Recovery Course of Persistent Subretinal Fluid After Successful Repair of Rhegmatogenous Retinal Detachment

Short Title: Submacular fluid after retinal reattachment

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Keywords: Macula-off; ellipsoid zone; persistent submacular fluid; pars plana vitrectomy, rhegmatogenous retinal detachment, scleral buckle.

Abstract

Objectives: To investigate best corrected visual acuity (BCVA), subretinal fluid (SRF) absorption time or ellipsoid zone (EZ) restoration time and various variables in patients with persistent SRF after successful primary repair of rhegmatogenous retinal detachment (RRD).

Methods: This retrospective multicenter study allowed independent analysis of the healing pattern by two observers based on composite of serial cross-sectional macular optical coherence tomography (OCT) scans. Univariate and multivariate analyses were implemented.

Results: One hundred and three cases had persistent SRF after pars plana vitrectomy, scleral buckling, or pneumatic retinopexy. By univariate analysis, SRF resolution time correlated positively with the number of retinal breaks ($p<0.001$) and with increased myopia ($p=0.011$). Using multivariate analysis, final BCVA (log MAR)

correlated positively with age, duration of RRD, initial BCVA (OR=3.28; [95%CI= 1.44-7.47]; p=0.015), and SRF resolution time (OR=0.46 [95%CI 0.21-1.05]; p=0.049). EZ restoration time was longer with increasing number of retinal tears (OR=0.67; [95%CI 0.29-1.52]; p=0.030), worse final BCVA, and presence of macula-off RRD (OR=0.26; [95%CI 0.08-0.88]; p=0.056). SRF resolution time correlated marginally with prone position.

Conclusions: Final BCVA is better in younger subjects and in eyes with shorter duration of RRD. It is a self-limited disorder with good visual prognosis.

Introduction

The macula's healing process can vary in rhegmatogenous retinal detachment (RRD) repair managed by scleral buckling (SB) and/or pars plana vitrectomy (PPV). Postoperative macular abnormalities include epiretinal membrane development, cystoid macular edema, reduced vascular density in the deep and superficial retinal plexus, and persistent subretinal fluid (SRF [1-22]. Residual SRF is made up of tiny, non-shifting, subtle pockets of loculated fluid that frequently affect the macular area. It is extremely difficult to detect with indirect ophthalmoscopy and is more likely to be suspected with slit lamp biomicroscopy. In eyes with macroscopically successful RRD repair but insufficient vision recovery, little is known about the fine structural macular healing process when there is sub-foveal persisting SRF [2-19]. The features and temporal stages of microstructural healing when persistent subretinal blebs are noted were examined in this study using serial spectral domain or swept source optical coherence tomography (OCT).

Methods

This was a retrospective compendium of cases of persisting SRF 1 month after a straightforward successful primary RRD repair (any procedure). The participants in this collection were invited from various retinal societies around the world. The study was completed with IRB approval and in accordance with the Helsinki Principles. Because the study was anonymous and retrospective in nature, patient consent was not necessary and was waived. Participants submitted individual patient data and serial OCT scans ranging from the first month after surgery till SRF resolution date. Criteria for inclusion included: persistence of SRF after 1 month after surgery diagnosed by OCT and a minimum follow-up OCT of 3 months. Criteria for exclusion included: previous retinal surgery; simultaneous cataract surgery with the retinal surgery; need for subsequent retina surgery; poor quality of OCT scans; previously published case series; presence of a giant retinal tear; combined tractional rhegmatogenous retinal detachment; significant preretinal fibrosis; history of ocular trauma; diabetes mellitus, Alzheimer's disease, cirrhosis, kidney disease, uncontrolled systemic hypertension or uncontrolled hyperlipidemia; preexisting ocular diseases such as nanophthalmos, macular hole or cyst or degeneration, glaucoma, uveitis, and retinal vascular disorders.

Each patient's cross-sectional OCT pictures of the macular area from various visits were compiled into a serial montage. Two senior observers (AMM, SHU) independently analyzed the healing patterns and following parameters based on video and/or raster and/or radial OCT: resolution of SRF and restoration time of the ellipsoid zone (EZ). In case of disagreement, the OCT scans were reviewed till an agreement was reached. A standardized data collection sheet was developed for grading each case. The best corrected visual acuity (BCVA) was measured by Snellen charts and was converted to log MAR. Data on gender, age, race, lens

status, duration of symptoms, extent of retinal detachment, number of retinal tears, BCVA, and refractive error were collected. Using OCT data acquired at the 1-month postoperative timepoint, persistent SRF was classified into 3 patterns: single discrete bleb (or focal group), multiple discrete blebs (or multifocal group), and shallow diffuse bleb (diffuse group) (Figures 1-4).

Primary outcome measures included the time to resolution of SRF, time for healing of EZ, and final BCVA.

Statistical analysis

Continuous data were presented as means ± standard deviations. Statistical analyses were performed using Chi-square, two-tailed paired *t* test, one-way analysis of variance (ANOVA), Fisher test and Pearson correlation coefficient R. Multivariate analysis was carried using SPSS 22 (IBM SPSS, Armonk, New York, USA) (multiple multivariate regression and multiple discriminate function). The measures of association were expressed as odds ratios (OR) with 95% confidence intervals (CI). *P* values of less than 0.05 were considered statistically significant. P values of 0.05 to 0.07 were defined to indicate borderline significance.

Literature search

We performed a literature search for similar studies. The terms “residual subretinal fluid”, “persistent subretinal fluid”, “subretinal fluid absorption” AND “scleral buckle”, “vitrectomy”, and “pneumatic retinopexy” were used in a literature search that ran from January 1991 (when OCT was introduced) through December 2022 using PubMed, Google Scholar, and their cross references. The final review excluded case reports, publications with missing data, publications in a language other than English, German, Spanish, Italian or French, non-peer reviewed articles, and articles

that did not meet the inclusion criteria outlined above. The full texts of included articles were reviewed by the corresponding authors.

