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INCREASED RISK OF CYSTOID MACULAR EDEMA AFTER CATARACT SURGERY IN EYES PREVIOUSLY VITRECTOMIZED FOR IDIOPATHIC EPIRETINAL MEMBRANE

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Purpose: To assess the rate and risk factors of cystoid macular edema (CME) both after isolated vitrectomy and after subsequent phacoemulsification in eyes with primary noncomplicated rhegmatogenous retinal detachment (RRD) or idiopathic epiretinal membrane (ERM).

Methods: Retrospective observation of institutional patients undergoing vitrectomy for RRD or vitrectomy with internal limiting membrane peeling for ERM from 2016 to 2021, further analyzing those who later underwent phacoemulsification. The CME rate was assessed within the first 6 months after both vitrectomy and cataract surgery.

Results: The authors included 187 phakic eyes with ERM and 311 with RRD undergoing isolated vitrectomy. Postvitrectomy CME occurred in 12.8% of ERM cases compared with 1% in RRD cases ($P < 0.0001$). Stage-4 ERMs and intraoperative laser were found associated with CME. After uncomplicated phacoemulsification, the CME rate was higher in eyes vitrectomized for ERM (13.8%) compared with RRD (2%, $P = 0.0055$). Postvitrectomy CME was found to be associated with an increased risk of postcataract CME (odds ratio 13.588, $P = 0.0187$).

Conclusion: In eyes undergoing phacoemulsification postvitrectomy, the risk of CME is higher when vitrectomy was performed for ERM compared with RRD. The ERM-related intraretinal changes, together with the required surgical stress, may play a role in making these eyes more susceptible to CME.

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Pseudophakic cystoid macular edema (CME) is the most common cause of visual deterioration after uncomplicated cataract surgery, with rates ranging from 0.1% to 3.8%, specifically referred to as Irvine–Gass syndrome.[1–3]

Cystoid macular edema may also complicate other procedures, notably glaucoma surgery,[4] keratoplasty,[5,6] and vitreoretinal surgery, including macular surgery[7–9] and *ab externo*[10,11] or *ab interno*[12] repair of retinal detachment. Macular edema after vitreoretinal surgery has been reported to occur with various, but higher, frequencies, from 10% to 47%.[8,9,13,14]

Performing cataract surgery in previously vitrectomized eyes combines two risk factors—macular surgery and phacoemulsification—which may cumulatively increase the chance of postsurgical CME. Studies have indeed demonstrated that performing cataract surgery in eyes that underwent prior vitreous surgery for macular disease reveals a higher rate of CME (15%–42%).[7,15]

However, the evidence on the postsurgical CME rates in vitrectomized eyes is relatively limited in the

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literature. Therefore, the main purpose of this study was to investigate the frequency and distribution of CME after phacoemulsification in eyes previously vitrectomized for various retinal diseases, focusing on idiopathic epiretinal membrane (ERM) and primary noncomplicated rhegmatogenous retinal detachment (RRD).

Materials and Methods

In this longitudinal retrospective study, we reviewed the data of all the institutional patients operated from January 2016 to December 2021 at the Vitreoretinal Surgery Division of San Raffaele Scientific Institute, a tertiary referral center.

Ethics

All the procedures performed involving human participants were in accordance with the ethical standards of the Institutional Review Board of the San Raffaele Scientific Institute and with the 1964 Declaration of Helsinki and its later amendments. All patients, at the time of hospital admission, signed a general informed consent form that was specifically designed and approved by the Institutional Review Board of the San Raffaele Scientific Institute solely for observational retrospective studies.

Study Participants

Inclusion criteria.

- Adult patients scheduled for vitrectomy for ERM or RRD.
- Cases undergoing an isolated vitreoretinal procedure (excluding combined phacovitrectomies).

Exclusion criteria.

