-VEGF drugs. Secondary aims were to determine the impact of SRF, IRF, and sub-RPE fluid on VA at other time points, morphologic outcomes, treatment burden, and safety.

The PICOS framework (Table 1) was used to develop search strategies based on disease area, disease-modifying factors, interventions, and study types for EMBASE and PubMed: January 1, 2006, to August 1, 2020 (see **Table 1**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B511). A similar approach was used for CENTRAL (Cochrane Library), World Health Organization International Clinical Trials Registry Platform, the Cumulative Index to Nursing and Allied Health Literature, ClinicalTrials.gov, and OpenGrey. Manual searches of abstracts from recent key conferences (see **Table 2**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B511) were reviewed. Outcomes in patients with nAMD undergoing intravitreal anti-VEGF treatment, stratified by SRF or IRF, were included. Study exclusion criteria are reported in **Supplemental Digital Content 1** (see **Table 3**, http://links.lww.com/IAE/B511).

Titles and/or abstracts of retrieved studies were screened independently by two reviewers to identify those meeting inclusion criteria. The full texts of identified studies were assessed in detail; disagreement over a study's eligibility was resolved through discussion with a third reviewer. Data (patient baseline demographics and characteristics, number of patients, intervention, protocol, previous treatment (if applicable), type of outcome measure, VA according to fluid and fluid compartment presence/absence, and time point) were extracted to a standardized, prepiloted form for evidence synthesis.

Studies were assessed using the Cochrane risk of bias (RoB-2) tool for randomized controlled trials (see **Table 4**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B511) and the ROBINS-I tool for observational studies (see **Table 5**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B511). Each potential source of bias was judged as conferring low, unclear, or high risk of bias.

Results

Study Selection and Characteristics

After screening 1,797 titles and abstracts, 188 records were judged to be "potentially relevant"; 161 full-text records were excluded (per exclusion criteria) and 27 unique records were reviewed (Figure 1).

Table 2 summarizes results from studies that reported VA over time or change in VA from baseline stratified by presence or absence of SRF and/or IRF.

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All authors contributed to the conceptualization of the systematic literature review design, data curation, data interpretation, visualization, and provided critical review of the manuscript.

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No human participants were included in this study. The requirement for informed consent was waived because of the retrospective nature of the analysis.

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Table 1. Population, Intervention, Comparison, Outcome, and Setting (PICOS)

Item	Search Details
Population	
Disease	Neovascular age-related macular degeneration
Intervention	
Anti-VEGF therapy	Aflibercept, ranibizumab, bevacizumab, brolucizumab, abicipar used in patients with SRF and/or IRF at defined time points
Comparison	
Anti-VEGF therapy	Aflibercept, ranibizumab, bevacizumab, brolucizumab, abicipar used in patients with no SRF and/or IRF at defined time points
Outcome	
Primary: Functional outcomes at Year 1	Visual acuity, OCT data, CNV type (1–3 or PCV), fibrosis, RPE atrophy, macular atrophy, RPE detachment, vascular proliferation, treatment burden (number of injections and clinic visits), patient quality of life, uveitis, and safety
Secondary: Functional outcomes at other time points, morphologic outcomes, treatment burden, and safety	
Setting	
Study design	Randomized and observational studies

CNV, choroidal neovascularization; IRF, intraretinal fluid; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

Functional Outcomes at Year 1

Randomized studies. In a post hoc analysis of the EXCITE trial, baseline SRF was identified as a key predictor of favorable best-corrected visual acuity (BCVA) gains at 1 year ($P = 0.05$).[6] Best-corrected visual acuity and central retinal thickness only correlated strongly at baseline.

In the CATT trial, in patients with nAMD treated with ranibizumab or bevacizumab, baseline IRF, SRF, and sub-RPE fluid were significantly associated with 1-year visual acuity outcomes in univariate analysis, but not in multivariate analysis after adjustment for baseline variables.[16]

In a post hoc analysis of the CATT trial,[13] IRF negatively affected vision at all evaluated time points within the first year of treatment, particularly when there was foveal involvement. visual acuity in eyes with foveal IRF was two lines lower than in those without fluid and one line lower than in eyes with

