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RETINAL DISORDERS

Relation of anatomy with function following the surgical treatment of idiopathic epiretinal membrane: a multicenter retrospective study

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Abstract

Purpose To investigate the prognostic factors associated with functional and anatomical outcomes and to assess the longitudinal course of visual acuity and retinal morphology after vitreoretinal surgery for idiopathic epiretinal membrane (ERM).

Methods This multicenter, retrospective study included a total of 634 eyes who underwent surgery for idiopathic ERM in 22 academic centers nationwide in Turkey. Data on best-corrected visual acuity (BCVA) and optical coherence tomography features (central foveal thickness (CFT), ERM and foveal contour morphology, ellipsoid zone (EZ) integrity) were collected and compared at baseline, 6-month, 12-month, and 24-month follow-ups. Prognostic factors for functional (having ≥ 20/25 Snellen BCVA) and anatomical (having normal/shallow foveal contour) recoveries after surgery were investigated by means of multivariate regression analyses. A cutoff value of preoperative BCVA optimizing functional recovery was calculated using receiver operating characteristic curve analysis.

Results At a median follow-up of 24 months, 37.4% of the eyes achieved ≥ 20/25 BCVA and 54% regained normal or shallow foveal contour. Functional recovery was more likely in eyes with better baseline BCVA and intact EZ ($R^2 = 0.356$, $p < 0.001$). The cutoff baseline BCVA value for good visual prognosis was 0.35 logarithm of the minimum angle of resolution (Snellen 20/44) (sensitivity 60%, specificity 85%, $p < 0.001$). Anatomical recovery was negatively associated with advanced age, higher baseline CFT, foveal herniation–type ERM morphology, and internal limiting membrane (ILM) peeling ($R^2 = 0.225$, $p < 0.001$). The negative effect of ILM peeling on anatomical recovery was not significant after the first postoperative year ($p = 0.05$). Mean BCVA values and foveal morphology progressively improved at each visit. Cases with convex baseline foveal contour continued to change towards normal foveal depression over 24 months of follow-up, which took longer than the eyes with shallow/flat contoured cases. One-third of eyes with severe baseline EZ defects showed recovery at follow-up and achieved significantly greater visual acuity gains than the remaining eyes with persistent defects ($p < 0.001$).

Conclusions Functional and anatomical restoration of the eyes appears to be a slow process after ERM surgery. This process may take much longer in eyes with worse foveal morphology at baseline. Although photoreceptor disruption may be reversible in some eyes, full functional recovery is unlikely when it persists.

Keywords Epiretinal membrane · Vitreoretinal surgery · Macular anatomy · Ellipsoid zone disruption

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Key Messages:

- Previous studies mostly suggested that photoreceptor damage may not be reversed even after successful removal of the ERM, leading to permanent impairment in vision.
- This multicenter large-scale study shows that anatomical and functional recovery continue in long-term after idiopathic ERM surgery. Outer retinal layer disruption may be expected to resolve even beyond a year postoperatively, resulting in vision improvement. However, full functional recovery is unlikely if it persists.
- A good visual prognosis may be expected if surgery is recommended for eyes with better VA than 20/44.
- Advanced age, higher baseline CFT, foveal herniation type ERM morphology, and ILM peeling seems to have negative effects on the anatomical results in short term but this effect disappears in the long term. Cataract, EZ disruption and rhegmatogenous complications were the main factors independently associated with worse vision after surgery.

Introduction

Idiopathic epiretinal membrane (ERM) is a common macular disease characterized by abnormal fibrocellular proliferation on the inner retinal surface. Its prevalence has been reported from 5.3 to 28.9%, depending on the age distribution of the study population [1–3]. With the growing elderly population and advances in diagnostic and surgical techniques, more patients now are being diagnosed with ERM and scheduled for surgery. Although surgical removal of ERM is a safe and standardized procedure with favorable outcomes for the majority of the patients, there remain some cases that fail to achieve sufficient anatomical and functional recoveries [4–7]. It is therefore necessary to identify preoperative factors that predict the outcomes and possible reasons of failure and to determine whether additional measures such as internal limiting membrane (ILM) peeling or tamponade use help improve the outcomes. Well-known prognostic factors affecting visual outcomes include preoperative visual acuity (VA), duration of symptoms, integrity of outer retinal layers, and the occurrence of the complications [8–11]. Data demonstrating a long-term course of visual and anatomical outcomes, on the other hand, is still limited. Several studies reported a progressive improvement in best-corrected visual acuity (BCVA) that could extend up to 1 year after surgery [6, 12–15]. However, there is a lack of data demonstrating longitudinal changes in macular anatomy, notably foveolar profile and outer retinal layer.

The purpose of this study was to conduct a retrospective review of a large group of patients who underwent pars plana vitrectomy (PPV) for idiopathic ERM to investigate the longitudinal course of functional and anatomical outcomes, and prognostic factors.

Methods

This nonrandomized, retrospective, multicenter study was conducted by the Turkish Ophthalmological Association-Vitreoretinal Surgery Unit to evaluate the functional and anatomical outcomes of the patients who underwent vitreoretinal surgery for idiopathic ERM, focusing on the influence of initial clinical details on final results. Members of the society who wish to contribute were requested to fill out the study-specific data entry forms for each patient operated for idiopathic ERM and followed for at least 6 months. The study organizers received data on 723 ERMs operated on by 31 vitreoretinal surgeons from 22 centers. The institutional review board of each center and the Ethics Committee of the Turkish Ophthalmological Association approved the study protocol, which adhered to the tenets of the Declaration of Helsinki.

Only patients older than 50 years of age with idiopathic ERM were included in this study, and patients presenting with any cause of secondary ERM (including diabetic retinopathy, retinal vein occlusion, ocular inflammation, retinal detachment, or previously vitrectomized eye), high myopia (axial length > 26 mm or spherical equivalent > 6 diopters), severe media opacities with weak optical coherence tomography (OCT) signal strengths, or any macular or optic nerve disease that could interfere with visual function were excluded. Demographic data, surgical details, preoperative and postoperative (6 months, 12 months, 24 months, and final) visual acuities, lens status and OCT features, and complications were collected for each case. The BCVA was documented on the logarithm of the minimum angle of resolution (logMAR) scale. Surgical details included the gauge of the instruments, vitreous dye or tamponade use, whether combined phacoemulsification was performed, and whether ILM was peeled. Spectral domain (SD)-OCT scans were used for evaluation of all cases. Investigated OCT features included central foveal thickness (CFT), ERM and foveal contour morphology, and ellipsoid zone integrity. CFT was defined as the distance between the vitreoretinal interface and the inner border of the retinal pigment epithelium at the center of the fovea, provided automatically by the software and with manual correction as required. ERM morphology of all study eyes could be grouped into the following 4 types: diffuse type (globally adherent membrane with diffuse thickening), pseudohole type (steepened foveal pit), foveal herniation type (superficial layers of the retina bulged towards the vitreous space causing full thickness retinal fold), and vitreomacular traction (VMT) type (through a focal and adherent ERM) (Fig. 1). Foveal contour was graded as "normal" if foveal depression was preserved, "shallow" if the contour was slightly flattened but still concave, "flat" if the fovea presented a horizontalized contour, or "convex" if marked foveal convexity was present. Ellipsoid zone (EZ) was defined as the second hyperreflective band of the outer retinal layers, on horizontal and vertical SD-OCT scans. EZ disruption was graded as previously described [16, 17]: "intact," "mild disruption" (subfoveal localized involvement), and "severe disruption" (generalized involvement within the macula) (Fig. 2). To eliminate the confounding effect of the lens status, analyses investigating the effect of OCT features on functional outcomes were performed after excluding the eyes that were reported to have visually significant cataract at 6-month, 12-month, 24-month, and final follow-ups.