- Pseudophakic eyes.
- Spherical equivalent >-6.5 diopters or axial length >26 mm.
- Secondary ERM (e.g., diabetic retinopathy, uveitis, retinal vein occlusion, retinal dystrophies, and trauma).
- Uncompensated glaucoma.
- Complicated cases of RRD, including: traumatic or relapsed cases, presence of proliferative vitreoretinopathy $>$ stage A,[16] giant retinal tear, retinoschisis-associated RRD, coloboma-associated retinal detachment.
- Postvitrectomy complications, such as RRD recurrence, vascular occlusions, optic neuropathies, etc.
- Imaging acquisition jeopardized by optical media opacity (cornea or lens).
- Individuals with diabetes without retinopathy.

Study Protocol

We longitudinally evaluated the frequency of postsurgical CME following uncomplicated vitreoretinal procedures, grouping eyes according to the retinal pathologic conditions (ERM and RRD).

Eyes later undergoing uncomplicated phacoemulsification for visually impairing cataracts were assessed for CME within the first 6 months after cataract surgery.

All institutional patients underwent a preoperative ophthalmologic evaluation, then standard controls at 1 week and at 1, 3, 6 and 12 months, then as required per clinician's decision. Spectral-domain optical coherence tomography were performed on every visit except at 1 week. For this reason, this point of observation was excluded from the analysis.

Surgical Procedure

Surgeries were conducted under retrobulbar block by senior vitreoretinal consultants (M.C., L.I.) using the Constellation machine (Alcon Surgical, Fort Worth, TX), with a 23 gauge or 25 gauge according to the surgeon's preference. Perfluorocarbon liquid (perfluorodecalin; Bausch+Lomb, Rochester, NY) was used at the surgeon's discretion. Membranes (ERM and internal limiting membrane) were peeled when needed with the conjugated dye TWIN (AL.CHI.MI.A., Italy). To facilitate sclerotomy sealing, fluid–air exchange was routinely done at the end of all macular surgeries and, if required, air–gas exchange was also performed in selected cases. For tamponade with gas, either C_3F_8 or SF_6 (AL.CHI.MI.A. S.R.L., Italy) was used, respectively, diluted at 6% and 10%. Phacoemulsification was carried out under topical anesthesia using the Centurion machine (Alcon Surgical), with the same standard surgical procedure.

Data Collection

Data gathered during preoperative examination included general and ocular medical history, distance best-corrected visual acuity (BCVA), and spectral-domain optical coherence tomography. Best-corrected visual acuity is regularly measured in dedicated offices with continuously monitored luminance, using the Early Treatment in Diabetic Retinopathy

Study charts. The Snellen notation was converted into logMAR for statistical purposes.

Surgery-related variables for idiopathic ERMs included stage (Govetto classification[17]), number of dye injections, and surgery duration. Surgery-related variables for RRD were macula status, number of involved quadrants, type of tamponade and retinopexy, use of perfluorocarbon liquid, and surgery duration.

Spectral-domain optical coherence tomography images were acquired using the Spectralis device (Heidelberg Engineering, Heidelberg, Germany). Macular raster scans were acquired using the follow-up function. The central circle on the Early Treatment in Diabetic Retinopathy Study map was considered as the central foveal thickness (CFT) value. The presence of CME was assigned only in cases that showed, within the first 6 months of follow-up: 1) a new onset of macular hyporeflective cystoid intraretinal spaces at spectral-domain optical coherence tomography that were not present before vitrectomy (Figure 1); 2) definite worsening in size and number of pre-existing cystoid spaces with an increase in CFT of 10% or more over baseline.