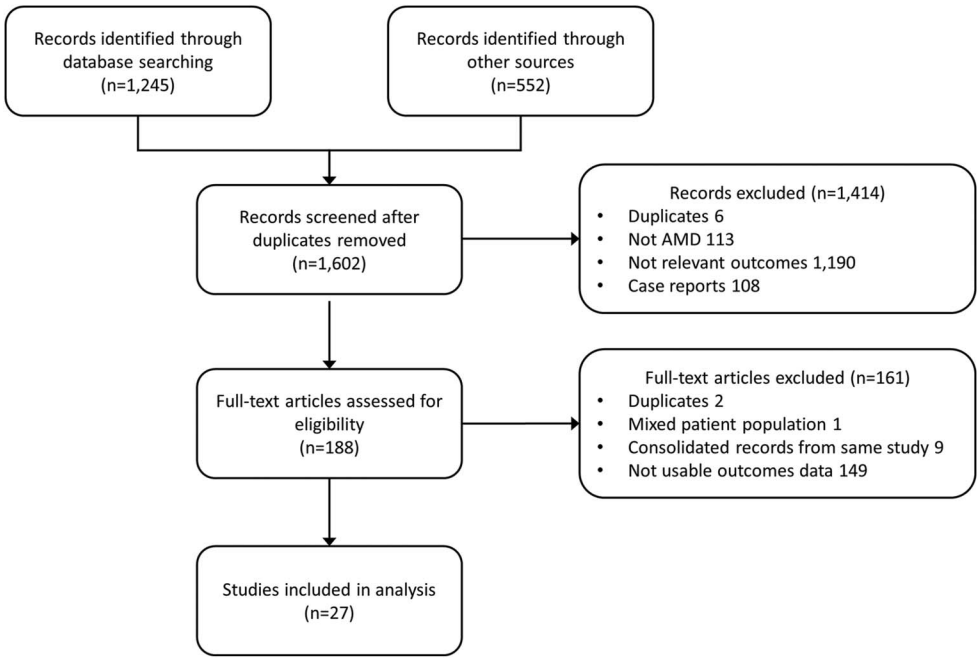

Fig. 1. PRISMA flow diagram.

Table 2. Visual Acuity Per Presence or Absence of SRF and/or IRF

Ref	Study Design	Bias Risk	Treatment/Protocol	Previous Treatment	N
Chatziralli et al 2016[27]	Interventional	Low	AFL Fixed dose	PRN RAN	431
Ebneter et al 2015[36]	Observational	Mod	RAN Monthly	Treatment-naive	31
Ersoy et al 2014[32]	Observational	Mod	RAN or BEV Physician discretion	Mixed	30
Dervenis and Younis 2016[24]	Observational	Low	RAN PRN	Treatment-naive	62
Chakravarthy et al 2020[29]	Observational	Low	Mixed Mixed	Mixed previous anti-VEGF	321 eyes
de Massougnes et al 2018[30]	Observational	Low	RAN or AFL Mixed	Treatment-naive	104 eyes
Inan et al 2019[25]	Observational	Low	RAN PRN	Treatment-naive	65 eyes
Jaffe et al 2016[37] (VIEW 1 and 2)	RCT post hoc	Low	RAN or AFL Q4W (RAN4/AFL4) or Q8W (AFL8)	Treatment-naive	1,815 eyes
Jaffe et al 2013[13] NCT00593450 (CATT)	RCT post hoc	Low	RAN or BEV Monthly or PRN	Treatment-naive	1,185
Kodjikian et al 2018[19] NCT01170767	RCT post hoc	Low	RAN or BEV PRN	Not reported	404
Lin et al 2020[38]	Observational	Low	BEV or RAN PRN	Treatment-naive	77 eyes
Ogasawara et al 2018[31]	Observational	Low	AFL Fixed	Treatment-naive	107 (109 eyes)
Pokroy et al 2018[26]	Observational	Mod	BEV PRN	Treatment-naive	73 eyes
Regillo et al 2015[17] NCT00891735 (HARBOR)	RCT	Low	RAN Monthly or PRN	Treatment-naive	500
Ritter et al 2014[18] NCT00433017 (MONT BLANC)	RCT	NI	RAN or RAN + PDT PRN	Treatment-naive	255
Waldstein et al 2016[12] NCT00637377 NCT00509795 (VIEW 1 and 2)	RCT post hoc	Low	RAN or AFL Q4W (RAN4/AFL4) or Q8W (AFL8)	Treatment-naive	1,815
Waldstein et al 2016[6] NCT00275821 (EXCITE)	RCT post hoc	Low	RAN Monthly or quarterly	Treatment-naive	353
Wickremasinghe et al 2012[22]	Interventional	NI	RAN or BEV PRN	Treatment-naive	214 eyes
Wickremasinghe et al 2016[23]	Observational	Mod	RAN T&E	Treatment-naive	103 eyes
Kim et al 2017[28]	Observational	Mod	RAN or BEV N/A	Treatment-naive	35
Schmidt-Erfurth et al 2020[20] (HARBOR)	RCT post hoc	Low	RAN Monthly or PRN	Treatment-naive	1,095

Table 2. (*Continued*)

Ref	Study Design	Bias Risk	Treatment/Protocol	Previous Treatment	N
Sharma et al 2016[14] (CATT)	RCT	Low	RAN or BEV Monthly or PRN	Treatment-naive	1,185
Ying et al 2014[9] (CATT)	RCT	Low	RAN or BEV Monthly or PRN	Treatment-naive	1,030
Shin et al 2013[39]	Observational	Low	Mixed Mixed	Mixed	20
Gianniou et al 2015[40]	Observational	Low	RAN Q4W	Persistent SRF or IRF	76 eyes
Guymer et al 2019[11] NCT01972789	RCT post hoc	Low	RAN T&E	Treatment-naive	349
Jang et al 2015[41]	Observational	Low	RAN Monthly	Treatment for ≥12 months	44 (45 eyes)
Jaffe et al 2019[10] (CATT)	RCT	Low	RAN or BEV Physician discretion	Treatment-naive	523
Ying et al 2018[21] (CATT)	RCT	Low	RAN or BEV Physician discretion	Treatment-naive	647