Statistical analysis

Descriptive statistics as frequencies, percentages, mean (± 1 standard deviation), and median values (minimum, maximum) were first calculated for all variables of interest. The normal distribution of the continuous variables was tested using the Kolmogorov–Smirnov test, and the homogeneity of variance was tested using Levene's test. Since some of the variables did not meet the assumptions necessary for parametric statistical tests, the comparisons were carried out with the Mann–Whitney *U* test, Wilcoxon matched-pairs signed-rank test, and correlation analysis with Spearman's test for continuous data. Pearson's chi-square, Fisher's exact, likelihood ratio, and McNemar's tests were used for comparisons of categorical data. Multivariate logistic regression models were fitted to identify factors related to functional and anatomical recoveries. Functional recovery was described as having 20/25 or better Snellen VA and anatomical recovery as having normal or shallow foveal contour at final follow-up. The factors which revealed a p value of ≤ 0.20 in univariate analyses were included in the models. A receiver operating characteristic (ROC) curve for preoperative visual acuity that optimized the prediction of functional recovery was constructed. Statistical analyses were performed using SPSS v22.0, and significance was set as a 2-tailed p value < 0.05.

Results

Seven hundred and twenty-three eyes that underwent PPV for ERM removal were reported by 31 vitreoretinal surgeons from 22 centers. After excluding 89 eyes for various reasons (Fig. 3), 634 eyes of 615 patients (330 female, 304 male) were included for the statistical analysis.

The mean follow-up was 27 ± 18 (6–156) months. Of the 634 eyes, 566 (89%) had at least 12 months and 384 (61%)

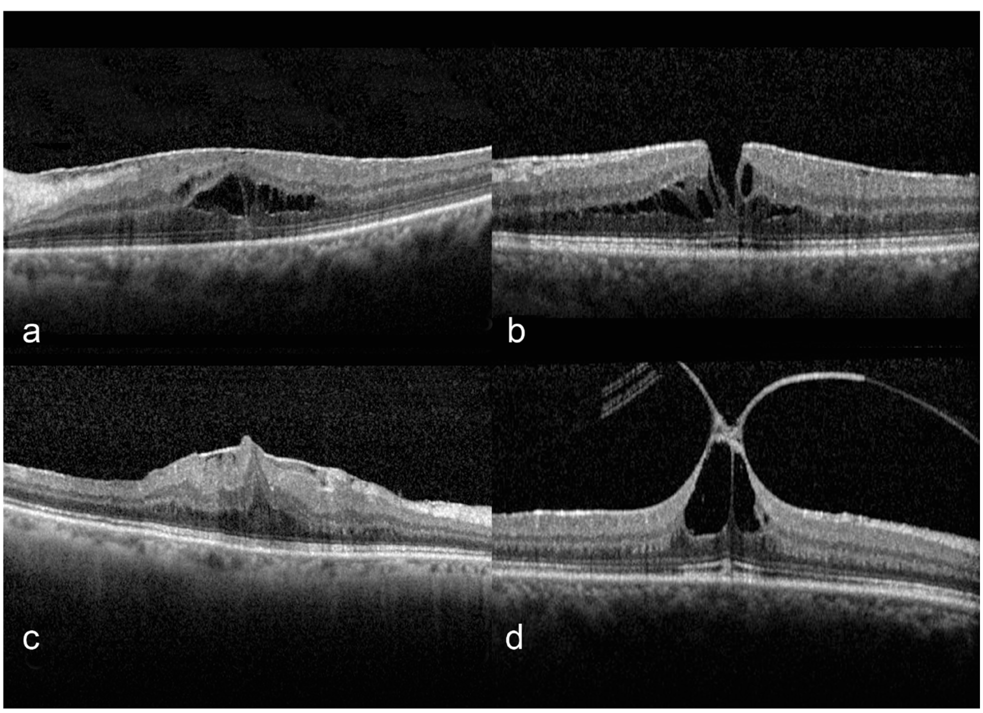

Fig. 1 SD-OCT classification of ERM morphology. Images show examples of diffuse-type ERM with cystoid spaces (**a**), pseudohole-type ERM (**b**), foveal herniation–type ERM (**c**), and vitreomacular traction–type ERM (**d**)

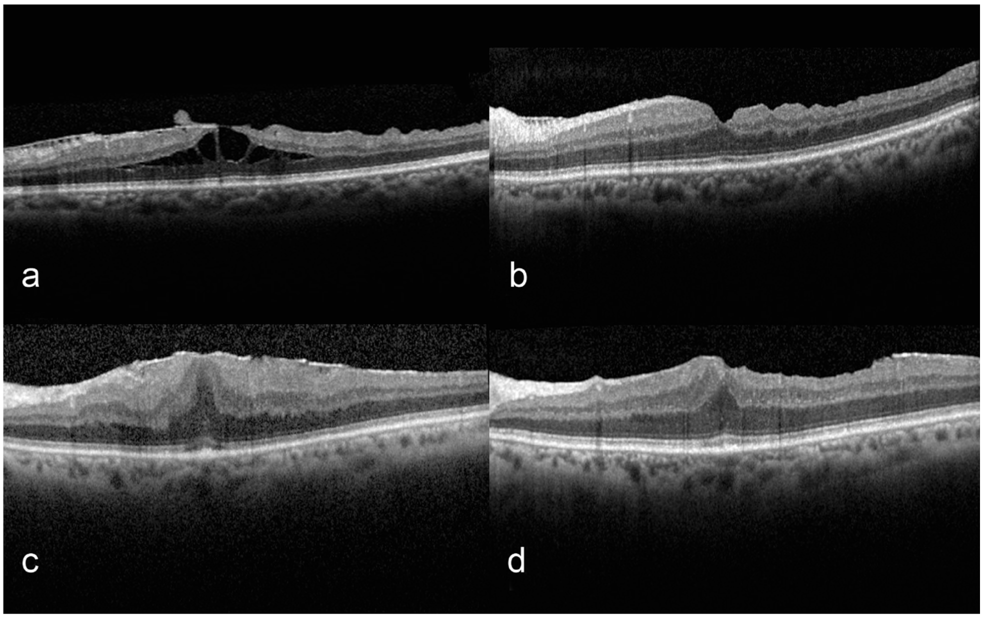

Fig. 2 Preoperative OCT of a diffuse-type ERM case with convex foveal contour and no EZ defect (**a**). OCT at 2 years of follow-up: Note the normal foveal contour with intact EZ with some irregularities in the temporal part (**b**). Preoperative OCT of a diffuse-type ERM case with convex foveal contour and severe EZ defect (**c**). OCT at 12 months of follow-up: Note that the central foveal dip started to form with improved EZ (**d**)

had at least 24 months of follow-up. Two hundred and twelve eyes (33%) were pseudophakic preoperatively, and 216 eyes (34%) underwent simultaneous cataract surgery, leaving 206 eyes (33%) phakic after ERM surgery. Patient demographics and ocular findings are displayed in Table 1, and surgical details are listed in supplemental Table 1.