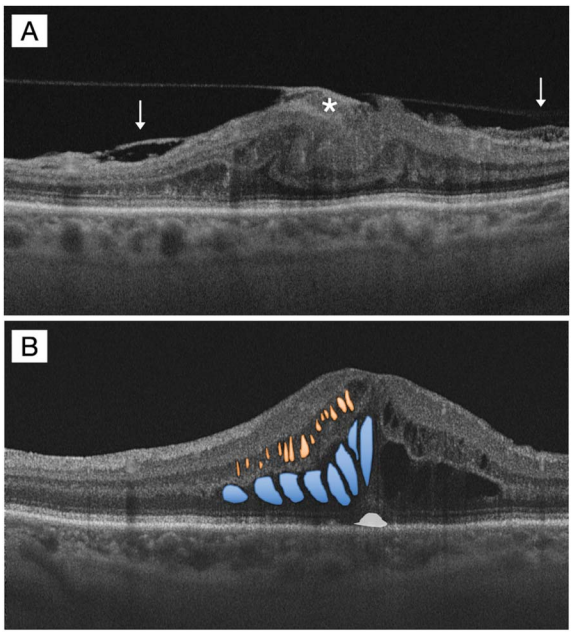

Fig. 1. Example of postsurgical CME. Spectral-domain optical coherence tomography of a case of a Stage-4 idiopathic ERM undergoing vitrectomy (**A**). Together with a partially detached ERM (white arrows) combined with a vitreomacular traction, a few peculiar characteristics can be appreciated: the loss of the foveal depression, the retinal layering disorganization, and the ectopic inner foveal layer (white asterisk). **B.** The same case 1 month after vitrectomy with ERM peeling presenting CME. Hyporeflective roundish spaces are evident in the Henle (blue) and in the inner nuclear (orange) layers, together with a tiny neuroretinal central elevation (grey).

Medication

Standard therapy after vitreoretinal procedure was association of netilmicin and dexamethasone 4 times a day for 3 weeks and tropicamide twice a day for 1 week; after cataract extraction was the combination fluoroquinolone or chloramphenicol and dexamethasone 4 times a day for 1 week, followed by nonsteroidal anti-inflammatory agents for 3 weeks.

The treatment regimen for the management of CME in our center is dexamethasone 0.2% drops 4 times a day plus bromfenac 0.9 mg/mL drops twice a day for 4 weeks. According to the clinician's judgement, treatment can be halted, tapered, or switched to second-line agents that includes intravitreal steroids (triamcinolone acetonide 80 mg/mL or dexamethasone implant 700 μg).

Statistical Analysis

Statistical analyses were performed using Past (Palaeontologia Electronica) version 4.11.

The alternative hypothesis H1 was that the CME rate after cataract surgery might statistically differ between the study groups. Based on previously published data,[1,2,5,13,14] we calculated that to detect, between the study groups, a clinically significant difference of $>15\%$ in the CME rate (effect size), with an 80% power and $\alpha = 0.05$, at least 23 patients per group would have been required. Distribution normality was tested with the Shapiro–Wilk test. The Chi-squared or Fisher exact test was used to compare noncontinuous variables. When parametric analysis was possible, the *t*-test for unpaired data or the one-way analysis of variance were used for comparisons between groups, whereas the Mann–Whitney *U* test or the Kruskal–Wallis test was applied to assess the significance of such differences when parametric analysis was not possible. Dunn post hoc with Bonferroni corrected *P* values was adopted to assess the differences between pairwise groups. In all analyses, the Bonferroni correction was adopted for *P* values, and only <0.05 were considered significant.

Results

Population

Figure 2 reviews the protocol enrolling process. We found 1,247 eyes of 1,199 patients operated for ERM, of which 187 eyes of 180 patients were eventually eligible for the study. Among 862 cases of phakic primary RRD, 311 eyes of 305 patients fulfilled the enrollment criteria. Rhegmatogenous retinal detachment group turned out to be slightly younger (Table 1).