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Chatziralli et al 2016[27]	ETDRS letters (by presence of fluid at BL) *P* values adjusted for time	BL: 63.2 ± 13.5 Week 8: 61.9 ± 14.0 Week 16: 62.3 ± 14.7 Week 24: 61.0 ± 16.1 Week 48: 62.3 ± 17.2	BL: 70.8 ± 12.3 Week 8: 70.7 ± 14.1 Week 16: 70.9 ± 12.8 Week: 24: 70.1 ± 13.3 Week 48: 71.0 ± 12.8 *P* = 0.900 vs. no fluid	BL: 61.2 ± 17.3 Week 8: 62.0 ± 17.4 Week 16: 62.0 ± 16.3 Week 24: 62.2 ± 17.1 Week 48: 60.6 ± 17.7 *P* = 0.049 vs. no fluid	BL: 59.6 ± 15.4 Week 8: 59.3 ± 16.6 Week 16: 59.2 ± 18.1 Week 24: 60.4 ± 16.6 Week 48: 59.8 ± 17.7 *P* < 0.001 vs. no fluid	At 12 months: No significant increase in VA from BL prog risk factors: age, increased CST, IRF, PED, subfoveal thickening
Ebneter et al 2015[36]	Change in BCVA (ETDRS letters)	N/A	BL: 59.4 ± 13.3 3 months: 65.2 ± 9.1	BL: 50.0 ± 10.8 3 months: 55.3 ± 10.0	BL: 46.4 ± 18.4 3 months: 54.0 ± 14.1	Neither BL nor improvement of BCVA at Month 3 was statistically significant between the groups

Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Ersoy et al 2014[32]	Change in logMAR BCVA per response	Response defined as absence of IRF or SRF at any visit. After 3 injections: −0.07 ± 0.23 At last visit: 0.07 ± 0.32	Nonresponse defined as persistent SRF at all visits. After 3 injections: −0.06 ± 0.17 (P = 0.657 vs. response) At last visit: 0.08 ± 0.30 (P = 1.0 vs. response)	N/A	N/A	Mean follow-up of 40.25 ± 13.5 months Eyes with SD-OCT phenotype + isolated PED and SRF often nonresponsive to anti-VEGF, different mechanism may be involved vs. AMD
Dervenis and Younis 2016[24]	Mean ± SD ETDRS letters	No SRF BL: 0.62 ± 0.26 Month 4: 0.63 ± 0.52 Month 6: 0.65 ± 0.53 No IRF Baseline: 0.54 ± 0.22 Month 4: 0.36 ± 0.20 Month 6: 0.44 ± 0.29	BL: 0.59 ± 0.30 Month 4: 0.42 ± 0.39 Month 6: 0.48 ± 0.36	BL: 0.63 ± 0.30 Month 4: 0.62 ± 0.47* Month 6: 0.57 ± 0.45 *P = 0.045 vs. no IRF at baseline	N/A	PED at presentation was associated with lower CMT RPE disruption was associated with worse VA at Month 6. IRF presence was associated with worse VA at Month 4
Chakravarthy et al 2020[29]	Change in VA (ETDRS letters)	5 letters gain (no SRF/IRF at ≥2 visits)	3-Letter difference between groups P = 0.042 Sensitivity analysis: No association (P = 0.111)	3-Letter difference between groups P = 0.006 Sensitivity analysis: Association (P = 0.036)	N/A	At 12 months: Higher number of monitoring visits associated with absence of fluid correlate with better VA gain Significant association of IRF with VA

Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
de Massougnes et al 2018[30]	BCVA change (by presence of foveal SRF; ETDRS letters)	1.8 ± 18.1	9.4 ± 11.8 *P* = 0.092 vs. no fluid	N/A	N/A	At 12 months: Visual improvement associated with VA at BL, foveal SRF, and female gender AFL favored (vs. RAN) for PED reduction
Inan et al 2019[25]	BCVA (logMAR)	No SRF BL: 0.95 ± 0.53 12 months: 0.77 ± 0.52 No IRF BL: 0.69 ± 0.4 12 months: 0.60 ± 0.4	Baseline: 1.02 ± 0.55 (*P* = 0.66 vs. no SRF) 12 months: 0.87 ± 0.54 (*P* = 0.43 vs. no SRF)	Baseline: 1.17 ± 0.5 (*P*<0.001 vs. no IRF) 12 months: 0.97 ± 0.5 (*P* = 0.01 vs. no IRF)	N/A	At 12 months: Anatomic improvement and increased VA observed in groups with and without PED, IRC, and SRF Inverse correlation between pretreatment CMT, IRC and posttreatment IRC, and final BCVA
Jaffe et al 2016[37] (VIEW 1 and 2)	ETDRS letters LS mean change from baseline	RAN4: 9.5 AFL4: 8.9 AFL8: 9.8 (without IRF or SRF at all 4 initial visits)	N/A	N/A	RAN4: 8.5 AFL4: 11.7 AFL8: 7.5 (IRF or SRF at all 4 initial visits)	At 12 months: Pattern of visual outcomes was similar regardless of fluid type Eyes with persistent early fluid may benefit from AFL4 vs. AFL8 or RAN4