Results

This retrospective study involved 33 ophthalmic centers in 11 nations from 4 continents. Following retinal reattachment surgery, 103 eyes from 103 patients had persistent SRF. Average age±SD was 52.7±15.2 (range 10-80; median 56). A majority of 94 people were Caucasians, followed by 6 Asians and 3 African Americans. There were 48 women and 55 men in the population. The lens status included 13 eyes that were pseudophakic and 90 that were phakic. The mean±SD spherical equivalent in diopters was -2.45±3.05 (range +6.0 to -11.0; median -1.75). Hyperopia >0.50D was present in 3 eyes, low myopia (-0.5.0D to -3.0D) in 42 eyes, moderate myopia (-3.25D to -6.0D) in 15 eyes and high myopia (<-6.0D) in 15 eyes. The duration of RRD had a mean±SD of 28.9±78.7 days (range 1-700; median 7) with 75 eyes having a duration of ≤15 days. The majority had macula-off RRD while 16 eyes had macula-on RRD. The mean±SD number of clock hours involved by RRD was 5.2±1.8 (range 2-12; median 5) with a majority of 77 eyes being between 4 and 7 clock hours. RRD involved preferentially the temporal quadrants in 63 eyes, superior quadrants in 49 eyes and the inferior quadrants in 31 eyes. The number of retinal tears was 1.5±1.0 (range 1-6; median 1) with 68 eyes having a single tear detected and 20 eyes having 2 tears. Most retinal tears were distributed temporally (66 eyes), superiorly (55 eyes) or inferiorly (28 eyes).

Surgery

Surgical intervention included pneumatic retinopexy in 7 eyes, and the rest was divided equally between SB and PPV: PPV in 40 eyes, SB in 39 eyes, and 17 with SB-PPV. In 45 eyes, intraoperative perfluorooctane was utilized to flatten the retina,

and 22 and 23 eyes, respectively, underwent internal or external subretinal drainage of subretinal fluid. In 29 eyes, neither perfluoro propane injection nor intraoperative drainage were carried out. The gas injected consisted of SF6 in 46 eyes, C3F8 in 16 eyes and C2F6 in 4 eyes. Prone position was maintained for several days postoperatively in 45 eyes.

No therapy was prescribed one month after surgery in the hope to facilitate SRF absorption in 83 patients. Attempted therapies in 20 eyes included a combination of: topical nepafenac (9 eyes), corticosteroid in 7 eyes (topical in 3 eyes, subtenon in 2 eyes and oral in 2 patients), topical dorzolamide in 6 eyes, oral acetazolamide in 2 patients, oral spironolactone in one patient, and intravitreal injections of aflibercept in 2 eyes, ranibizumab in one eye and bevacizumab in one eye. Cystoid macular edema (transient) was noted in 5 eyes and epiretinal membranes in 8 eyes.

Functional outcomes

Initial (at 1-month postoperatively) mean±SD BCVA 1.08±0.87 (Snellen equivalent 20/240) improved significantly (p=0.001) thereafter to 3-month BCVA 0.35±0.27 (Snellen equivalent 20/45) (paired t-test=10.7), to 12-month BCVA 0.25±0.24 (Snellen equivalent 20/36) (paired t-test=9.4) and to final BCVA 0.21±0.24 (Snellen equivalent 20/32) (paired t-test=10.5). The mean±SD of the follow-up was 25.4±23.1 months (range 3-120; median 16) with 83 patients returning to their periodic visits one year postoperatively and beyond.

Anatomic outcomes

SRF, when located in the fovea, was of the focal type in 28 (28.9%) (Fig.1), multifocal in 34 (35.1%) (Figs.2, 3) and diffuse in 35 (36.1%) (Fig.4). Six eyes had extrafoveal SRF distributed as diffuse in 4 and focal or multifocal in one each. The type of SRF correlated with age with the focal group seen in older patients compared

to the rest (p=0.016). There was a tendency for male predominance in the focal group and female predominance in the multifocal group; more so if the tear was superior (p=0.013) or if RRD involved the superior quadrants (p=0.008) or if RRD involved the macula (macula-off RRD) (p=0.038). The multifocal group had the highest percentage of superior RRD. Also, there was a preponderance of PPV surgery in the focal bleb group and SB surgery in the diffuse bleb group (Table 1). SRF resolved after a mean of 11.2±6.4 months (2-39; median 10) from surgery. The ellipsoid zone (EZ) recovered after 11.7±6.9 months (range 2-57; median 11) (Figs. 1, 2, 4). At the final follow-up visit, 22 eyes (21.4%) still had EZ and ELM disruption (Fig.3).

Using additional univariate analysis, the time for SRF resolution correlated positively with the number of retinal breaks (R=0.34; p=0.001) and with increasing myopia (R=-0.25; p=0.011). Intraoperative drainage of subretinal fluid or use of intravitreal perfluorooctane injection correlated with increasing age (p=0.008) and initial BCVA (p=0.021).

Multiple regression analysis showed the following interrelationships (Table 2). Final BCVA (log MAR) correlated positively with age, duration of RRD, initial BCVA and time to resolution of SRF. Final BCVA was highly associated with initial BCVA (OR=3.28; [95%CI 1.44-7.47]; p=0.015), and more so when SRF resolution time was less than 10 months (OR 5.0 [95%CI 1.35-18.56]; p=0.015). Final BCVA correlated with SRF resolution time (OR=0.46 [95%CI 0.21-1.05]; p=0.049) and more so with macula-off RRD (OR=0.39 [95%CI 0.16-0.94]; p=0.029). EZ restoration time correlated with the number of retinal tears (OR=0.67; [95%CI 0.29-1.52]; p=0.030), final BCVA (log MAR) (OR=0.58; [95%CI 0.26-1.30]; p=0.037), and macula-off RRD

(OR=0.26; [95%CI 0.08-0.88]; p=0.056). SRF resolution time correlated marginally with prone position (OR=1.32 [95%CI 0.56-3.11]; p=0.070); SRF class did not correlate with any variables. In other words, final vision related to initial vision and tended to be better in younger patients, and with shorter duration of RRD in macula-off cases. The time interval for EZ restoration was longer in eyes with multiple tears.

Result of literature review

The literature review [1, 6-8, 10,12-18, 20, 21, 25-28] yielded a total of 561 cases (240 prospective and 321 retrospective cases) from 8 nations: 3 medical centers in China and Israel, 2 centers in South Korea and Japan, and one center in Italy, Switzerland, England, and Ireland. Patient characteristics included a male predominance (57.9%) and a mean±SD age of 47.3±18.6 years. High myopia was detected in 29.9% of eyes and 87% of the patients were phakic. RRD had the following fundus features: macula-off in 92.6% of eyes; number of tears 1.7±1.0; superior location of retinal tears in 59% of eyes; superior location of RRD in of 57% of eyes; and extent of RRD in clock hours 5.7±2.0. The duration of RRD was 15.2±43.6 days. The SRF type was focal in 30.7%, multifocal in 24.7% and diffuse in 44.5%. Most surgeries were made up of SB (78.8% of cases), with intraoperative use of intravitreal tamponade or drainage of subretinal fluid carried in 59% of cases. In this review, the mean±SD time to resolution of SRF was 9.8±6.7 months (Table 3). BCVA improved from 0.76±0.79 (Snellen equivalent 20/115) to 0.20±0.24 (20/32 Snellen equivalent) at a mean±SD follow-up of 21.1±16.1 months.