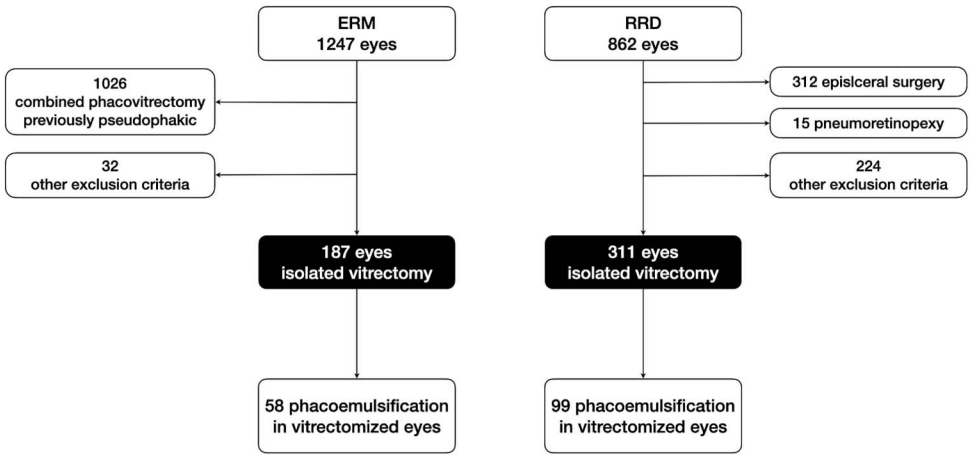

Fig. 2. Flow chart of the study design. Flow chart illustrating the study design. According to the inclusion/exclusion criteria, the sample was cleaned to obtain the sample of eyes affected by idiopathic ERM and non-complicated RRD that underwent isolated vitrectomy (without cataract surgery, black boxes). Among the latter, those eyes that were subsequently operated for cataract were also analyzed.

Surgeries

All ERM cases included in the study were idiopathic and phakic, as per protocol. The distribution of ERM stages was as follows: 12 (6.4%) in 1, 35 (18.7%) in 2, 125 (66.8%) in 3, 15 (8%) in 4. At the conclusion of surgery, 156 eyes (83.4%) received air, 21 (11.2%) balanced saline solution, and the remaining 10 eyes (5.3%) SF_6 because of the intraoperative detection of rhegmatogenous lesions. All the latter cases were treated with intraoperative laser retinopexy. Average surgery duration was 23 ± 4 minutes. The number of required dye injection was 1.13 ± 0.41.

All the included RRD cases confirmed to be, as per protocol, noncomplicated and with a 100% single-surgery attachment rate. The majority (n = 256, 82.3%) were macula on. In total, 92.6% (n = 288) received C_3F_8 and 7.4% (n = 23) received SF_6. No eye was treated with silicone oil in our series. Perfluorocarbon liquid was used in 280 procedures (90.0%). The most employed retinopexy technique turned out to be cryo (n = 187, 60.1%), followed by a combination of laser + cryo (n = 85, 27.3%), and by laser only (n = 39, 12.5%). Internal limiting membrane peeling was never performed in our RRD series. Mean surgery duration was 41 ± 13 minutes.

We found 58 eyes out of those vitrectomized for ERM and 99 eyes out of those vitrectomized for RRD that underwent uncomplicated phacoemulsification (Figure 2). Phacoemulsification was done 485 ± 425 days (∼1.3 years) after vitrectomy (range 27–1829; median 390), without time differences between groups.

Postsurgical Cystoid Macular Edema

After isolated vitreoretinal procedure. Because only a few RRD cases were presurgically examined with spectral-domain optical coherence tomography, the baseline CFT data of these eyes were not considered. The CFT of these RRD eyes remained unchanged from 1 month till the time of cataract extraction. Eyes with ERM although disclosed a continuously reducing CFT after vitrectomy till the time of phacoemulsification (see **Table**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/C413). At the time of cataract surgery, eyes vitrectomized for ERM disclosed a thicker macula than those for RRD ($P < 0.0001$).

The rate of postvitrectomy CME turned out to be higher in eyes with ERM (12.8%, n = 24) compared with eyes operated for RRD (1%, n = 3; $P < 0.0001$) (Figure 3A).

Out of the 3 eyes disclosing CME after RRD repair, all were macula on, and retinopexy was done with cryo. Macular edema was found in all cases at 1 month.