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Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Jaffe et al 2013[13] NCT00593450 (CATT)	Mean ± SE VA (ETDRS letters)	No SRF 68 No IRF 71.2 ± 0.7	Foveal SRF: 71 Extrafoveal SRF: 70 $P = 0.051$	Foveal IRF: 62.4 ± 1.3 Extrafoveal IRF: 67.2 ± 1.0 $P < 0.0001$	N/A	At 12 months: Little association between fluid type and VA At all time points residual IRF, especially foveal IRF, correlated with worse VA vs. no IRF
Kodjikian et al 2018[19] NCT01170767	Fluid as predictor of BCVA (letters) on multivariate analysis	N/A	Change in BCVA SRF at BL No: 3.5 ± 1.8 Yes: 3.8 ± 0.9 ($P = 0.90$)	Change in BCVA IRF at BL No: 6.4 ± 1.4 Yes: 0.9 ± 1.2 ($P < 0.01$)	N/A	At 12 months: IRF was associated with lower BCVA score, less improvement in BCVA, and poor prognosis
Lin et al 2020[38]	Extended remission (absence of hemorrhage, IRF/SRF, and leakage for 52 weeks after cessation of anti-VEGFs)	N/A	N/A	Extended remission achieved earlier in eyes with isolated IRF at BL HR 2.05; 95% CI 1.929–4.520; $P = 0.045$ vs. eyes with IRF + SRF	N/A	At 12 months: Extended remission achieved earlier in eyes with isolated IRF at presentation
Ogasawara et al 2018[31]	Association of VA loss and fluid	N/A	Univariate standardized β: −0.103 $P = 0.501$ Multivariate standardized β: −0.203 $P = 0.039$	Univariate standardized β: 0.195 $P = 0.189$ Multivariate N/A	N/A	At 12 months: Highest gains in BCVA were associated with no PED, SRF, and poor BCVA at BL
Pokroy et al 2018[26]	Mean ± SD BCVA LogMAR	No SRF BL: 0.87 ± 0.66 Month 12: 0.93 ± 0.67 No IRF BL: 0.43 ± 0.43 Month 12: 0.47 ± 0.45	BL: 0.61 ± 0.51 Month 12: 0.66 ± 0.59 $P = 0.01$ vs. no SRF	BL: 0.88 ± 0.59 Month 12: 0.95 ± 0.67 $P < 0.001$ vs. no IRF	N/A	At 12 months: BL IRF was prognostic for poorer VA Supports use of SHRM as a prognostic biomarker

Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Regillo et al 2015[17] NCT00891735 (HARBOR)	BCVA of ≥20/40 at Month 12	N/A	SRF at BL Yes: 56% No: 40%	N/A	N/A	At 12 months: Presence of SRF at BL was predictive of improved VA outcomes
Ritter et al 2014[18] NCT00433017 (MONT BLANC)	BCVA (ETDRS letters)	N/A	SRF at BL No significant effect on BCVA ($P = 0.704$)	IRF at BL Significantly reduced BCVA gain ($P = 0.006$)	N/A	At 12 months: IRC had a strong negative predictive value for visual improvement in both groups
Waldstein et al 2016[12] NCT00637377 NCT00509795 (VIEW 1 and 2)	Change in BCVA (ETDRS letters) ± SE vs. no fluid	Index	2.11 ± 0.89 $P = 0.018$ vs. no SRF	−2.77 ± 0.73 $P < 0.001$ vs. no IRF	N/A	At 12 months: Greater fluid resolution in all compartments with AFL4 vs. ALF8 or RAN4 IRC was associated with lower BL VA and poorer VA outcomes
Waldstein et al 2016[6] NCT00275821 (EXCITE)	Change in BCVA per BL fluid status	No SRF at BL Freq: 11.3 letters Infreq: −1.0 letters	SRF at BL Freq: 6.3 letters Infreq: 5.4 letters	N/A	N/A	At 12 months: BL SRF was predictive of BCVA gains
Wickremasinghe et al 2012[22]	BCVA (logMAR)	N/A	BL: 0.55 12 months: 0.54 ($P = 0.07$ vs. IRF)	BL: 0.79 ($P = 0.006$ vs. SRF alone) 12 months: 0.78	N/A	At 12 months: Dry eyes/eyes with SRF had improved BCVA vs. eyes with residual IRF; BL IRF confers significantly worse prognosis for visual outcome

