

Surgery Outcomes of Lamellar Macular Eyes with or without Lamellar Hole-Associated Epiretinal Proliferation: A Meta-Analysis

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Research article

Keywords: lamellar macular hole, lamellar hole-associated epiretinal proliferation, surgery, best corrected visual acuity, ellipsoid zone

Posted Date: August 19th, 2020

DOI: <https://doi.org/10.21203/rs.2.18331/v7>

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Version of Record: A version of this preprint was published on August 25th, 2020. See the published version at <https://doi.org/10.1186/s12886-020-01617-4>.

Abstract

Background: Given the two different kinds of epiretinal membranes, this study aimed to compare both the structural and functional outcomes of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation (LHEP) after surgery.

Method: Publications up to July 2020 that compared the surgical outcomes of lamellar macular hole with and without LHEP were included. Forest plots were created by using a weighted summary of proportion meta-analysis. Fixed or random effects models were used on the basis of I² heterogeneity estimates. Meanwhile, to evaluate the stability of the meta-analysis, a sensitivity analysis was carried out.

Results: Eight pertinent publications that contained a total of 176 eyes without LHEP and 173 eyes with LHEP were included. They were all retrospective studies and had a follow-up of at least 6 months. In all studies, the preoperative best corrected visual acuity showed no significant differences between the two groups, and the visual acuity improved in both groups after surgery. The pooled result for the improved best corrected visual acuity was 0.18 (95% confidence interval (CI), 0.10 to 0.26; $P < 0.01$) between the with and without LHEP groups. The restored ellipsoid zone odds ratio was 0.80 (95% CI, 0.26 to 2.44; $P = 0.69$) for the group with LHEP compared to the group without LHEP.

Conclusion: Patients without LHEP had better postoperative visual acuity than patients with LHEP. No significant difference in restored ellipsoid zone was found between the two groups.

Background

Lamellar macular hole (LMH) firstly described in biomicroscopic and angiographic findings by Gass in a case, is a partial-thickness loss of foveal tissue [1]. The formation of LMH is attributable to cystoid macular edema, contraction of the perifoveal epiretinal membrane and vitreous traction [2]. Later, Witkin et al. redefined the diagnosis of LMH, including: (1) irregular foveal contour; (2) break in the inner fovea; (3) intraretinal split; and (4) intact foveal photoreceptors [2].

The development of ultrahigh-resolution optical coherence tomography (UHR-OCT) contributes to revealing more microscopic structures of LMH. UHR-OCT has visualized the trapped vitreous or posterior hyaloid, termed epiretinal membranes (ERMs), in most cases of LMH. Two types of ERM, tractional ERM (T ERM) and lamellar hole-associated epiretinal proliferation (LHEP), are known as thick ERM and dense ERM, respectively. Based on the results of OCT, T ERM is described as a dense reflective line above retina, while LHEP is a homogenous medium with much lower reflectivity. Moreover, T ERM has better contractile properties compared with LHEP [3]. In general, these two kinds of ERM can exist in LMH patients simultaneously or separately, and T ERM is more common than LHEP.

Whether to operate surgery on LMH patients remains controversial. Pars plana vitrectomy with internal limiting membrane (ILM) peeling, the most common surgery among LMH patients, is reportedly useful, in particular for those with significantly low visual acuity [4-6]. However, some patients did not gain better best-corrected visual acuity (BCVA) and even developed full-thickness macular hole (FTMH) after surgery. Moreover, a previous study reported that some patients could be in a functionally and morphologically steady state just by observation since the natural progress of LMH was stable [7].

To figure out the differences in prognosis among patients with or without LHEP, some previous studies focused on the surgical outcomes of patients with and without LHEP, but their results were inconsistent. Based on those studies, this meta-analysis aimed to compare both the structural and functional outcomes of patients with and without LHEP after surgery.

Methods

A comprehensive search for studies that compared surgical outcomes of LMH patients with and without LHEP was carried out in PubMed, Medline, Embase and Clinical trials. The searching strategy was: "Lamellar macular hole" or "LMH" or

“epiretinal membrane” or “ERM” or “lamellar hole-associated epiretinal proliferation” or “LHEP” and “surgery” or “operation” or “vitrectomy”. All references of included articles were also screened to guarantee no omission of literature.