Out to the 24 eyes that presented CME after ERM peeling, 5 were in Stage 4 and 19 were in Stage 3. Cystoid macular edema was found in 17 cases (70.8%)

Table 1. Demographics of the Two Investigational Groups (Idiopathic ERM and RRD) That Were Phakic and Underwent an Isolated (Without Cataract Surgery) Vitreoretinal Procedure

	Idiopathic ERM	RRD	*P*
Gender (female:male)	98:82	148:163	0.1602
Age (years)	61.2 ± 4.9 Range 46–68; median 62	57.8 ± 6.7 Range 44–69; median 58	0.0194

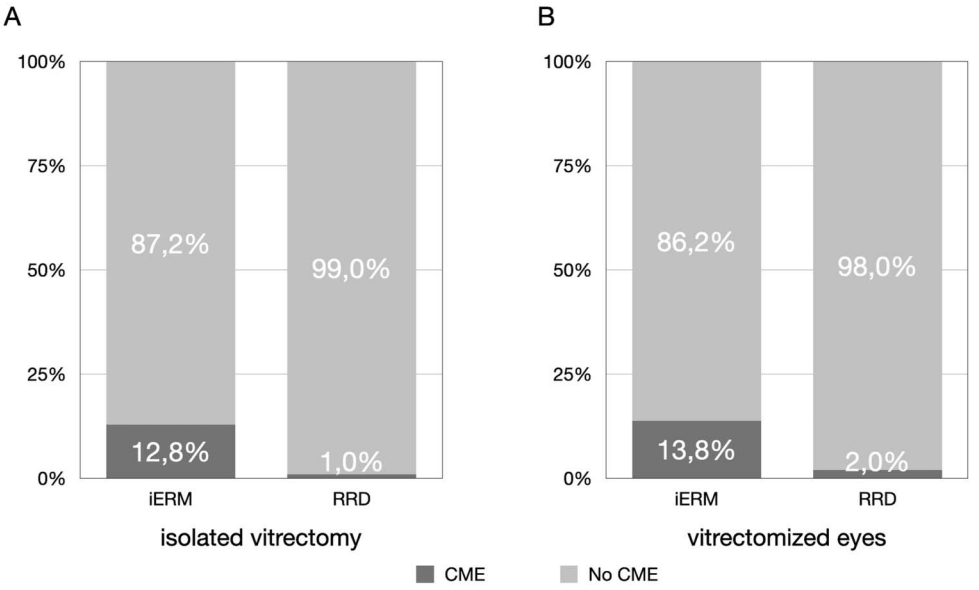

Fig. 3. Rate of postsurgical CME. The histograms represent the rate of postsurgical CME in eyes affected by idiopathic ERM and noncomplicated RRD. The rate of CME is higher in eyes with ERM both after isolated vitrectomy (without cataract surgery [**A**]) and after phacoemulsification in vitrectomized eyes (**B**).

at the 1-month control and in 7 eyes (29.1%) at the 3-month control.

After cataract surgery (vitrectomized eyes). The CME rate turned out to be significantly higher in eyes previously vitrectomized for ERM (13.8%, n = 8) compared with eyes previously vitrectomized for a primary noncomplicated RRD (2%, n = 2; $P = 0.0055$) (Figure 3B). The odds ratio of developing CME is 7.76 (95% CI, 1.588–37.93; $P = 0.0113$) in eyes previously vitrectomized for ERM.

Macular edema was found in all cases at the 1-month visit. Out of these 8 eyes (previously vitrectomized for ERM) that presented postcataract CME, 7 (87.5%) were those that already had CME after the vitreoretinal procedure. The 2 eyes previously vitrectomized for RRD that disclosed postcataract CME had, on the contrary, a new onset of macular edema.

The average CFT of eyes previously operated for ERM showed a significant, but moderate, increase and decrease, remaining overall stable between the precataract time and the last follow-up ($P = 0.9999$). The CFT of eyes previously operated for RRD remained overall stable after cataract surgery (see **Table**, **Supplemental Digital Content 2**, http://links.lww.com/IAE/C414).

Treatment

All the eyes that developed CME after ERM surgery received an initial topical therapy according to the reported regimen. Most (91.6%, n = 22) gradually and completely resolved the edema with topical therapy within 6 months from presentation. Two eyes were treated with a single 700 μg dexamethasone implant injection, done after 2 months of topical therapy. One eye resolved the edema, whereas the second disclosed an overall chronic and poorly responsive edema that was found to be still present at the last available follow-up visit also after phacoemulsification. Vitrectomized eyes for ERM experiencing CME after cataract surgery all resolved their fluid just with topical therapy.