Functional outcomes

The mean preoperative BCVA was 0.62 ± 0.34 (0.1–2) logMAR (Snellen equivalent, 20/83), which improved to 0.42 ± 0.32 (0–2.8) (Snellen equivalent, 20/52), 0.38 ± 0.32 (0–2.8) (Snellen equivalent, 20/48), and 0.35 ± 0.33 (0–2.8)

Fig. 3 Flow chart of patients who met the inclusion/exclusion criteria for the study population

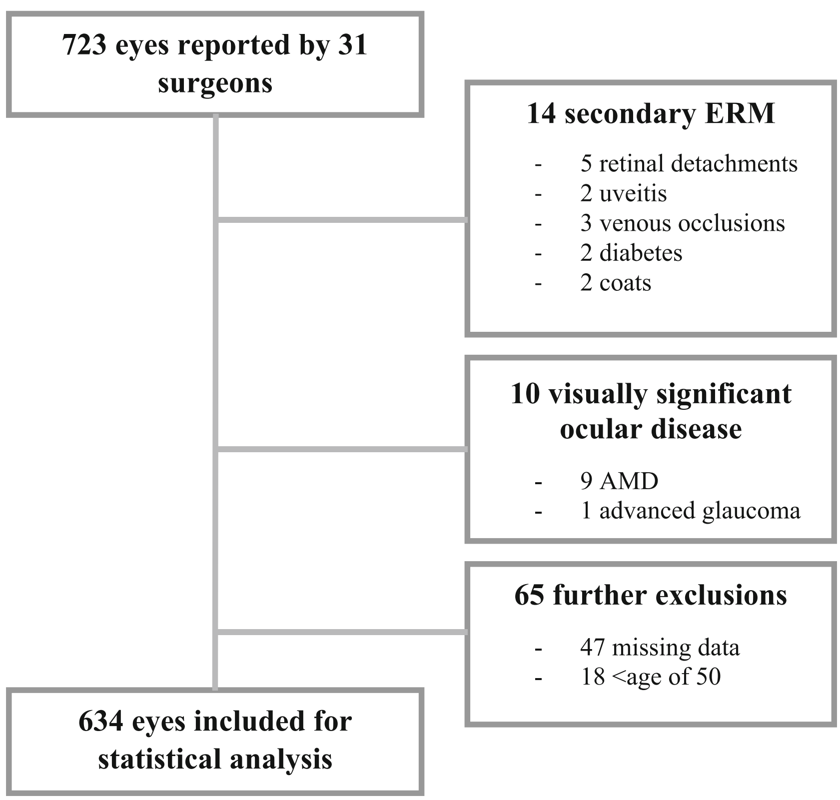

Table 1 Baseline, 6-month, 12-month, 24-month, and final characteristics of the study population undergoing epiretinal membrane surgery

Characteristics	Baseline ($n = 634$)	6-month ($n = 634$)	12-month ($n = 566$)	24-month ($n = 384$)	Final follow-up ($n = 634$)	*p* value
Age (years, mean ± SD)	69 ± 7.2 (50–91)	–	–	–	–	–
Sex, *n* (%)						
Female	330 (52)	–	–	–	–	–
Male	304 (48)	–	–	–	–	–
Systemic disease, *n* (%)						
None	284 (44.8)	–	–	–	–	–
Diabetes	134 (21.2)	–	–	–	–	–
Hypertension and hypertensive heart disease	216 (34.0)	–	–	–	–	–
Lens status, *n* (%)						
Phakic (clear lens)	90 (14.2)	36 (5.7)	18 (3.2)	12 (3.1)	15 (2.4)	
Phakic (cataract)	332 (52.4)	120 (18.9)	79 (14)	21 (5.5)	63 (9.9)	
Pseudophakic	212 (33.4)	478 (75.4)	469 (82.9)	351 (91.4)	556 (87.7)	
BCVA (logMAR, mean ± SD)	0.62 ± 0.34	0.42 ± 0.32	0.38 ± 0.32	0.35 ± 0.33	0.35 ± 0.33	< 0.001[a]
Central foveal thickness (μm, mean ± SD)	467 ± 107	374 ± 84	356 ± 81	345 ± 79	352 ± 86	< 0.001[a]
ERM configuration, *n* (%)						
Foveal herniation	127 (20.1)	–	–	–	–	–
Diffuse	354 (55.8)	–	–	–	–	–
Pseudohole	74 (11.7)	–	–	–	–	–
Vitreomacular traction	79 (12.4)	–	–	–	–	–
Foveal contour status, *n* (%)						
Normal	0 (0)	124 (19.5)	142 (25.1)	109 (28.4)	175 (27.6)	< 0.001[b]
Shallow	24 (3.8)	141 (22.2)	147 (25.9)	114 (29.7)	170 (26.8)	
Flat	244 (38.5)	261 (41.2)	203 (35.9)	126 (32.8)	215 (34)	
Convex	366 (57.7)	108 (17.1)	74 (13.1)	35 (9.1)	74 (11.6)	
Ellipsoid zone status, *n* (%)						
Intact	343 (54.1)	347 (54.7)	311 (54.9)	206 (53.6)	354 (55.9)	0.257[b]
Mild disruption	198 (31.2)	214 (33.8)	180 (31.8)	122 (31.8)	198 (31.1)	
Severe disruption	93 (14.6)	73 (11.5)	75 (13.3)	56 (14.6)	82 (13)	

BCVA best-corrected visual acuity

[a] Wilcoxon paired-samples signed-rank test (computed for 384 eyes that have 6-month, 12-month, and 24-month follow-up data)

[b] McNemar–Bowker x^2 test (computed for 384 eyes that have 6-month, 12-month, and 24-month follow-up data)

logMAR (Snellen equivalent, 20/44) at 6 months, 12 months, and 24 months, respectively, after surgery. Comparisons at each follow-up visit indicated a progressive increase in visual acuity over time ($p < 0.001$ at every time point compared to previous one). Overall, 71.1% gained more than 2 lines and 37.4% of the eyes achieved ≥ 20/25 Snellen BCVA, while 6.2% of the cases lost 2 or more lines.

Age, gender, and presence of a systemic illness were not associated with postoperative VA or BCVA change. The eyes with significant cataract at final exam ($n = 63$, 10%) had significantly lower BCVA than the remaining study population (0.47 ± 0.30 vs. 0.33 ± 0.32, $p < 0.001$).