Discussion

In the current study, final visual acuity correlated with shorter duration of RRD, younger age and better initial visual acuity. Also, the restoration time of EZ took longer with eyes with more tears and with macula-off RRD. Similarly in the literature

[10], variables involved in persistence of SRF have included advanced age [3], inferior RRD [3, 9], longer durations of RRD [3, 9], macula-off RRD, increased choroidal thickness [22], and type of surgical intervention (more in SB than PPV) [25]. In eyes where SRF is not drained, SRF absorption advances swiftly when the retina tears are closed. It is still unclear why minute SRF residues can take months to vanish completely. Active RPE pump, hydrostatic pressure, and oncotic pressure gradients (greater oncotic pressure in choroid) favor SRF absorption. There is a flow of tissue fluid from the choroid to the retina because the hydrostatic pressure in the choroid is lower than that in the retina [29]. The increased oncotic pressure in the extravascular stroma is a result of the fenestrated capillaries' high protein permeability, which promotes the flow of fluid from the retina to the choroid [30]. The rich membrane RPE pump system (membrane pumps, endocytosis, passive diffusion), which also includes the Na-K-ATPase system, enables ion concentrations on either side of RPE to reach a dynamic equilibrium and ensures normal retinal function [30].

With advanced age, the RPE pump is impaired [2-12]; the regular degradation of the shed photoreceptor lipoprotein is defective; and the transport of nutrients from the choriocapillaris to the photoreceptors is damaged from the presence of an age-related hydrophobic barrier formed by accumulated sub-RPE lipoproteins. Likewise, with long duration RRD, there is a high protein content of SRF, compromised RPE function from ocular hypotony, disrupted blood retinal barrier and protracted choroidal edema [26-30].

Veckeneer et al [9] noted the inferior RRD to be more susceptible for postoperative SRF and for its longer persistence. In contrast, Long et al [3] found that inferior

breaks had better outcomes than superior tears using multivariable analyses. The location of the breaks and the RRD location did not influence the final BCVA or SRF resolution in the current study. Long-term retentions of vitreous diffusion in the SRF may result in the re-modification of macromolecules and protein components [23], which would reduce the RPE's ability to absorb SRF. The photoreceptors degenerate, a cystic space forms in the retina, and the retina atrophies when the retina is detached for an extended period of time. This prevents SRF from being absorbed.

SRF persistence demonstrates how the surgical procedure impacts its occurrence by contrasting SB (52.3%-55.6%) [10, 18] to PPV (0-15%) [25, 26] and pneumatic retinopexy (16%) [2]. In 2 meta-analyses [19, 23], patients undergoing SB have higher odds of having residual SRF compared with PPV. SB is thought to be more associated with residual SRF for several reasons: incomplete drainage of subretinal fluid, use of cryopexy which disrupts the blood retinal barrier, compression of vortex veins, and decrease in subfoveal choroidal flow [8]. Our study does not address specifically the incidence of SRF after different surgical procedures.

The question of whether intervention is necessary for eyes with SRF is an intriguing one. Although a brief loss of vision was initially observed, multiple investigations [2, 14, 18] indicated that one year after SB, PPV, or pneumatic retinopexy, there had been a good visual recovery. We were able to demonstrate an association between the duration of SRF persistence and both final acuity and EZ healing times, in contradistinction with other studies [19, 23]. In general, the good visual recovery in most cases is like cases with central serous chorioretinopathy. In both conditions the

small shallow SRF does not appear to affect the nutritional needs of the foveolar photoreceptors. As a result, medical or surgical intervention seems rarely necessary.

There has been no definitive treatment to aid SRF reabsorption. In an attempt to reappose the photoreceptors with the RPE, persistent SRF could be surgically removed by internal drainage. Other anecdotal therapies have included SB removal, selective retinal therapy, systemic steroids, carbonic anhydrase inhibitor and topical prostaglandin inhibitor [2-19].

The main limitations of this study are its retrospective nature, the inclusion of patients from different centers, the wide variations in surgical techniques, albeit different follow-up regimens, variety of interventions to resolve SRF, and absence of potential variables like sleep apnea, body weight, and systemic medications. The current study excluded more complex RRD such as giant retinal tear, combined phacoemulsification-vitrectomy, and severe proliferative vitreoretinopathy. Absence of fundus autofluorescence, microperimetry, color vision perception, and contrast sensitivity are drawbacks. Another drawback is the absence of measurements related to the height of SRF, the deep macular vascular layer and to the choroid. Recently vessel density of the deep capillary plexus appeared to be a good predictor of visual recovery following successful RRD repair as it appears strongly associated with the time of restoration of the photoreceptor layers and the postoperative BCVA [24]. The role of the choroid in the etiology of SRF was recently discovered [22].

In conclusion, based on literature review and current findings, delayed resorption of SRF in the macular area after retinal surgery appears self-limited with no need to intervene as visual acuity usually recovers well. Final visual outcome is less

favorable in older patients, and in eyes with longer duration of RRD that involves the macula.

Abbreviations

BCVA=best-corrected visual acuity; log MAR=logarithm of the minimum angle of resolution; SRF=subretinal fluid; RRD=rhegmatogenous retinal detachment.

Conflicts of Interests

The authors declare no competing interests.

Funding

The authors declare no funding.

Author Contributions

LL-G, AMM, MP, SB, LH, SU, AGE contributed to the conception and methodology of the manuscript. All authors contributed to the data collection. AMM and HAM drafted the manuscript. ARC, AMM, HAM did the statistical analysis. LL-G, SGS, SS, KT, AGE, MP, SU helped to draft the manuscript. All authors provided comments and revised the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

Compliance with ethics guidelines

All procedures were in accordance with the ethical standards of the Rafic Hariri University Hospital Review Board and Ethics Committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was not required as the study was retrospective and anonymous.

Data Sharing

The complete data can be shared upon request to the corresponding authors

References

1- Obeid A, Ehmann D, Adam M, Kasi S, Shahlaee A, Klufas MA, et al. Comparison of residual subfoveal fluid by intraoperative OCT after Macula-Involving RRD repair using direct drainage, drainage Retinotomy, or Perfluoro-n-Octane. Ophthalmic Surg Lasers Imaging Retina. 2019;50:497–503.

2- Bansal A, Lee WW, Sarraf D, Sadda SR, Berger AR, Wong DT, et al. Persistent subfoveal fluid in pneumatic retinopexy versus pars plana vitrectomy for rhegmatogenous retinal detachment: posthoc analysis of the PIVOT randomised trial. Br J Ophthalmol. 2022.doi:10.1136/bjo-2021-320981

3- Long K, Meng Y, Chen J, Luo J. Multifactor analysis of delayed absorption of subretinal fluid after scleral buckling surgery. BMC Ophthalmol. 2021;21:86.