Study selection

For study selection, the inclusion criteria were: 1) having LMH patients with T ERM or LHEP or both; 2) providing basic and clinical information of patients; 3) operating surgery for patients; 4) reporting both preoperative and postoperative BCVA; 5) having a median follow-up at least 6 months. Exclusion criteria were: 1) having inadequate information of included patients; 2) only observing patients without surgery during the whole progress; 3) having patients with other ophthalmologic diseases that affect the progress of LMH.

Data extraction and validity assessment

All information in the involved studies were separately extracted by two authors with a standardized protocol, including basic characteristics, like authors, year, cohort size and country; detail information of studies, including study design, follow-up period and surgery method; information of patients, including age, gender, preoperatively and postoperatively eye-related data. Newcastle-Ottawa Scale (NOS) was used by two authors to score the quality of all included studies separately, and disagreements were resolved by another author with more experience.

Quantitative data synthesis

The summary odds ratio (OR) of LMH patients with and without LHEP with 95% confidence intervals (95% CI) were calculated, and the weighted mean difference (WMD) was calculated with the 95% CI for BCVA. A P value < 0.05 was considered to be statistically significant. Both fixed effect and random effects models were used to pool studies. When I^2 index, which measures the extent of the heterogeneity, was less than 50%, the conclusions were drawn from the results of the fixed effects model, otherwise using random effects model. To identify the potential publication bias, funnel plots were used. Sensitivity analysis was carried out to evaluate the stability of the meta-analysis by omitting one study each time. All statistical analyses were conducted by Review Manager (version 5.2; Cochrane Collaboration, Oxford, UK; <http://ims.cochrane.org/revman>) and STATA software (version 11.0; Stata Corp LP, College Station, TX).

Results

Characteristics of the available studies

A total of 287 records were obtained by the searching method mentioned above (Figure 1). After removing duplications and articles written in other languages, 155 articles were left. By reading the titles and abstracts, 14 papers on LHEP reporting surgical outcomes were identified. Then, the full texts of all articles were read and 6 of them were discarded because they included patients with FTMH [8, 9], recruited LMH patients with high myopia [10], had incomplete information [11, 12] or was an observational study without surgery [3]. Finally, eight studies with 176 eyes without LHEP and 173 eyes with LHEP were included [13-20]. All studies included were retrospective studies.

Outcomes of meta-analysis

No significant heterogeneity was observed in the comparing model of BCVA ($I^2 = 7\%$, $P = 0.36$), while heterogeneity existed in the model of restored ellipsoid zone (REZ) ($I^2 = 68\%$, $P = 0.04$). So fixed-model analysis was used in the meta-analysis of BCVA and a random-model was used for REZ. The WMD of the improved logarithm of the minimum angle of resolution BCVA between with and without LHEP groups was 0.18 (95% CI, 0.10 to 0.26) with statistically significant difference ($P < 0.001$). Only three studies reported the status of ellipsoid zone both before and after surgery. The pooled data revealed an OR of 0.80 (95% CI, 0.26 to 2.44) in the rate of REZ and the difference was not statistically significant at the 95% CI level ($P = 0.69$) (figure 2).

Publication bias and validity assessment

To assess potential publication bias in the meta-analysis, funnel plots were visually inspected, and no funnel plot asymmetry was visualized (Figure 3). By Egger test, no publication bias existed in the studies with BCVA reported ($P=0.543$). Sensitivity analysis showed that the statistical findings of BCVA did not change by removing any one of the studies, indicating the stability of this meta-analysis (Figure 4). According to the results of NOS, all included studies had high quality with scores equal to or greater than 7.

Discussion

Given the different clinical characteristics of LMH patients with ERMs, surgical efficacy remains controversial. To figure out whether surgery is appropriate for all LMH patients, we conducted this meta-analysis. The results suggested that although BCVA improved in all patients after surgery, BCVA in LHEP patients was lower than that in T ERM patients, and REZ rate was not significantly different between the two groups.

The existence of ERM has been detected for several decades, while its pathogenesis and category remain unclear. T ERM is tractional and the retinal surface under it is usually plicate. The LMH with T ERM always has short diameter and shallow cleft, limited in the inner part of retina and described as "high hat" by Govetto et al. In contrast, LHEP is an atypical ERM without traction, having larger and deeper LMH under it [21]. In a previous study, glial cells and hyalocytes were found in both membranes, while α -SAM was only found in T ERM, explaining the tractional ability of T ERM [22].