Baseline CFT was correlated with preoperative and postoperative VA ($r = 0.19$ and $r = 0.21$, respectively, $p < 0.001$), whereas it was not associated with BCVA change ($p = 0.71$). Figure 4 shows BCVA and CFT time course. Preoperative and postoperative VA and BCVA change did not differ significantly based on the baseline foveal contour ($p = 0.06$, 0.38, and 0.34, respectively). However, eyes that achieved normal postoperative foveal contour, compared to shallow, flat, and convex contours, had greater VA gain (− 0.38 ± 0.34 vs. − 0.28 ± 0.36, − 0.28 ± 0.32, and − 0.22 ± 0.40, respectively, $p = 0.005$) and better final VA (0.24 ± 0.22 vs. 0.34 ± 0.33, 0.34 ± 0.31, and 0.40 ± 0.38, respectively, $p < 0.001$).

Concerning morphological patterns, preoperative VA was best in the pseudohole type (0.53 ± 0.31, range 0.15–1.3), followed by the diffuse (0.60 ± 0.34, range 0.1–3), VMT (0.66 ± 0.35, range 0.05–1.9), and foveal herniation (0.68 ±

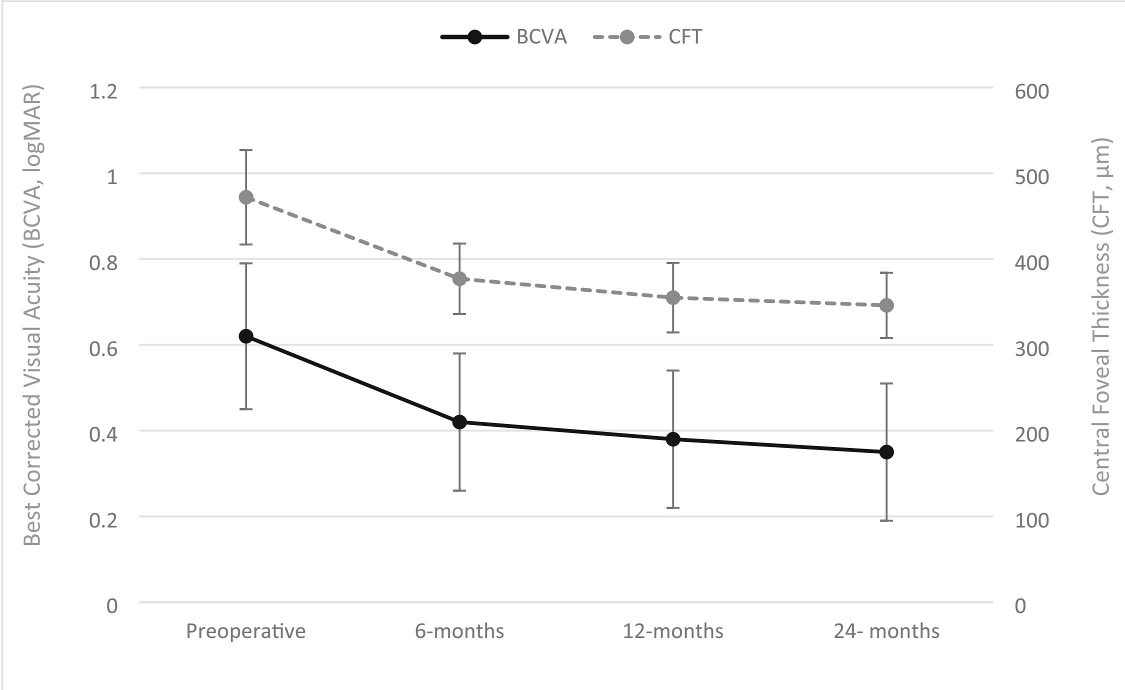

Fig. 4 Changes from baseline in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) through the follow-up period in the eyes with at least 24 months of follow-up ($n = 363$, eyes with significant cataract were excluded). Circles indicate mean values, and vertical error bars represent 2 standard errors from the mean. $p < 0.05$ at each follow-up visit compared to previous BCVA or CFT value

0.36, range 0.2–2) types, with a significant difference between pseudohole-VMT ($p = 0.01$) and pseudohole-foveal herniation ($p = 0.002$) groups. BCVA and CFT in all subtypes significantly improved after surgery (for all, $p < 0.001$). BCVA improvement was greatest in the foveal herniation type, but least in the pseudohole type. CFT reduction was greatest in the VMT type, but least in the pseudohole type. However, visual gain or the final BCVA did not differ significantly based on the baseline OCT pattern ($p = 0.22$ and 0.12, respectively). Preoperative and postoperative BCVA and CFT values in each ERM type are shown in Fig. 5.

Presence of an ellipsoid zone defect was associated with poor vision, and severity of the defect was closely correlated with BCVA levels ($p < 0.001$). Mean baseline and final logMAR BCVA was 0.55 ± 0.32 (0.05–3) and 0.24 ± 0.28 (0–2.8) for the eyes with intact EZ, 0.66 ± 0.34 (0.15–2) and 0.38 ± 0.32 (0–1.5) for the eyes with mild EZ defects, and 0.85 ± 0.35 (0.2–1.9) and 0.57 ± 0.40 (0–1.3) for the eyes with severe defects. Nonetheless, all groups experienced similar gains in BCVA from baseline ($p = 0.41$). Interestingly, the mean BCVA of the eyes with intact EZ at baseline continued to improve during the entire follow-up, whereas EZ defective eyes reached their potential in 6 to 12 months after surgery. Regarding patients with follow-up over 24 months, the mean BCVA significantly improved from 0.37 ± 0.34 at 6 months to 0.30 ± 0.29 at 12 months and to 0.25 ± 0.22 at 24 months in the eyes with intact EZ ($p < 0.001$ at each time point). For the eyes with a mild EZ defect at baseline, the mean BCVA improved from 0.51 ± 0.28 at 6 months to 0.43 ± 0.29 at 12 months ($p = 0.01$), whereas it did not show significant improvement beyond 1 year ($p = 1.0$). Vision was stabilized even earlier in the eyes with a severe EZ defect and did not show any significant change after 6 months ($p > 0.05$ at every time point). Further analyses to investigate this difference indicated an EZ recovery taking place up to 6 months and associated with visual gains. Regarding eyes followed for at least 24 months, 20 out of 55 (36%) eyes with severe defects at baseline had either intact EZ or mild defects at 6 months and maintained this status during a median follow-up of 36 (24–80) months. Of the 114 eyes with mild EZ defects at baseline, 21 (18%) recovered to intact EZ and 16 (14%) ended up with severe disruption; the EZ status of these eyes did not show any change after 12 months. Although not significant, the eyes that showed progression of mild disruption tended to have complications more often (23.5% vs. 9.5%, $p = 0.09$). None of the eyes with an intact EZ before surgery developed a severe defect during the entire follow-up; however, 11% showed newly developed mild disruptions of the EZ. Eyes that achieved EZ recovery showed significantly greater VA gains compared to those that did not (− 0.33 vs. − 0.08, $p < 0.001$), and the final BCVA closely correlated with postoperative EZ status (0.20 ± 0.19 in eyes with intact EZ, 0.35 ± 0.31 with mild defects, and 0.77 ± 0.39 with severe defects ($p < 0.001$)).