4- Meng Y, Long K, Chen J, Luo J. Effect of High Myopia on Delayed Absorption of Subretinal Fluid after Scleral Buckling Surgery. J Clin Med. 2022;11:3906.doi:10.3390/jcm11133906

5- Oellers P, Eliott D. Overloaded Dysfunctional RPE Leads to Delayed Absorption of Subretinal Fluid After Retinal Detachment Repair. Ophthalmic Surg Lasers Imaging Retina. 2017;48:852-5.

6- Fu Y, Chen S, Gu Z-H, Zhang YL, Li LY, Yang N. Natural history of persistent subretinal fluid following the successful repair of rhegmatogenous retinal detachment. Int J Ophthalmol. 2020;13:1621-8.

7- Kang SW, Kim JH, Shin WJ, Kim JI. Subretinal fluid bleb after successful scleral buckling and cryotherapy for retinal detachment. Am J Ophthalmol. 2008;146:205-10.

8- Wang XY, Shen LP, Hu RR, Xu W. Persistent subretinal fluid after successful scleral buckle surgery for macula-off retinal detachment. Chin Med J. 2011;124:4007-11.

9- Veckeneer M, Derycke L, Lindstedt EW, van Meurs J, Cornelissen M, Bracke M, et al. Persistent subretinal fluid after surgery for rhegmatogenous retinal detachment: hypothesis and review. Graefes Arch Clin Exp Ophthalmol. 2012;250:795-802.

10- Kim YK, Woo SJ, Park KH, Yu YS, Chung H. Comparison of persistent submacular fluid in vitrectomy and scleral buckle surgery for macula-involving retinal detachment. Am J Ophthalmol. 2010;149:623-9.

11- Abouzeid H, Becker K, Holz FG, Wolfensberger TJ. Submacular fluid after encircling buckle surgery for inferior macula-off retinal detachment in young patients. Acta Ophthalmologica. 2009;87:96-9.

12- Mimouni M, Jaouni T, Ben-Yair M, Almus S, Derman L, Ehrenberg S, et al. Persistent loculated subretinal fluid after rhegmatogenous retinal detachment surgery. Retina. 2020;40:1153-9.

13- Kim JM, Lee EJ, Cho GE, Bae K, Lee JY, Han G, et al. Delayed absorption of subretinal fluid after retinal reattachment surgery and associated choroidal features. Korean J Ophthalmol. 2017;31:402-11.

14- Gharbiya M, Malagola R, Mariotti C, Parisi F, De Vico U, Ganino C, et al. Spectral-domain optical coherence tomography analysis of persistent subretinal fluid after scleral buckling surgery for macula-off retinal detachment. Eye. 2015;29:1186-93.

15- Hagimura N, Iida T, Suto K, Kishi S. Persistent foveal retinal detachment after successful rhegmatogenous retinal detachment surgery. Am J Ophthalmol. 2002;133:516-20.

16- Woo SJ, Lee KM, Chung H, Park KH. Photoreceptor disruption related to persistent submacular fluid after successful scleral buckle surgery. Korean J Ophthalmol. 2011;25:380-6.

17- Desatnik H, Alhalel A, Treister G, Moisseiev J. Management of persistent loculated subretinal fluid after pneumatic retinopexy. Brit J Ophthalmol. 2001;85:189-92.

18- Seo JH, Woo SJ, Park SH, Yu YS, Chung H. Influence of Persistent Submacular Fluid on Visual Outcome After Successful Scleral Buckle Surgery for Macula-off Retinal Detachment. Am J Ophthalmol. 2008;145:915-22.

19- Soni C, Hainsworth DP, Almony A. Surgical management of rhegmatogenous retinal detachment: A meta-analysis of randomized controlled trials. Ophthalmology. 2013;120:1440-7.

20- Gibran SK, Cleary PE. Ocular coherence tomographic examination of postoperative foveal architecture after scleral buckling vs vitrectomy for macular off retinal detachment. Eye. 2007;21:1174-8.

21- Otsuka Y, Oishi A, Suda K, Tsujikawa A, Kurakazu T. Multiple subretinal fluid blebs after pars plana vitrectomy for rhegmatogenous retinal detachment repair. Graefes Arch Clin Exp Ophthalmol. 2019;257:921-9.

22- Chantarasorn Y, Oellers P, Eliott D. Choroidal Thickness Is Associated with Delayed Subretinal Fluid Absorption after Rhegmatogenous Retinal Detachment Surgery. Ophthalmology Retina. 2019;3:947-55.

23-Dhoot AS, Popovic MM, Nichani PAH, Eshtiaghi A, Mihalache A, Sayal AP, et al. Pars plana vitrectomy versus scleral buckle: A comprehensive meta-analysis of 15,947 eyes. Surv Ophthalmol. 2022;67:932-49.

24-Stoebener S, Salleron J, Zessler A, Pastor G, Angioi-Duprez K, Berrod JP, et al. Association of Microvasculature Changes with Visual Outcomes after Successful Retinal Detachment Surgery. Ophthalmology Retina. 2022;6:886-92.

25-Wolfensberger TJ. Foveal reattachment after macula-off retinal detachment occurs faster after vitrectomy than after buckle surgery. Ophthalmology. 2004;111:1340-3.

26-Benson SE, Schlottmann PG, Bunce C, Xing W, Charteris DG. Optical coherence tomography analysis of the macula after scleral buckle surgery for retinal detachment. Ophthalmology. 2007;114:108-12.

27-Ricker LJAG, Noordzij LJ, Goezinne F, Cals DW, Berendschot TT, Liem AT, et al. Persistent subfoveal fluid and increased preoperative foveal thickness impair visual outcome after macula-off retinal detachment repair. Retina. 2011;31:1505-12.

28-Kobayashi M, Iwase T, Yamamoto K, Ra E, Hirata N, Terasaki H. Influence of submacular fluid on recovery of retinal function and structure after successful rhegmatogenous retinal reattachment. PLoS One. 2019;14:e0218216. doi: 10.1371/journal.pone.0218216.

29-Colenbrander MC. Hydrostatische Druckverhältnisse im Auge. Fluorescein erscheint erst in der Aderhaut und dann in der Netzhaut - Wie kann man das erklären? [Hydrostatic pressures within the eye (author's transl)]. Klin Monbl Augenheilkd. 1975;167:94-101.

30-Nickla DL, Wallman J. THE MULTIFUNCTIONAL CHOROID. Prog Retin Eye Res. 2010;29:144-68.