All the eyes experiencing CME after RRD repair were accordingly treated, as per protocol, with topical therapy, and completely resolved the edema. The eyes that presented CME after cataract surgery similarly recovered just with topical therapy.

Visual Acuity

After vitrectomy, the uneventful ERM cases (no CME) continuously improved vision from baseline to 6 months ($P < 0.0001$ per each pairwise comparison). By contrast, the ERMs presenting postvitrectomy CME showed a static trend, with only a moderate improvement at the 6-month control ($P = 0.03478$). Its BCVA turned out indeed significantly worse compared with the no-CME group in any time-point assessment (Figure 4).

Best-corrected visual acuity after phacoemulsification kept significantly worse in eyes disclosing CME ($P = 0.0001$).

Average baseline BCVA in the RRD group was 0.15 ± 0.32 logMAR, which, in turn, was higher in the macula-on (0.00 ± 0.02 logMAR) compared with the macula-off subgroup (0.84 ± 0.10 logMAR; $P <$

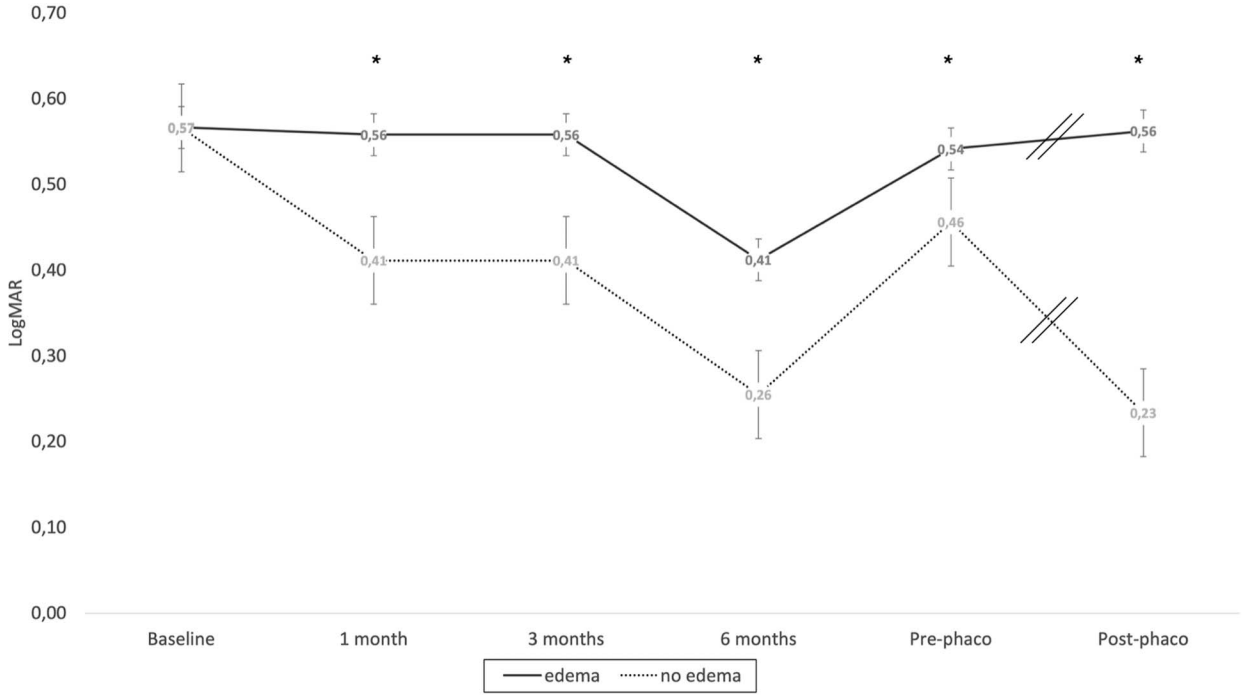

Fig. 4. Best-corrected visual acuity changes in eyes with idiopathic ERMs. The graph shows the trends of the average best-corrected visual acuity in eyes undergoing vitrectomy for idiopathic ERM. The dashed lines depict the subgroup experiencing postsurgical CME, whereas the solid lines describe the subgroup with an unremarkable outcome. Visual acuity showed a significant improvement till the 6-month visit, while a subsequent deterioration because of cataract formation. Eyes presenting CME disclosed a significantly lower (asterisks) visual function in any of the postvitrectomy visits. After cataract (the double forward slashes point a change in the sample numerosity), the visual discrepancy is remarkable.