The possible effects of surgical techniques on visual outcome were evaluated. The use of different gauge vitrectomy

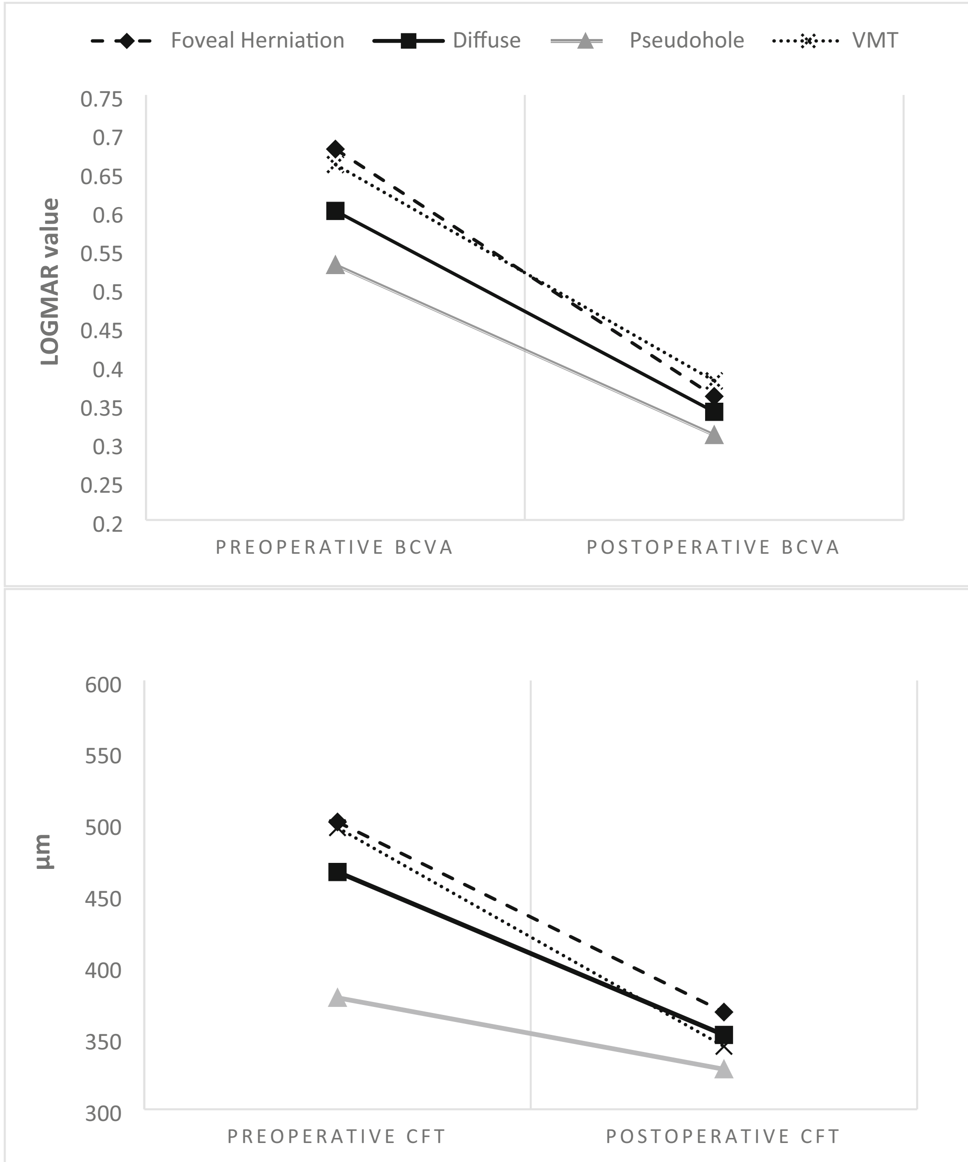

Fig. 5 Preoperative and postoperative best-corrected visual acuity (BCVA) and central foveal thickness (CFT) in each ERM type. BCVA and CFT in all subtypes significantly improved after surgery (Wilcoxon signed-rank test; for all $p < 0.001$). BCVA improvement was greatest in the foveal herniation type, but least in the pseudohole type. CFT reduction was greatest in the VMT type, but least in the pseudohole type

systems and different stains did not have any effect on postoperative VA ($p = 0.25$ and 0.29, respectively) or BCVA change ($p = 0.12$ and 0.40, respectively). Although ILM-peeled eyes had better final VA than the non-peeled eyes (0.30 ± 0.22 vs. 0.38 ± 0.33, $p = 0.001$), this was probably attributable to a significantly better baseline VA in these eyes (0.61 ± 0.37 vs. 0.66 ± 0.28, $p = 0.005$), and the mean visual gain was similar between the ILM-peeled and non-peeled groups ($p = 0.31$). Air or gas tamponade use also did not make any significant contribution to BCVA gain ($p = 0.59$).

A binomial logistic regression was performed using forward stepwise selection method to ascertain the effects of potential predictors on the likelihood of functional recovery (Table 2). The factors linked to a 20/25 or better final BCVA ($p \leq 0.20$) at univariate analysis (baseline VA, CFT, presence of systemic illness, EZ integrity, ERM morphology, gauge, dye, tamponade, ILM peeling, and complications) were fitted in the model. Baseline foveal contour was excluded from the analysis because of collinearity with the CFT. The regression model was statistically significant ($p < 0.001$), and it explained 35.6% (R^2) of the variance in postoperative functional recovery. The odds of reaching a 20/25 or better final BCVA increased with baseline BCVA ($p < 0.001$) and decreased with mild or severe EZ disruption ($p < 0.001$ and $p = 0.002$, respectively). Using the ROC curve analysis, we found that the cut-off value of preoperative BCVA for predicting functional recovery at final follow-up was 0.35 logMAR (Snellen equivalent, 20/44), with 60% sensitivity and 85% specificity. The area under the ROC curve was 0.79 (95% CI, 0.73–0.85, $p < 0.001$) (Fig. 6).

A separate analysis was conducted to assess the possible factors related to poor visual prognosis ($R^2 = 0.27$, $p = 0.01$).

Table 2 Multivariate logistic regression analysis of potential predictors for the functional recovery at final follow-up

	Functional recovery[a]		
	Categorical (C) (referent category first)[b] or scaled (S)	Odds ratio (95% CI)	*p* value
Baseline BCVA	S (logMAR)	0.014 (0.005–0.038)	< 0.001
Baseline EZ integrity	C (intact vs. mild disruption, severe disruption)	0.37 (0.23–0.59)	< 0.001
		0.31 (0.15–0.66)	0.002

CI confidence interval, *BCVA* best-corrected visual acuity, *EZ* ellipsoid zone

[a] Functional recovery was defined as having 20/25 or better-corrected Snellen acuity at the last follow-up

[b] For independent variables with multiple categories, each row represents a comparison of each category against the referent category in sequential order

A total of 6.2% of the cases lost 2 or more lines during the follow-up. Of these, 1.3% was attributable to the cataract progression. Other factors independently associated with worse vision after surgery (loss of ≥ 2 lines) were the development of severe EZ disruption (OR 12.7; 95% CI, 4.5–35; $p < 0.001$) and rhegmatogenous complications (OR 4.9; 95% CI, 1.8–13.7; $p = 0.02$).