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Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Wickremasinghe et al 2016[23]	Mean ± SD BCVA (ETDRS letters)	59.4 ± 12.9	61.2 ± 11.9	54.6 ± 17.8* $P < 0.001$ vs. no fluid/SRF	N/A	At 20.8 months (mean): New occurrence of IRF/SRF more likely to lead to BCVA loss vs. dry eyes or persistent IRF/SRF
Kim et al 2017[28]	BCVA (logMAR)	N/A	BL: 0.95 ± 0.23 24 months: 1.34 ± 0.38 ($P = 0.03$)	IRF with or without SRF BL: 1.06 ± 0.19 24 months: 1.79 ± 0.60 (P value not provided)	N/A	At 24 months: Presence of IRF was associated with worse visual prognosis
Schmidt-Erfurth et al 2020[20] (HARBOR)	Correlation of fluid location and quantification with BCVA Association of 100 nL increase in fluid in central 1 mm with function	N/A	Weak prognostic effect on vision +1.10 letters; $P = 0.0046$	Volume-dependent negative effect on vision −4.00 letters; $P < 0.0001$	N/A	At 24 months: Volume-dependent negative impact of IRF on vision and a weak positive prognostic effect of SRF Dosage and regimen parameters directly correlated with resulting fluid volumes
Sharma et al 2016[14] (CATT)	Mean ± SE BCVA (ETDRS letters)	No foveal SRF/IRF: 69.7 ± 1.2 ($P = 0.049$ vs. any type of foveal or extrafoveal fluid)	No SRF: 66.6 ± 0.7 Foveal SRF: 72.8 ± 1.5 Extrafoveal SRF: 69.6 ± 1.2 ($P = 0.0005$ foveal SRF vs. extrafoveal SRF or no SRF)	No IRF: 72.2 ± 0.8 Foveal IRF: 59.3 ± 1.5 Extrafoveal IRF: 65.3 ± 0.9 ($P < 0.0001$ for both groups vs. no IRF)	N/A	At 24 months: Foveal IRF, abnormally thin retina, greater thickness of the subretinal tissue complex, and subfoveal geographic atrophy or scar had the worst VA Foveal SRF had better VA than no SRF

Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Ying et al 2014[9] (CATT)	Sustained VA loss Yes: n = 61 No: n = 969	N/A	Sustained VA loss Yes: 19.2% No: 36.8% ($P = 0.006$)	Sustained VA loss Yes: 82.5% No: 51.0% ($P < 0.001$)	N/A	At 24 months: Higher proportions of IRF seen in eyes with sustained VA loss
Shin et al 2013[39]	Mean BCVA	N/A	20/100	20/1,000	N/A	Mean follow-up 31.5 months: VA outcomes were worse for eyes with IRF vs. SRF BEV-refractory patients with IRF may respond to RAN; patients with SRF may be refractory to BEV and RAN
Gianniou et al 2015[40]	Mean VA (letters) change from baseline	N/A	Refractory SRF BL: 65.3 (11.9) 12 months: +10.4 (13.3) 24 months: +8.2 (14.4) 36 months: +8.6 (11.6)	Refractory IRF BL: 53.7 (17.2) 12 months: +7.0 (13.8) 24 months: +7.5 (17.0) 36 months: +7.4 (17.4)	N/A	At 12, 24 and 36 months, VA increased with RAN Higher risk of fibrosis, atrophy, or VA loss with refractory cysts vs. refractory SRF

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Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Guymer et al 2019[11] NCT01972789	Mean change from baseline in BCVA	"Intensive" not tolerating SRF 12 months: 4.0 ± 14.4 24 months: 3.0 ± 16.3	"Relaxed" tolerating SRF 12 months: 4.3 ± 12.7 (P = 0.63 vs. intensive) 24 months: 2.6 ± 16.3 (P = 0.99 vs. intensive)	N/A	N/A	At 24 months: Relaxed treatment was noninferior to intensive treatment Patients on relaxed treatment had fewer injections, and significantly more extended/ maintained 12-week treatment intervals vs. patients on intensive treatment
Jang et al 2015[41]	Mean VA change	N/A	Treatment-refractory SRF BL: 65.3 letters 12 months: +10.4 letters 24 months: +8.2 letters 36 months: +8.6 letters	N/A	N/A	Across 36 months: RAN retreatment in nAMD with refractory SRF may still allow good and maintained visual improvement
Jaffe et al 2019[10] (CATT)	Mean VA	N/A	No SRF: 61 letters Extrafoveal SRF: 57 letters Foveal SRF: 68 letters (P = 0.02)	No IRF: 68 letters Extrafoveal IRF: 57 letters ($P < 0.001$) Foveal IRF: 44 letters ($P < 0.001$)	N/A	At 5 years: 60% of eyes had IRF and 38% of eyes had SRF IRF was significantly associated with worse VA and VA loss from baseline to year 5

Table 2. (*Continued*)

Ref	Outcome	No Fluid	SRF	IRF	Both SRF and IRF	Key Points
Ying et al 2018[21] (CATT)	Mean VA and change from BL	N/A	BL SRF None: −9.1 (2.3) Extrafoveal: −2.4 (1.3) Foveal: −2.2 (1.4) *P* = 0.03	Not significant on multivariate analysis	N/A	At 5 years: Absence of BL SRF was associated with worse VA and more VA loss vs. presence of SRF

AFL, aflibercept; AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; BEV, bevacizumab; BL, baseline; CI, confidence interval; CMT, central macular thickness; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Freq, frequent; HR, hazard ratio; Infreq, infrequent; IRC, intraretinal cyst; IRF, intraretinal fluid; LogMAR, logarithm of the minimum angle of resolution; LS, least squares; Mod, moderate; N/A, not applicable; nAMD, neovascular age-related macular degeneration; NI, no information; PDT, photodynamic therapy; PED, pigment epithelial detachment; PRN, pro re nata; Q4W, every 4 weeks; Q8W, every 8 weeks; RAN, ranibizumab; RCT, randomized controlled trial; RPE, retinal pigment epithelium; SD, standard deviation; SD-OCT, spectral-domain optical coherence tomography; SE, standard error; SHRM, subretinal hyperreflective material; SRF, subretinal fluid; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

extrafoveal IRF at all evaluated time points ($P < 0.0001$). Conversely, foveal involvement of SRF or sub-RPE fluid at 1 year did not significantly affect visual acuity ($P = 0.051$ and $P = 0.40$, respectively). Intraretinal fluid had a greater negative effect on visual acuity than did SRF or sub-RPE fluid at all time points and was independently associated with worse visual acuity over the course of treatment.