Legends

Fig.1- Serial horizontal foveal OCT scans in this focal SRF type denoted recovery of the EZ at 20m. There was a transient CME appearing at 5m and lasting two months. LHEP appeared at 39 m. The patient presented with one week duration of superior 6-clock-hour RRD from 3 nasal and temporal horseshoe tears. During vitrectomy, the retina was flattened using perfluorooctane, followed by exchange for SF6 gas. Log Mar vision improved from 0.54 to 0 at the last follow-up 48 m postvitrectomy.

Fig.2- Serial horizontal foveal scans at 1, 5, 8 and 14 months after retinal surgery for right eye RRD. Multifocal SRF with ERM with gradual resolution of SRF 14 m postoperatively and central delay in the complete restoration of the ellipsoid zone. ELM is fully restored. This patient presented with 5 days of visual loss. The macula-off RRD involved 6 clock hours inferiorly and nasally with one inferonasal tear underwent scleral buckle with transcleral subretinal drainage. No gas was injected. The patient received no treatment for the SRF. Log MAR visual acuity improved from 1.3 to 0.54 at 60 months of follow-up.

Fig.3- Serial horizontal OCT scans of this multifocal type (star sign) of SRF. SRF resolution is noted at 29m. There is incomplete restoration of ELM and EZ layers at 35m (arrows). This patient had macula-off 6-clock-hour RRD of 120 days duration with a single supertemporal break. The patient underwent scleral buckle and gas injection without SRF drainage and assuming prone position postoperatively. Log MAR visual acuity improved from 3 to 0 36m postoperatively.

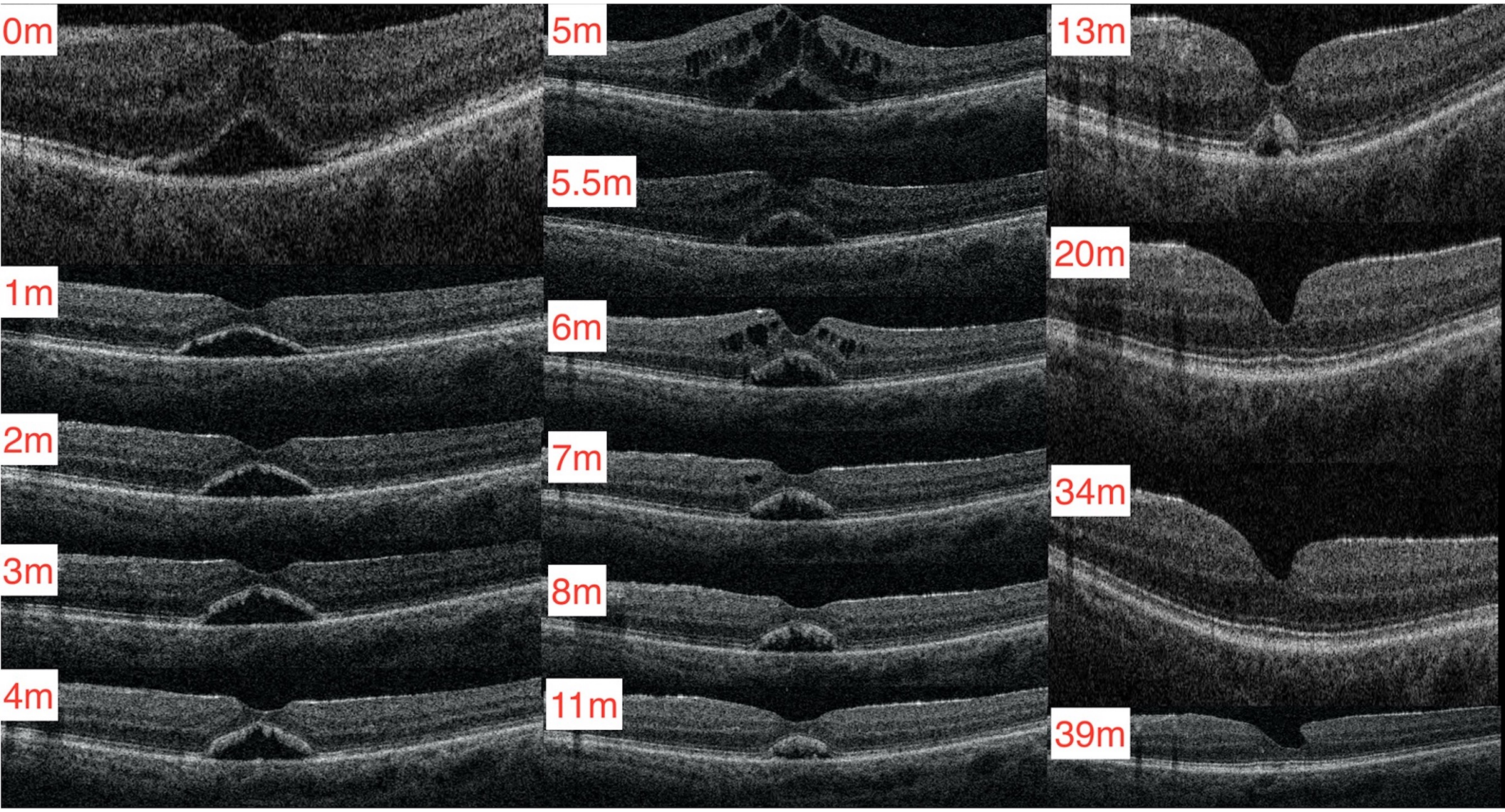
Fig.4- Serial horizontal foveal OCT scans of the right eye at 1,2,4,6 and 12 months after retinal surgery. There is diffuse type of SRF with gradual decrease in SRF and complete restoration of the ellipsoid zone one year after surgery for RRD. This patient developed macula-off RRD of 4 days duration from inferior retinal tear. The patient underwent a combined scleral buckle vitrectomy with intraoperative use of perfluorooctane and injection of C3F8 gas at end of surgery. Log MAR visual acuity improved from 0.54 to 0 at the one-year follow-up.

Summary Box

- **What is already known:** Persistent subretinal fluid leads to poor vision and there is no established therapeutic modality to fasten its resolution.
- **What this study adds:**
- Persistent subretinal fluid had a good visual prognosis with faster recovery in younger patients and in eyes with macula-on rhegmatogenous retinal detachment.
- Ellipsoid zone restoration was faster in eyes with fewer tears.
- Persistent subretinal fluid after successful reattachment surgery has a self-limiting course; There is no need for surgical intervention in persistent subretinal fluid.