Anatomical outcomes

CFT decreased significantly after surgery, and comparisons at each follow-up visit indicated a progressive improvement over time (all $p < 0.001$, Table 1). None of the eyes had

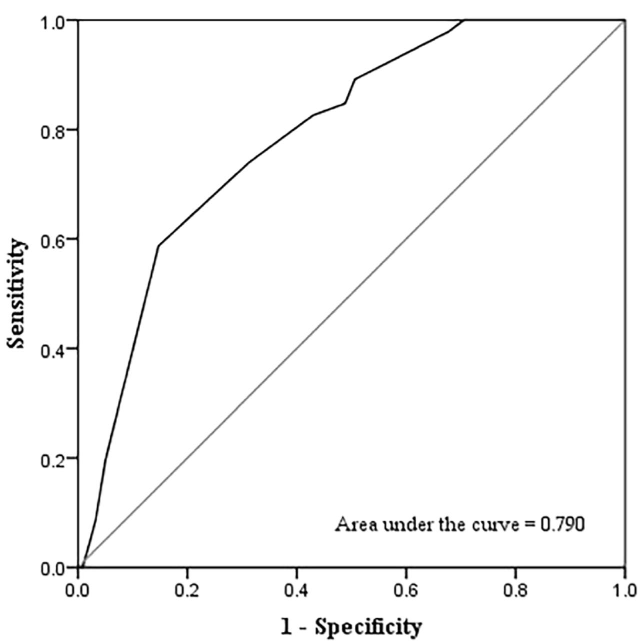

Fig. 6 The receiver operating characteristic (ROC) curve for preoperative visual acuity was constructed to obtain a cutoff value allowing optimized prediction of visual recovery of 20/25 Snellen acuity. Each point on the graph shows the calculated sensitivity and specificity for a different threshold. The area under the ROC curve was 0.79 (95% CI, 0.73–0.85), and the cutoff value for preoperative logMAR BCVA was 0.35 (Snellen equivalent, 20/44) (sensitivity 59.7%, specificity 85.3%)

normal foveal depression before surgery in this study. At a median follow-up of 24 months, 54.4% of the patients achieved normal or shallow foveal contour, 33.9% had flat contour, and 11.7% had convex contour. Anatomical recovery rates significantly correlated with the initial foveal contours; it was 100% in patients initially presenting with shallow foveal contour, 62% in those with flat contour, and 46% in those with convex contour ($p < 0.001$). Long-term results demonstrated a marked anatomical improvement over time, more remarkably in cases with convex contour at baseline. Regarding patients with follow-up over 24 months, anatomical recovery rates increased from 43% at 6 months to 52% at 12 months and 59% at 24 months ($p < 0.001$). Separate analyses based on the initial foveal contour status did not show significant anatomical changes after 12 months in patients with a shallow or flat baseline contour ($p > 0.05$). However, cases with convex contour continued to regain normal foveal depression at longer term, reaching recovery rates of 50% over a 24-month follow-up period ($p < 0.001$). Anatomical recovery rates differed by ERM morphology; it was highest for pseudohole (78.8%), followed by diffuse type (62%) and VMT (60%), and significantly lowest for foveal herniation (32.2%) ($p < 0.001$). Anatomical recovery was slightly lower in the presence of a mild or severe EZ defect (55% and 50%, respectively) compared to cases with an intact EZ layer (62%); however, the difference did not reach statistical significance ($p = 0.05$).

A binomial logistic regression was performed using forward stepwise selection method to ascertain the effects of potential predictors (age, CFT, EZ integrity, ERM morphology, gauge, tamponade use, ILM peeling) on the likelihood that patients regain foveal contour after surgery. The logistic regression model was statistically significant ($p < 0.001$), and it explained 22.5% (R^2) of the variance in final anatomical recovery. According to the model, anatomical recovery was negatively associated with advanced age ($p = 0.01$); higher baseline CFT ($p < 0.001$); foveal herniation configuration on OCT compared to diffuse type, pseudohole, and VMT pattern ($p < 0.001$, $p = 0.001$, and $p = 0.008$, respectively); and ILM peeling ($p = 0.001$). A series of multivariate regression analyses were then conducted to investigate the factors linked to anatomical recovery at 6-month, 12-month, and 24-month follow-ups. While the same predictors were linked to the anatomical outcomes at 6 months and 12 months, ILM peeling was not found to be a significant predictor of anatomical recovery at 24 months of follow-up (Table 3). This was consistent with a greater postoperative proportional decrease in CFT (− 138 ± 114 μm vs. − 105 ± 93 μm, $p = 0.02$) and a thinner mean CFT (341 ± 87 μm vs. 364 ± 76 μm, $p = 0.01$) in the non-ILM-peeled eyes than the ILM-peeled eyes in the first postoperative year. The differences in CFTs and ΔCFTs between the groups were not evident at later time points examined beyond 1 year ($p = 0.64$ and $p = 0.08$, respectively).

Further investigation was carried out to determine whether ILM peeling or tamponade use was preferred in cases with poorer anatomy, initially. Baseline anatomical findings, i.e., preoperative foveal contour, CFT, EZ defect, and ERM configuration, did not differ significantly between those with and without ILM peeling ($p = 0.99$, $p = 0.49$, $p = 0.29$, and $p = 0.27$, respectively). These results showed that there was no predilection in favor of ILM peeling in cases of poor baseline anatomy. However, there was a preference for tamponade use in the foveal herniation cases more frequently than other types of ERM (86% of foveal herniation; 72% of pseudohole; 67% of VMT; 62% of diffuse-type cases) ($p < 0.001$). Separate analyses investigating the role of tamponade use on anatomical outcomes in different ERM types did not reveal any significant contribution of tamponade in final anatomy for any ERM morphology ($p > 0.05$). Recovery rates were similar or even lower in patients with pseudohole, VMT, and diffuse-type ERM when a tamponade was used. Although not significant ($p = 0.15$), only foveal herniation cases showed higher recovery rates with the tamponade use; 27 out of 78 (34.6%) that had either air or gas tamponade regained foveal contour at the last follow-up, whereas only 1 of the 9 cases (11%) without a tamponade achieved a favorable anatomical outcome.