In a post hoc analysis of the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) trials,[12] multivariate modeling indicated that IRF at baseline was associated with a smaller improvement in BCVA at Week 52 (−2.77 letters; $P < 0.001$ vs. no IRF), as was baseline pigment epithelial detachment (PED; −1.88 letters, $P = 0.012$ vs. no PED). SRF at baseline was associated with a larger BCVA change at Week 52 (+2.11 letters; $P = 0.018$ vs. no SRF).

In a retrospective exploratory analysis of the HARBOR trial,[17] SRF at baseline was associated with a 2-fold greater likelihood of achieving a Snellen equivalent of 20/40 or better at 1 year than if SRF was absent (multivariate analysis, odds ratio: 2.0; 95% confidence interval 1.2–3.3). Patients with SRF and small lesions (≤4.51 disk area of total choroidal neovascularization leakage) were more likely to gain ≥15 letters than those with SRF and large lesions (odds ratio: 2.5; 95% confidence interval 1.5–4.3). In a post hoc analysis,[8] baseline horizontal IRF extension in the fovea, and IRF volume, had the highest predictive power for concomitant BCVA. Baseline SRF and PED parameters did not contribute to baseline BCVA, regardless of macular location.

In the MONT BLANC trial,[18] baseline IRF was associated with a significantly reduced BCVA gain ($P = 0.006$) at 1 year in patients treated with as-needed ranibizumab (monotherapy or with photodynamic therapy), as analyzed by generalized estimation equations. Baseline SRF did not impact BCVA ($P = 0.704$). In a complementary analysis of the GEFAL trial,[19] stepwise multivariate analysis identified an association between baseline IRF and a smaller BCVA change at 1 year compared with absence of IRF (+0.89 vs. +6.35 letters; $P < 0.01$). Baseline SRF did not impact BCVA ($P = 0.98$).

Data on the association between sub-RPE fluid and BCVA were scarce and evaluated only in CATT[13] and VIEW.[12]

Functional Outcomes at Other Time Points

Randomized studies: Year 2. Post hoc analyses of the CATT trial[14] found that, at Week 104, eyes with foveal SRF had better visual acuity than those without

SRF ($P = 0.0005$) and eyes with foveal IRF had worse visual acuity than those without IRF ($P < 0.0001$). The negative effect of IRF on visual acuity was evident at all time points and worsened over time. Furthermore, eyes with sustained visual acuity loss at 2 years were more likely to have IRF ($P < 0.001$) and thinner SRF ($P = 0.04$), but less likely to have SRF ($P = 0.006$).[9] visual acuity was better in eyes with foveal sub-RPE fluid at Week 104 than eyes with extrafoveal or no sub-RPE fluid ($P = 0.048$).[14] Sub-RPE fluid at Week 104 was not associated with sustained visual acuity loss at 2 years ($P = 0.13$).[9]

In the prospective FLUID trial,[11] patients received ranibizumab in an intensive (complete resolution of SRF and IRF) or relaxed (complete resolution of IRF and tolerance of ≤200 μm of SRF in height) treat-and-extend regimen. Two-year results showed no negative effect on vision when SRF up to 200 μm was tolerated, and treatment burden was reduced (15.8 vs. 17.0 injections at Year 2 in the relaxed and intensive groups, respectively).

In a post hoc analysis of the HARBOR trial,[20] multivariable mixed-effects modeling showed that a 100 nL increase in IRF negatively affected visual acuity (−4.00 letters; $P < 0.0001$), but SRF was associated with good visual acuity outcomes (+1.10 letters; $P = 0.0046$). Pigment epithelial detachment did not affect visual acuity (−0.35 letters; $P = 0.0021$).

Randomized Studies: Year 5. Similar to the 1- and 2-year analyses of CATT, the presence and foveal involvement of IRF at Year 5 was independently associated with worse visual acuity, with the strength of this association greater by Year 5. Eyes with foveal SRF had better visual acuity than eyes without foveal SRF on univariate analysis, but the relationship was not significant on multivariate analysis ($P = 0.14$).[10] A trend towards better visual acuity was found in eyes with foveal sub-RPE fluid at Year 5 compared with eyes without sub-RPE fluid ($P = 0.006$) or with extrafoveal sub-RPE fluid ($P = 0.01$).[10] The absence of baseline SRF was a significant predictor of worse visual acuity at 5 years ($P = 0.03$).[21]

Real-World Studies

The association between fluid and visual acuity outcomes has also been assessed in observational studies. Of the 16 real-world studies identified in this systematic review (details in Table 2), statistical data comparing visual outcomes between patients without fluid to those with SRF and/or IRF were available for 11 studies. Owing to variability in study methodology, patient populations, and data analyses, any conclusions should be interpreted with caution.