Availability of Data and Materials

The complete data can be shared upon request to the corresponding authors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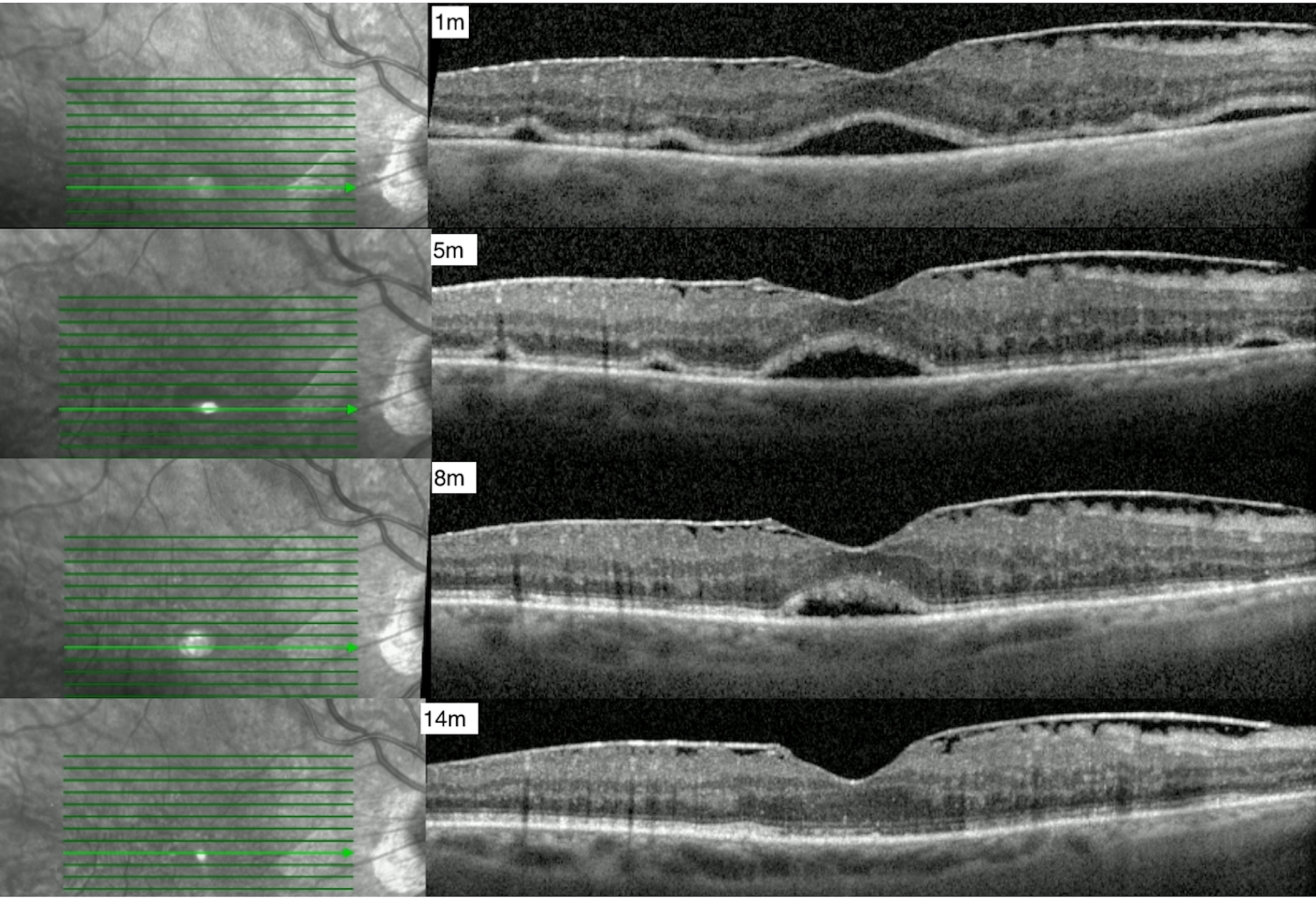
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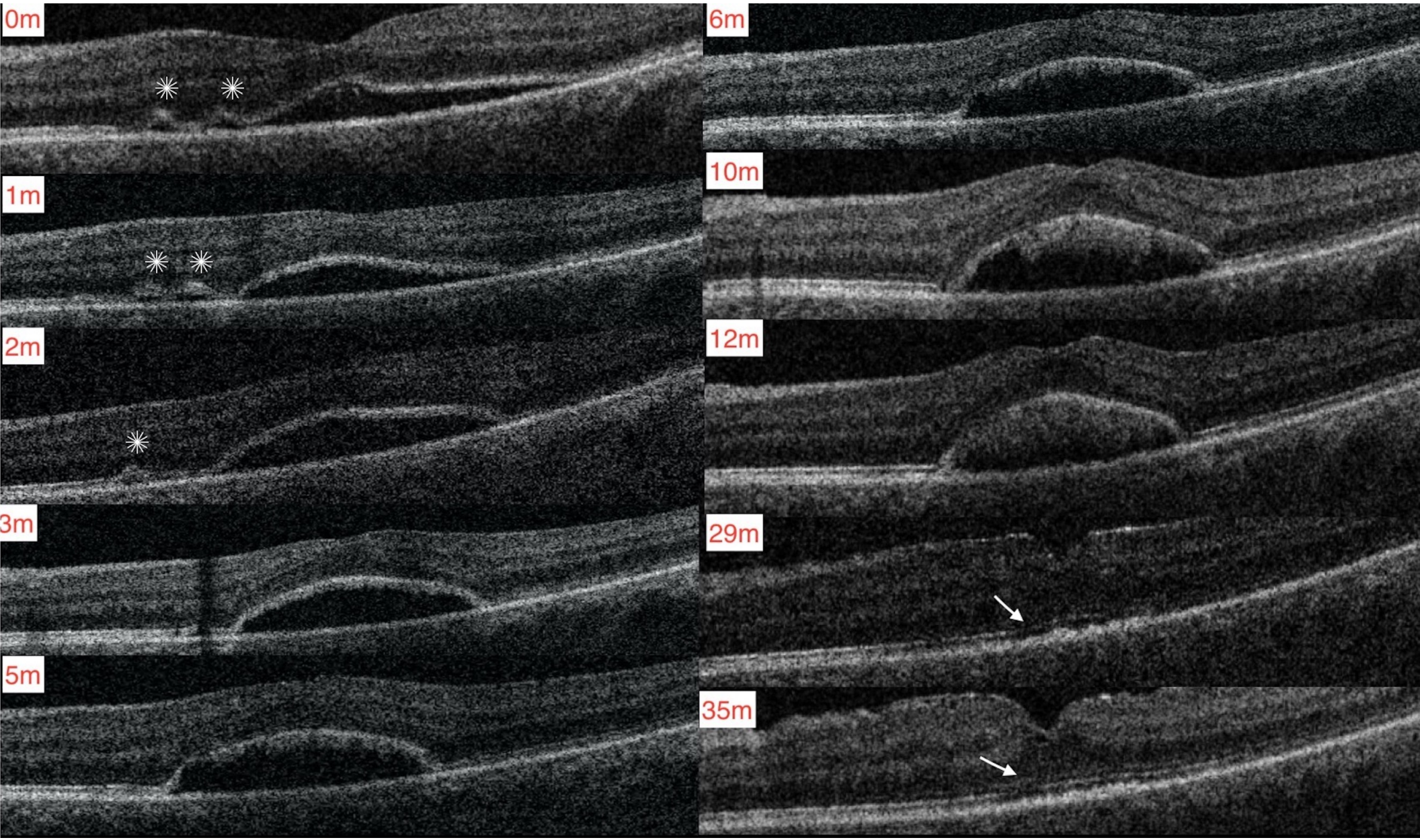
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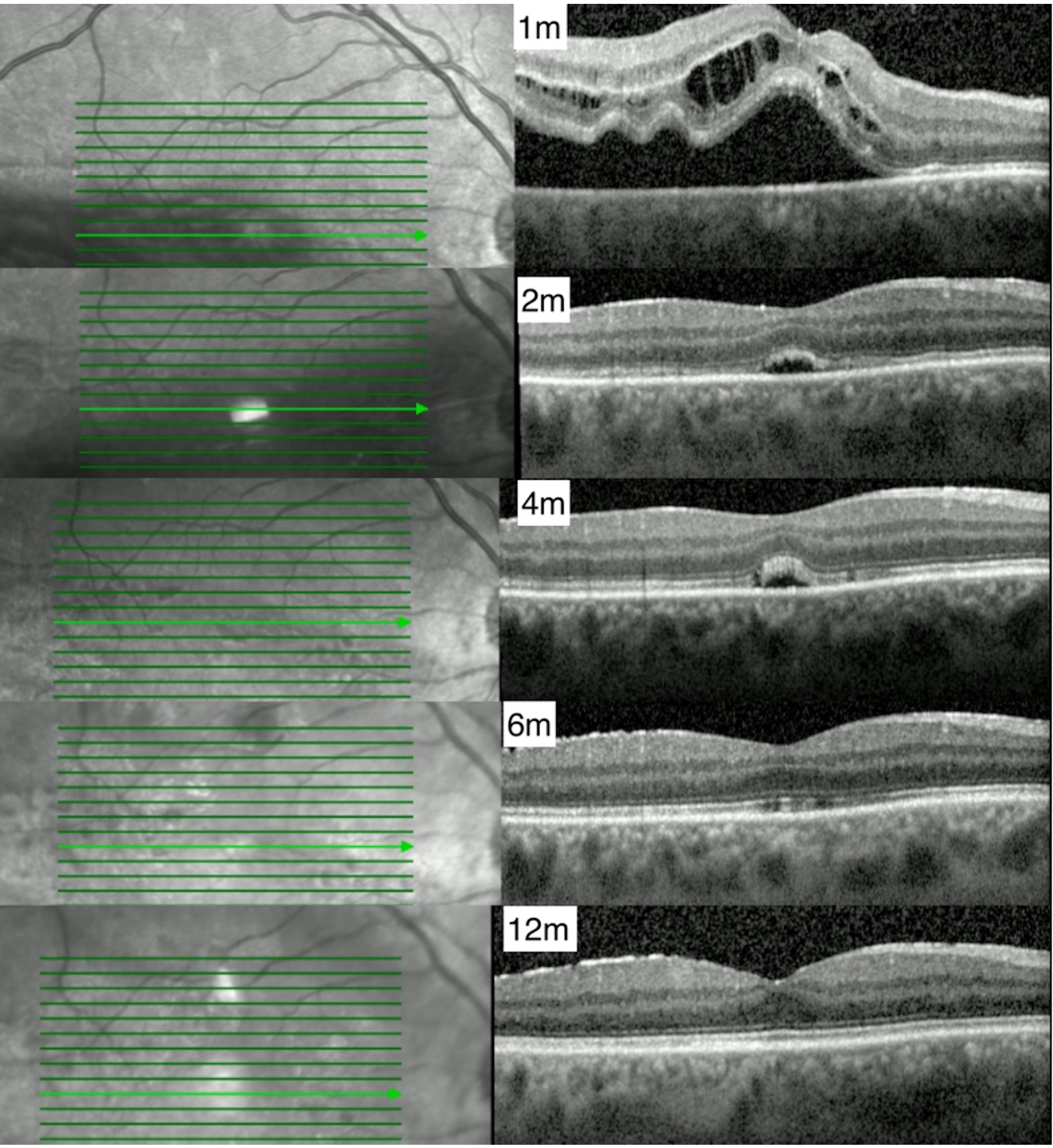
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Table 1- Factors involved in delayed absorption of SRF after RRD repair (Asterisk represents a significant correlation; p-value was calculated using one-way ANOVA or Chi square)