A subgroup analysis was conducted to assess possible factors related to the poorest anatomical prognosis (i.e., convex foveal contour in the early and late postoperative periods). Multivariate analysis ($R^2 = 0.13$, $p = 0.007$) revealed that higher baseline CFT (OR 1.005; 95% CI, 1.003–1.008; $p < 0.001$), diffuse type (OR 10.7; 95% CI, 1.4–80; $p = 0.02$), and foveal herniation–type ERM configuration (OR 10.3; 95% CI, 1.3–81; $p = 0.03$) were significantly associated with poor anatomical outcomes in the first 6 months after surgery. Moreover, eyes that underwent combined surgery (OR 1.8; 95% CI, 1.1–3; $p = 0.016$) and/or ILM peeling (OR 1.9; 95% CI, 1.1–3.2; $p = 0.014$) were almost 2 times more likely to have poor anatomy in the early postoperative period. However, multivariate analysis of 24-month results ($R^2 = 0.14$, $p = 0.005$) indicated that only baseline CFT, the effect of which was minimal but significant (OR 1.007; 95% CI, 1.004–1.01; $p < 0.001$), and the occurrence of complications

Table 3 Multivariate logistic regression analysis of potential predictors for the anatomical recovery at 6-month, 12-month, 24-month, and final follow-ups

	Categorical (C) (referent category first)[a] or scaled (S)	Anatomical success[b] 6-month		12-month		24-month		Final	
		Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	S (years)	0.967 (0.94–0.995)	0.020	0.963 (0.935–0.993)	0.015	0.954 (0.921–0.989)	0.01	0.964 (0.936–0.992)	0.014
Baseline CFT	S (μm)	0.995 (0.993–0.998)	< 0.001	0.995 (0.993–0.997)	< 0.001	0.995 (0.992–0.997)	< 0.001	0.994 (0.991–0.996)	< 0.001
Baseline ERM configuration	C (foveal herniation vs. diffuse, pseudohole, VMT)	2.15 (1.20–3.83)	0.009	1.99 (1.12–3.53)	0.019	3.41 (1.80–6.46)	< 0.001	2.71 (1.59–4.63)	< 0.001
		5.27 (2.24–12.37)	< 0.001	3.85 (1.54–9.62)	0.004	3.99 (1.24–12.92)	0.021	4.47 (1.85–10.75)	0.001
		3.24 (1.51–6.9)	0.002	3.49 (1.52–8.05)	0.003	1.76 (0.68–4.59)	0.244	2.75 (1.31–5.79)	0.008
ILM peeling	C (no, yes)	0.38 (0.25–0.57)	< 0.001	0.46 (0.29–0.72)	0.001	0.59 (0.35–0.99)	0.051	0.48 (0.32–0.74)	0.001

CI confidence interval, *CFT* central foveal thickness, *ERM* epiretinal membrane, *VMT* vitreomacular traction, *ILM* internal limiting membrane

[a] For independent variables with multiple categories, each row represents a comparison of each category against the referent category in sequential order

[b] Anatomical success was defined as the restoration of a normal or shallow foveal contour after surgery

(OR 2.5; 95% CI, 1.3–4.8; $p = 0.005$) were associated with the eyes that failed to show any anatomical improvement in the long term.

Complications

The most common complication reported in this series was the formation or progression of cataract. Of 206 eyes that were left phakic after PPV, 128 (62%) had undergone cataract surgery during the follow-up. Use of gas tamponade did not have an effect on cataract formation ($p = 0.41$). Iatrogenic retinal breaks were reported in 15 eyes (2.4%) and postoperative retinal detachment in 4 eyes (0.6%). Six eyes (1%) developed foveal or extrafoveal macular holes in the postoperative period; five (83%) of which had ILM peeled. The effect of ILM peeling on macular hole formation was not statistically significant ($p = 0.36$); however, the sample size was too small and unbalanced for comparison. There was no case of endophthalmitis. Other complications are listed in supplemental Table 2.

Discussion

This nationwide, multicenter study that included 22 major facilities throughout Turkey aimed to comprehensively study the outcomes of idiopathic ERM surgery and the prognostic factors related to visual and anatomical restoration of the eyes after surgery. Concerning functional results, BCVA improvement was comparable to the results of previous studies [5, 6, 8], with more than 70% of the eyes achieving VA gain of ≥ 2 lines. Furthermore, visual improvement continued over time. In a study by Pesin et al. [10], it was reported that the incidence of the eyes with improved VA increased over the years (43% at 6 to 12 months, 54% at 1 to 2 years, 60% at 2 to 3 years) and best final VA could be obtained after 1 year. We observed a similar trend of VA increment in our study group; it was greatest in the first 6 months following surgery, then less but significant improvement was observed during the rest of the follow-up period. However, initial BCVA and final BCVA were slightly lower compared to those reported in the recent literature [5, 6, 18]; this might indicate that, in current practice, surgeons may have a higher threshold for operating on ERM patients or patients may be referred late to vitreoretinal centers. Because of the relatively slow progressive nature of the ERM and the mild initial symptoms it caused, it is common for patients to be observed for long periods, which may limit the functional potential. In one study, a delay of the surgical procedure from a point when the logMAR VA was 0.3 or less to a point when the logMAR VA was 0.6 or more resulted in an increase of 0.21 unit in postoperative logMAR score [19]. Confirming this, we found that the patients with better baseline VA and intact EZ were more likely to recover ≥ 20/25 VA after surgery. The finding that a better preoperative VA predicts a better visual recovery is plausible and confirmed by many other studies [8, 20–22], since that the ERM in these eyes apparently causes minimal structural disturbance or is present for a shorter period of time. In the present study, the ROC analysis defined 20/44 as the cutoff level of preoperative VA that optimized the rate of functional recovery. The specificity of this value was good, with an acceptable sensitivity. Hence, a good visual prognosis may be expected if surgery is recommended for eyes with better VA than 20/44. As for EZ integrity, multivariate analysis showed that it was a strong prognostic factor for functional recovery, in agreement with previous studies [5, 6, 8, 9]. Further, the degree of the EZ disruption highly correlated with the VA levels. An important finding was that the patients with disrupted EZ could achieve progressive anatomical and functional recoveries 6 to 12 months after ERM surgery. Previous reports [8, 23, 24] mostly suggested that photoreceptor damage may not be reversed even after successful removal of the ERM. However, Inoue et al. [25] reported that 7 out of 17 eyes with disrupted photoreceptor inner segment/outer segment (IS/OS) junction recovered to normal at 24 months. Similarly, Mathews et al. [26] showed that the integrity of EZ has improved in the majority of cases. Our results supported these in a larger population; we have found that 18% of the mild and 36% of the severe EZ disruptions recovered up to 1 year and maintained thereafter. These eyes showed significantly higher BCVA gains compared to that of the remaining eyes, which had persistent and severe defects of EZ (ΔlogMAR BCVA − 0.33 vs. − 0.08). These results indicate that although the preoperative EZ status seems to determine the final VA, it may not necessarily predict the BCVA improvement because of the possible recovery of outer layers. Rather, if an eye still shows severe disruption of EZ at 6 to 12 months postoperatively, a very limited visual improvement, if any, may be expected. It is important to be aware of the fact that, despite the potential of anatomical and functional recoveries in these eyes with EZ defects, overall, their visual outcomes were inferior compared to the eyes with intact EZ and not all of the cases were able to achieve recovery. Concerning anatomical results, more than half of the eyes regained normal (28%) or shallow (27%) foveal contour at a mean follow-up of 27 months. Mathews et al. [26], who investigated foveal contour changes 4 months after ERM removal, reported that only 17% of the patients regained normal contour. The longer follow-up period in the present study could explain the higher rates of anatomical recovery we observed. Our results showed that progressive improvement in foveal anatomy could occur over time, most markedly in the cases of convex contour at baseline. While shallow/flat contoured cases returned to normal anatomy within the first postoperative year, foveal anatomy of the convex contoured cases continued to improve during the 2nd postoperative year, half of which regained foveal depression at follow-up. Our findings indicate that there is a slower but progressive remodeling in eyes with convex contour; hence, the recovery rates may be expected to increase in the longer term.