Only two observational studies were prospective.[22,23] In one study[22] of patients treated with ranibizumab treat-and-extend, baseline BCVA was significantly worse in eyes with IRF than eyes with SRF alone ($P = 0.006$). After three injections, eyes that were dry (no IRF/SRF) had better BCVA at Year 1 compared with residual IRF ($P = 0.05$), whereas eyes with SRF alone had similar BCVA compared with those that were dry. Furthermore, eyes with residual IRF had a greater chance of BCVA loss at Year 1 compared with eyes that were dry ($P = 0.01$). In a retrospective analysis of another prospective study of patients treated with ranibizumab treat-and-extend,[23] eyes with IRF had significantly lower BCVA at any time point than eyes that were dry or those with SRF ($P < 0.001$).

Five retrospective, observational studies found that eyes with baseline IRF had worse vision at Month 4,[24] Year 1,[25–27] or Year 2[28] than eyes without as determined by multivariate analysis. In addition, eyes with ≥2 clinic visits without IRF had significantly greater gains in visual acuity compared with eyes with fewer IRF-free visits.[29] Three retrospective, observational studies found that eyes with baseline SRF had better vision at Year 1[30,31] or Year 2[28] than eyes without. In one study, baseline foveal SRF was a significant predictor of positive change in BCVA at Year 1 (+10.6 letters greater than eyes without SRF; $P = 0.001$).[30] However, four studies found that baseline SRF did not significantly affect visual acuity at Months 4 and 6,[24] or Year 1.[25–27] Another study found that visual acuity in eyes with ≥2 clinic visits without SRF was not significantly different from those with fewer SRF-free visits.[29] In addition, in eyes with SRF and PED, BCVA was not significantly different between patients with persistent SRF and those without SRF or IRF at any visit.[32]

Number of Injections

Association between fluid compartments and anti-VEGF injection frequency was assessed as a marker for treatment burden. Of the studies identified (Table 3), only the FLUID study found significant associations between fluid presence/absence and number of injections.[11] The mean number of injections was lower in the relaxed (tolerating ≤200 μm of SRF) group than that in the intensive (not tolerating SRF) group at Year 1 (8.9 ± 2.3 vs. 9.5 ± 2.6; $P = 0.001$) and Year 2 (15.8 ± 5.9 vs. 17.0 ± 6.5; $P = 0.001$).

Discussion

This review provides a comprehensive, objective, and systematic critique of the relationship between

Table 3. Association Between Fluid and Number of Injections

Ref	Study Design	Risk of Bias	Treatment	Protocol	Previous Treatments	Treatment Arm	N	No. of Injections	Time Point
Curry et al 2017[42]	Open-label	Mod	AFL	PRN	RAN	Eyes with IRF	9	Injection frequency 46 days (P = 0.02)	12 months
						Eyes with SRF	11	Injection frequency 41 days (P = 0.10)	
Dervenis et al 2016[24]	Observational	Low	RAN	PRN	Treatment-naive	SRF	42	3.9	12 months
						No SRF	20	3.3	
						IRF	32	3.7	
						No IRF	30	3.9	
Ersoy et al 2014[32]	Observational	Low	RAN or BEV	PRN	Mixed	Persistent SRF	14	7.1 (2.6)	12 months
						No persistent SRF	16	5.4 (1.8)	
Guymer et al 2019[11]	RCT	Low	RAN	T&E	Treatment-naive	"Intensive" not tolerating SRF or IRF	BL: 349	9.5 (2.6)	12 months
						"Relaxed" tolerating SRF ≤200 μm		8.9 (2.3)*	
						"Intensive" not tolerating SRF or IRF		17 (6.5)	24 months
						"Relaxed" tolerating SRF ≤200 μm		15.8 (5.9)*	
								*P = 0.001 relaxed vs. intensive arm	
Regillo et al 2015[17]	RCT post hoc	Low	RAN	PRN	Treatment-naive	SRF thickness >118.25 μm	117	8.9	12 months
						SRF thickness ≤118.25 μm	134	7.3	
Ritter et al 2014[18]	RCT	Low	RAN or RAN + PDT	PRN	Treatment-naive	With SRF	82 75	RAN+PDT: 5.3 (2.2) RAN: 5.6 (2.4)	12 months
						Without SRF	40 55	RAN+PDT: 4.4 (2.3)* RAN: 4.8 (1.8)	
						With IRF	60 69	*P < 0.01 vs. with SRF RAN + PDT: 5.0 (2.3)	
						Without IRF	62 61	RAN: 5.2 (2.0) RAN + PDT: 4.9 (2.2) RAN: 5.3 (2.4)	

AFL, aflibercept; BEV, bevacizumab; BL, baseline; IRF, intraretinal fluid; Mod, moderate; PDT, photodynamic therapy; PRN, pro re nata; RAN, ranibizumab; RCT, randomized controlled trial; T&E, treat-and-extend.

fluid compartments and visual acuity in patients with nAMD treated with anti-VEGF drugs. This is the first systematic review objectively approaching this topic based on published evidence in the peer-reviewed literature. The conclusions presented are primarily drawn from prespecified and post hoc analyses of randomized controlled trials in patients with nAMD and are corroborated by real-world evidence.