	Focal bleb	Multifocal blebs	Diffuse bleb	Total	p-value
Gender M:F	20:9	13:22	22:17	55:48	0.035*
Age (year)	59.2±11.5	51.6±16.1	48.7±15.5	52.7±15.2	0.016*
Caucasian Yes:No	27:2	32:3	35:4	94:9	0.89
Diopter	-2.0±3.1	-2.4±2.8	-2.8±3.3	-2.5±3.1	0.62
Phakia:Pseudophakia	23:6	31:4	36:3	90:13	0.27
No. Retinal Tears	1.4±0.7	1.7±1.2	1.5±0.9	1.5±1.0	0.33
Superior Tears	13:14	25:10	22:17	60:41	0.16
Temporal Tears	19:8	24:11	30:9	63:28	0.70
Superior RRD	14:13	25:10	22:17	61:40	0.03*
Temporal RRD	22:5	25:10	32:7	81:22	0.48
No. clock hour RRD	5.1±1.6	5.5±2.0	5.2±1.6	5.2±1.8	0.68
Macula-off RRD Yes:No	25:4	31:4	31:8	87:16	0.53
Duration RRD (days)	12.6±31.3	23.2±32.2	44.9±118.4	28.9±78.7	0.25
Scleral Buckle PPV Scleral Buckle PPV Pneumatic retinopexy	4 16 8 1	14 12 6 3	21 12 3 3	39 40 17 7	0.023*

Drainage of subretinal fluid or intravitreal tamponade Yes:No	22:7	27:8	25:14	74:29	0.39
Gas injection intraoperatively Yes:No	21:8	24:11	22:17	67:36	0.34
Prone position after surgery Yes:No	15:14	17:18	15:24	47:56	0.51
Medical therapy for SRF Yes:No	5:24	9:26	6:33	20:83	0.50
SRF resolution time (months)	10.1±6.4	12.4±5.7	11.0±6.9	11.2±6.4	0.34
EZ reformation time (months)	10.8±6.0	11.9±5.0	12.5±8.8	11.7±6.9	0.60
Initial BCVA (log MAR) (1 month after surgery)	0.99±0.84	1.13±0.80	1.10±0.97	1.08±0.87	0.76
Final BCVA (log MAR)	0.23±0.28	0.18±0.23	0.22±0.21	0.21±0.24	0.70
Follow-up (months)	26.1±23.1	24.3±22.9	25.7±22.5	25.4±23.1	0.96

Table 2- Multivariate analysis of variables related to anatomic and visual outcome (Asterisk represents significant or near significant correlations; values represent Odds Ratio (OR) followed by 95% confidence interval (CI); BCVA are expressed in log MAR.