0.0001). Owing to the reduced number of eyes presenting postvitrectomy and postcataract CME in the RRD group, these data were not averaged.

Regression Analysis

The logistic regression analysis found that higher ERM stages were associated with an increased rate of postsurgical CME (coefficient 1.5476, odds ratio 4.7 [95% CI, 1.9098–11.5671], $P = 0.0008$). The intraoperative use of laser was also found to be associated with CME occurrence ($P < 0.0001$). No other previtrectomy characteristics (Table 2) were associated with the chance of CME occurrence, neither in ERM nor in RRD.

The occurrence of postvitrectomy CME was found to be associated with an increased risk of postphacoemulsification CME (coefficient 2.3507, odds ratio 13.588 [95% CI, 1.543–119.7], $P = 0.0187$).

Discussion

Owing to its practical convenience, combining phacoemulsification with vitreoretinal surgery has become increasingly common. Although this combined approach is elegant and effective, it may expose patients to an increased risk of CME, as both surgeries carry predisposing factors for this condition. In particular, it has been shown that performing just cataract surgery in eyes affected by idiopathic ERM increases the risk of macular edema up to 15.7%.[15]

A logical strategy to reduce this risk is to perform vitrectomy first, followed by cataract surgery at a later date. Although this option may seem reasonable, it carries a high likelihood of rapid cataract development, with incidences of up to 50% after the first year and 85% within 5 years.[18] Furthermore, whether considering the latter option, it shall also be considered that phacoemulsification done in a vitrectomized eye for ERM itself increases the risk of CME.[7]

Being both strategies burdened by the chance of postsurgical CME, the management of phacoemulsification associated with vitreoretinal surgery remains hence controversial.

In our study, we observed a CME rate of 13.8% after uncomplicated phacoemulsification in eyes vitrectomized for idiopathic ERM, which is comparable with the 12.8% rate after isolated vitreoretinal procedures. These frequencies align with those previously published by Frisina[8] and Iuliano.[9] A recent meta-analysis, furthermore, also supports the equivalence,

Table 2. Association of Baseline (Previtrectomy) Clinical Characteristics and Occurrence of CME

	Baseline Clinical Characteristic	*P*
ERM	Age	0.7881
	Gender	0.8791
	Baseline BCVA	0.5871
	Surgery duration	0.4978
	Laser retinopexy	**<0.0001**
	Stage	**0.0008**
	No. of dye injections	0.8810
RRD	Age	0.5989
	Gender	0.9473
	Baseline BCVA	0.3865
	Surgery duration	0.1758
	Macula status	0.5733
	No. of detached quadrants	0.4832
	Type of tamponade	0.8999
	Type of retinopexy	0.1990
	Use of PFCL	0.4922

Bold *P* values denote significant associations.
PFCL, perfluorocarbon liquid.

in CME occurrence, between sequential and combined surgeries.[19]

Therefore, given these data, the option of combined surgeries (phacovitrectomy) in idiopathic ERMs seems to be a reasonable option because it exposes patients to a single surgical stress, hence to a single inflammatory "shot." This consideration shall be taken though cautiously, especially in relation to advanced-stage ERMs, where the risk of CME after surgery can be as high as 57.1%.[9]

By contrast, the risk of CME after RRD repair is less straightforward. Reported CME rates in the literature indeed vary widely, from 9.6% to 31%.[12,20–23] In our series, we although observed a lower rate (1%) of CME after primary noncomplicated RRD repair, which may appear noticeably conflicting. This discrepancy may be explained by our study's exclusion of more complex RRD cases, such as those with severe proliferative vitreoretinopathy or recurrent detachments (with multiple surgeries), factors known to increase the risk of CME. By intentionally excluding such complicated cases, we aimed to provide a more accurate estimate of the CME rate for uncomplicated RRD, which justifies the difference in our findings. A recent study by Souissi seems indeed to confirm our findings, reporting comparable rates of CME (3.1%).[24]