The findings suggest that baseline and persistent/new IRF negatively affect visual acuity throughout treatment[10,12,13,18–20] and the strength of this association increases from Years 1 and 2 to Year 5.[10] Location of IRF relative to the foveal center influences vision outcomes—foveal IRF is generally associated with worse visual acuity compared with extrafoveal IRF or absence of IRF. A post hoc analysis of the HARBOR study suggested that IRF has a volume-dependent negative impact on vision[20] but volumetric assessments are not commonplace in clinical practice and are not currently part of retreatment criteria.

Data regarding the role of SRF are unclear. Most studies suggested that SRF did not negatively affect visual acuity at baseline or throughout Year 1 of treatment.[6,13,19] At Year 2, one study corroborated the Year 1 findings,[11] and another found that SRF was associated with improved vision outcomes.[14] In the study exploring long-term effects of SRF on visual acuity, patients with foveal SRF at any time point had better vision at Year 5 than those without SRF.[10]

Few studies reported visual acuity outcomes stratified by the presence/absence of sub-RPE fluid. Some reported that there was no vision loss when sub-RPE fluid was present, but visual acuity benefits could not be ascertained.[9,13,14] One study reported that foveal sub-RPE fluid was associated with better visual acuity at Year 5, but the explanation for this effect is unclear.[10] In some instances, sub-RPE fluid may reflect Type 1 choroidal neovascularization, providing trophic support to the retina.[10]

Likewise, few studies associated the number of injections with fluid status, and because a difference between the number of injections according to IRF and SRF status was not apparent, it was not possible to draw any clinically meaningful conclusions.

There are several possible explanations why IRF but not SRF is associated with worse visual acuity. IRF may indicate Müller cell dysfunction, which adversely affects photoreceptor function and neural transmission through the retina.[33] Disruption of the blood–retinal barrier promotes capillary albumin escape and fluid accumulation in the interstitial space. Intraretinal fluid may indicate a damaged external limiting membrane.[34] It has been hypothesized that hyporeflective cystoid structures seen on optical coherence tomography may represent tissue loss mediated by non–VEGF-driven mechanisms, such as cell death,[10] and evidence suggests that some neurosensitive damage is not reversible by treatment.[13,35] Conversely, SRF may indicate an intact, functioning photoreceptor/external limiting membrane.[34] Decrease in SRF, which acts as a spatial buffer between photoreceptors and toxic metabolites, may result in misalignment and decay of photoreceptors, thereby affecting ellipsoid zone integrity.[34] Furthermore, Type 1 macular neovascularization might be a compensatory response to localized ischemia, and the source of the SRF bathes the photoreceptors with nutrients, oxygen, and neuroprotective substances that may improve photoreceptor function and lead to better visual acuity.[10,35]

Although the studies in this systematic review had a low/moderate bias risk, many were retrospective or evaluated fluid post hoc and were not formally powered to test our hypothesis. Different methodologies reported various outcomes, time points, and definitions of SRF/IRF, making a robust meta-analysis unfeasible. Different statistical methods (univariate or multivariate analysis) were applied for evaluating the association between IRF, SRF, and sub-RPE fluid with visual acuity, which may explain some differences in the findings across the various studies. In addition, we did not include data presented at international conferences that should be considered once validated in peer-reviewed publications.

Clinical insights are usually derived from robust evidence from prospective trials, but only the FLUID trial prospectively correlated fluid location with visual acuity,[11] demonstrating a need for additional randomized controlled trials to characterize the effects of fluid compartments on visual acuity. Comparisons of real-world evidence with randomized controlled trials data should be interpreted with caution; most real-world evidence was retrospective and varied in methodology. More observational studies are needed to support additional evidence generation.

A low correlation exists between overall changes in morphology and visual acuity in patients treated with anti-VEGF drugs, but our systematic review shows that the presence of IRF is associated with poorer visual acuity. Subretinal fluid does not negatively affect VA at Year 1, and data after Year 1 suggest that the presence of SRF is associated with better visual acuity than if absent.

To optimally manage patients with nAMD with anti-VEGF drugs, clinicians should understand the impact of fluid compartment changes on visual acuity. Current evidence suggests that after an initial treatment course, anti-VEGF regimens that do not tolerate IRF but tolerate stable persistent SRF (on the condition that

visual acuity is stable/improved) may enable patients to achieve their best visual acuity and minimize treatment burden. In addition to the fluid compartment, the location of the fluid relative to the foveal center should be considered when making retreatment decisions. Additional confirmatory studies are warranted to validate the differential effects of fluid compartments on functional outcomes (http://links.lww.com/IAE/B512).

Key words: antivascular endothelial growth factor treatment, neovascular age-related macular degeneration, retinal fluid compartments, subretinal fluid, intraretinal fluid, systematic literature review.

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