We also investigated the effect of different ERM morphologies on the outcomes. The classification system we used in the present study resembled that of Kinoshita et al. [20] who divided the ERMs into diffuse, cystoid macular edema, pseudolamellar hole, and VMT subtypes. However, we used diffuse type corresponding to their "diffuse" and "CME" types since both consisted of a globally adhering membrane widely covering the macular area with retinal thickening, and their prognoses were similar in terms of visual and anatomical improvement. Additionally, we observed a foveal herniation pattern in 20% of the cases. This subtype was previously classified as "outer retinal inward projection and inner retinal thickening" by Hwang et al. [27] and later defined as "foveal herniation" in a case by Ozdemir and Karacorlu [28] and in a study of 11 eyes by Ozkaya et al. [29]. However, data is limited regarding surgical outcomes of this subtype. In our series, these eyes had the worst mean preoperative vision, yet showed the best visual improvement after surgery. In contrast, they were negatively associated with anatomical recovery compared to other subtypes. In accordance with the literature, VMT types showed high BCVA gain and CFT reduction, whereas pseudohole type had the best preoperative VA and CFT and showed the least improvement after surgery. However, none of the subtypes significantly predicted functional recovery. Regarding anatomical recovery, multivariate analysis identified advanced age, higher baseline CFT, and additional ILM peeling as negative predictive factors in addition to the presence of foveal herniation. Removal of ILM during ERM surgery and its effects on anatomical outcomes remains controversial. Chang et al. [30] showed that ILM-peeled eyes had less proportional reduction in CFT than eyes that did not undergo ILM peeling. Similarly, Lee and Kim [31] studied 40 eyes and reported that ILM peeling caused higher final CFT along with a greater loss of normal foveal contour. Another study [32] showed a mild trend towards an increased CFT at 1 year postoperatively in the ILM-peeled group, although the results were insignificant. It is possible that the additional trauma to the retina resulting from ILM peeling may cause more disruption or swelling of the inner retinal layers postoperatively. However, many studies [33–35] have shown comparable results between the ILM-peeled and non-peeled groups at postoperative 18 months or later, suggesting that the negative effect of ILM peeling on anatomical outcomes is only temporary. Supporting this, we observed that the ILM-peeled eyes showed slower recovery and CRT reduction in the first postoperative year compared to the non-peeled eyes. With respect to the long-term outcomes, however, ILM peeling had no deleterious effect on anatomical outcomes, in terms of either CFT or foveal anatomy. Only concern might be the fact that nearly all eyes that were complicated with a macular hole in the postoperative period had their ILM peeled; however, the number was too small in our study to draw any conclusions. Previous studies on macular surgeries with ILM peeling reported paracentral macular holes in 0.6 to 2.6% [36]. Hence, avoiding routine ILM peeling in primary idiopathic ERM cases and reserving it to the recurrent or high risk of recurrence cases appears to be better until further evidence is available. We have also investigated the effect of air or gas tamponade use on the surgical results. Only few studies to date have focused on this topic; one compared the effect of air tamponade to balanced salt solution [37], and the other to SF6 [38]. Neither of the studies found any significant difference in anatomical and functional results between the groups. Our results were consistent with these, except that there might be a slight contribution for the foveal herniation cases which showed insignificant but higher recovery rates with the use of tamponade. Nevertheless, we cannot draw firm conclusions as only a small percentage of patients with foveal herniation did not receive tamponade.

Although idiopathic ERM surgery is generally accepted as an effective and safe procedure with a low risk of complications, not all patients do well after surgery. We observed that nearly 12% of the patients had poor anatomy, and 6% had significantly worse vision postoperatively. It is important to understand the possible perioperative factors associated with unfavorable outcomes to enhance patient counseling about expected results. As anticipated, the development of complications was an important factor related to both poor anatomy and poor function after surgery. Another factor was the development of severe EZ defect. The literature suggests a strong correlation between visual acuity levels and EZ integrity; however, the factors leading to the formation of postoperative EZ defects remain unclear [25, 39]. In the light of the results of this study, we may propose that it is highly unlikely, if any, for the eyes with intact EZ at baseline to develop a visually significant EZ defect after surgery. However, there appears to be a risk of mild preoperative EZ disruptions to progress after surgery and cause significant impairment in vision (14% in this study). Regarding the anatomical outcomes, we found that the negative effects of the poor prognosis indicators, such as preoperative configuration of the ERM, combined surgery, and ILM peeling, were only temporary and did not affect the long-term results.

The limitations of this study are mostly inherent in its retrospective design and evaluations based on self-reporting, which may both cause selection bias and affect the quality of the results. Heterogeneity in clinical practice among centers may also be a major confounding factor. Hence, participating surgeons were asked to provide detailed information regarding surgical techniques, and the analyses showed that the gauge, dye, or tamponade choice did not influence the outcome, in terms of either efficacy or safety. Moreover, different follow-up periods after 6 months may confound statistical analysis results for longer time points. To overcome this, some of the longitudinal data were analyzed in the patients that have at least 24 months of follow-up data. A further issue was the high rate of progressive nuclear sclerosis after surgery. In fact, only a small percentage (12%) remained phakic at their last follow-up, yet we excluded the cases with visually significant cataract to minimize its possible confounding effect. Despite these pitfalls, considering that a large number of surgeons from the major facilities throughout Turkey contributed, this study was able to yield a study population that closely represents the spectrum of patients encountered in clinical practice; hence, the outcomes reported here are expected to be largely applicable.

To the best of our knowledge, this is the largest series in the literature evaluating outcomes of ERM surgery and there was no such long-term study that showed the longitudinal course of retinal morphology and its correlation with function over a 2-year follow-up period. Another strength of the study is that the long-term surgical outcomes of foveal herniation type, which is not uncommonly encountered in clinical practice, have been examined in a large population for the first time.

In conclusion, the present study corroborates the findings of the previous studies regarding clinical and OCT characteristics and functional and anatomical results in a nationwide large population. Visual prognosis was better if surgery is recommended for eyes with better VA than 20/44. The prognostic utility of the preoperative ERM morphology was found to be limited to ascertaining the expected BCVA and CFT improvement for each subtype. Although anatomical recovery was less likely in the eyes with foveal herniation, this should not be alarming as the visual results were comparable to the other subtypes. EZ defects and rhegmatogenous complications were the main factors associated with worse vision after surgery. Overall, this study showed that the visual and anatomical restoration of the eyes appears to be a slow process that takes years to attain after ERM surgery. This process involves anatomical remodeling with the recovery of photoreceptor disruption, which may occur even after 1 year postoperatively. However, full functional recovery seems unlikely to be achieved in the eyes with persistent photoreceptor disruption, which should alert the vitreoretinal surgeons to lower their threshold for recommending surgery before the outer retinal layers deteriorate.

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Code availability Not applicable.
Data availability Data is available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was conducted in accordance with the ethical standards of the Turkish Ophthalmological Association-Vitreoretinal Surgery Research Committee and with the tenets of Helsinki Declaration. The study was approved by the Ethics Committee of the Turkish Ophthalmological Association.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

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