	Final BCVA	SRF resolution time	EZ restoration time
Age	OR=1.16 (95% CI 0.53-2.55) P=0.013*	P=0.60	P=0.44
No. retinal tears	P=0.84	P=0.87	OR=0.67 (95%CI 0.29-1.52) p=0.030*
RRD duration	OR=0.99 (95%CI 0.43-2.27) P=0.046*	P=0.12	P=0.90
Macula-off RRD	P=0.20	P=0.52	OR=0.26 (95%CI 0.08-0.88) P=0.056*
Prone position after surgery	P=0.34	OR=1.32 (95%CI 0.56-3.11) P=0.070*	P=0.20
Initial BCVA (1 month after surgery)	OR=3.28 (95%CI 1.44-7.47) P=0.022*	P=0.80	P=0.88
Final BCVA		OR=0.46 (95%CI 0.21-1.05) P=0.049*	OR=0.58 (95%CI 0.26-1.30) P=0.037*
SRF resolution time	OR=0.46 (95%CI 0.21-1.05) P=0.049*		P<0.001*

Table 3- Literature review of residual SRF after retinal surgery for RRD (SB=scleral buckle; PPV=pars plana vitrectomy; SBPPV=scleral buckle combined with pars plana vitrectomy; G=intravitreal gas injection; Drainage=Drainage of subretinal fluid during surgery; tamponade=use of intraocular tamponade to flatten the retina during surgery; F=focal group; M=multifocal group; D=diffuse group; BCVA= best-corrected visual acuity in Log MAR.

Author (first)	No. cases	Male %	Age	High myopia	Phakia	No. Tears	Superior Tears	Superior RRD	Clock hour RRD	Macula-off RRD	Duration RRD (days)	SB PPV G SBPPV	Drainage OR tamponade	SRF resolution (months)	Initial BCVA	Final BCVA	Follow-up (months)	SRF type F,M,D
Long [3]	28									100%		SB100%						
Woo [16]	42	51.30 %	39±29	35.90 %						100%	12±17	SB100%	7.70%	8.6±4.5	1.16±0.77	0.18±0.19	20±12	F33.3 % D66.7 %
Benson [26]	54											SB100%			0.3			F24% M27.8 % D48.1 %
Fu [6]	49	53.10 %	43.5±10.2	46.90 %	87.80 %	1.5±0.54			6.9±2.2	100%	14.8±12.3	SB100%	10.20%	13.2±10.0	1.25±0.30			F55.1 % M18.4 % D26.5 %
Desatnik [17]	7				100%	1.6			5.6	57%		G100%	0%	18.9	0.3	0.18		
Kim JM [13]	18	61.10 %	40.4±18.0	44.40 %	77.80 %	1.9±1.2		77%	5.3±0.2	61.10 %		SB83.3% PPV16.7%	66.70%		0.37± 0.51	0.09±0.14		
Kim Y-K [10]	40	60%	36.6±20.2	27.90 %	97.50 %	2.1±1.4	65%		5.5±2.1	87.50 %	13.9±24.6	SB70% PPV30%		13.1±6.1	1.13±0.83	0.21±0.34	15.4±9.1	
Kang [7]	11	54.50 %	51.2±13.2			1.7±0.8			6.3±2.7		11.8	SB100%		4.7±3.4	0.29±0.35	0.17±0.19	17.0±7.2	

Hagimura [15]	7									100%		SB100%						F57.1 % D42.9 %
Ricker [27]	37	67.60 %	55±14		78%				5.3±1.6	97%	6.1±5.6	SB100%	94%	8	1.10±0.94			
Mimouni [12]	23	56.50 %	47.8±18.7	65.20 %	87%	1.3±1.1		69.60%		91.30 %	7.6±8.8	PPV87% SBPPV13%	43.50%	5.9±3.7	1.15±0.99			
Feo [18]	23	52.20 %	43.6±16.5	26.10 %	100%	1.7±1.0		34.70%	5.7	100%	4.3±2.6	SB100%	13.04%		0.94±0.59	0.22±0.16	14.9±7.5	
Wang [8]	28	57.10 %	29.8±8.3							100%	12.1±6.8	SB100%	100%	6.3±2.3	0.35±0.27	0.30±0.23	28.9±3.4	F17.9 % D82.1 %
Wolfensberger [25]	6									100%	7.4±6.0	SB100%			1.3±0.8	0.13±0.17		
Gharbiya [14]	40	57.50 %	57.2±15.5		75%				6.6±2.1	100%		SB100%	100%	7.8±4.4				
Gibran [20]	22	81.80 %	64		90%						6	SB100%	77.20%		1	0.4	18	
Otsuka [21]	8	62.50 %	56.9±11.8	20.00 %			50%			87%	8.1±6.9	SBPPV100 %	62.50%		0.05±0.07			
Kobayashi [28]	15	66.70 %	43.2±16.9	26.70 %				40%	5.2±1.9	100%	13.1±13.4	SB86.7% PPV13.3%	73.30%		0.53±0.38	0.15±0.23	12	
Mansour (current study)	103	53.40 %	52.7±15.2	12.90 %	87%	1.5±1.0	58%	59%	5.2±1.8	84%	28.9±78.7	SB37.9% PPV38.8% SBPPV16.5 % G6.8%	71%	11.2±6.4	1.08±0.87	0.21±0.24	25.4±23.1	F28.2 % M35.0 % D37.9 %
Total	**561**	**57.90 %**	**47.3±18.6**	**29.90 %**	**87%**	**1.66±1.04**	**59%**	**57%**	**5.7±2.0**	**92.60 %**	**15.2±43.6**	**SB78.8% PPV13.7% SBPPV5.0 % G2.5%**	**59%**	**9.77±6.68**	**0.76±0.79**	**0.20±0.24**	**21.1 ±16.1**	**F30.7 % M24.7 % D44.5 %**

1