In relation to phacoemulsification in eyes vitrectomized for RRD, we found the rate of postcataract CME surgery keeps low (2%), especially if compared with the CME rate in eyes vitrectomized for ERM. In the literature, the likelihood of developing CME after cataract in previously vitrectomized eyes for RRD is reported to be slightly doubled (odds ratio 1.96 by Merad and 2.76 by Starr[21,22]). As noted earlier, the published data on cataract surgery in eyes with previous RRD repair is drawn from heterogeneous RRD cases, which may explain the wider range of reported CME rates.

It might be hence said that eyes vitrectomized for ERM have a significantly higher risk of developing postcataract CME compared to eyes vitrectomized for noncomplicated primary RRD. A few interesting clues might be inferred. It can be postulated that CME occurring after macular surgery might be addressed to the pathologic macular structural changes, including Müller cell dysfunction and intraretinal fibrosis.[25] Moreover, some ERMs are described to cause a breakdown of the blood–retinal barrier, which in turn may lead to an increased vascular permeability, to the release of pro-inflammatory cytokines and, eventually, to an increase in intraocular inflammation.[26,27]

These retinal changes, possibly together with the surgical tissue handling, might raise the risk of developing CME, making the macula more "vulnerable" and susceptible to edema. Our finding, especially regarding the increased risk of CME in relation to the ERM stage (the higher the stage, the higher the risk), corroborates this hypothesis: advanced stages may indeed present a significant breakdown of the blood–retina barrier or a malfunctioning glia, which is involved in the reuptake of intraretinal fluids.[28]

The role of internal limiting membrane peeling remains, however, controversial: considering that in our series, per protocol, we always peeled the internal limiting membrane, it should be also disclosed that eyes undergoing ERM removal without internal limiting membrane peeling might possibly show different rates of postsurgical CME than those found in our study.

The increased susceptibility of operated macula to CME is also supported by the finding that almost all (87.5%) eyes presenting CME after cataract surgery previously presented CME after vitrectomy and ERM peeling.

The present study has several limitations that should be disclosed, including the retrospective design and the limited numerosity. We acknowledge that, owing to the scarcity of isolated vitreoretinal procedures, the inclusion of such cases was relatively rare. Despite these drawbacks, strengths of our study were as follows: a careful patient selection; the exclusion of complicated RRD cases (such as those with proliferative vitreoretinopathy, myopic, or giant retinal tears), which may have jeopardized the results; and the novelty of providing a compared analysis in vitrectomized eyes for different retinal conditions.

In conclusion, the risk of CME after cataract surgery in vitrectomized eyes differs significantly depending on the underlying retinal pathologic conditions. Eyes vitrectomized for idiopathic ERM are at a notably higher risk of developing CME, especially in advanced stages, because of macular structural changes and increased inflammatory responses. By contrast, eyes vitrectomized for primary noncomplicated RRD have a much lower risk of postcataract CME, suggesting that the decision to spare the lens in such cases does not raise concerns about increased CME risk after subsequent cataract surgery.

For ERM cases, whether to perform sequential surgeries (vitrectomy followed by cataract surgery) or combined phacovitrectomy remains a matter of clinical judgment. Both strategies, according to the published data,[9] carry a similar risk of CME, and the choice should be tailored to the individual patient's condition, particularly considering the ERM stage and the potential for macular vulnerability.

Further prospective and randomized studied should be designed to confirm our findings and, possibly, integrate some therapeutic considerations. We, however, believe they can contribute to an improved understanding of this complex but very specific aspect, supporting surgeons in taking responsible decisions.

Key words: cystoid macular edema, epiretinal membrane, rhegmatogenous retinal detachment, vitrectomy, cataract surgery, postsurgical macular edema.

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