The origin of LHEP is not clear but there are two main theories. In one theory, as LHEP has abundant clusters of fibrous long-spacing collagen, fibroblasts and hyalocytes, the posterior detachment of vitreous body might induce both anterior and tangential traction and therefore plays a role in the formation of ERM [16, 22]. However, in another theory, cystic spaces in LHEP formed by leakage of fluid from retinal vessels within it suggested that LHEP might originate from the middle retinal layers since they share the same characteristics [3]. The proof that the yellow color of LHEP is xanthophyll mainly produced by muller cells, further certifies the relationship between LHEP and the middle retinal layers [23].

Based on the results of present studies, the postoperative BCVA recovery in LHEP patients is less than those without LHEP. Besides, previous studies also indicated that LMH or FTMH eyes with LHEP had worse visual outcomes after surgery [8, 13, 14, 24], probably attributable to the severer destruction of the retina in eyes with LHEP than without LHEP. However, there are also some studies reported similar surgery outcomes of eyes with and without LHEP [10, 12, 15, 16]. As there are no significant differences in preoperative BCVA ($<20/40$), surgery method (ILM and ERM peeling) and time of follow-up (>6 months) among these two kinds of studies, more studies with longer follow-up are required to determine the relationship between the poor visual outcomes and LHEP. Though many studies have reported the positive association between the REZ and postoperative BVCA [25, 26], no significant differences of REZ existed between with and without LHEP groups in present study. Previous studies reported that although the defection of ellipsoid zone before surgery was associated with worse postoperative BCVA, its restoration showed no direct association with functional recover [5, 27]. Additionally, several influential factors, including the physical conditions of patients, different preoperative BCVA, and time of follow-up, should also be taken into consideration. In the previous study that had higher REZ rate in LHEP patients, the preoperative BCVA of patients were lower than 20/40 [13], while in other two studies, the preoperative BCVA had wider range [14, 15].

Patients from six of the eight included studies underwent standard pars plana vitrectomy and conventional ERM and ILM peeling [13-17, 19]. However, the other two studies operated a new surgical method on patients [18, 20]. Comparing these two surgical methods, the difference between the two surgical methods lies in the disposition of ERM and ILM. Instead of peeling the membrane, the new method double inverted the ERM and flapped ILM [28, 29]. This kind of surgery can preserve LHEP and promote the recovery of LHM. A previous study indicated that the development of LHEP might be a part of recovery progress of LMH [15]. This new surgical method and its positive outcomes further raise doubts in the necessity of taking

surgery for LHM patients with ERM. Thus, whether surgery is necessary for patients with LHEP to get functional and morphological restoration requires more study to prove.

However, our study has some limitations. Firstly, a limited number of studies involved would inevitably lead to bias, and no subgroup analysis was made based on different surgical methods. Thus, more studies are required to obtain more convincing results. Secondly, only 5 studies reported the number of cataract patients, and the number of patients with combined phacoemulsification and intraocular lens implantation may influence the outcome of BCVA. Thirdly, different choices of the gas for the final tamponade, such as air, sulphur hexafluoride, or perfluoropropane gas, might have a distinct influence on the surgical results.

In conclusion, this study pooled the postoperative outcomes of LMH patients with and without LHEP and found that the postoperative BCVA of patients without LHEP was better than patients with LHEP, and REZ showed no significant difference between the two groups.

Abbreviations

BCVA, best corrected visual acuity; CI, confidence intervals; ERM, epiretinal membranes; DLMH, Diameter of Lamellar Macular Hole; FTMH, full thickness macular hole; ILM, internal limiting membrane; LHEP, lamellar hole-associated epiretinal proliferation; LMH, lamellar macular hole; NOS, Newcastle - Ottawa Scale; OR, odds ratios; REZ, restored ellipsoid zone; SFT, Shortest Foveal Thickness; T ERM, tractional epiretinal membranes; UHR-OCT, ultrahigh-resolution optical coherence tomography; WMD, weighted mean difference

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

MZ and LQ contributed to the study design. HY X and YF Z contributed to the data collection and analysis. HY X and YN X contributed to the writing of this manuscript. All authors read and approved this manuscript.

Acknowledgements

Not applicable

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Tables

Table 1. Demographic characteristics of the included studies

Author	Parolini et al.	Lai et al.	Ko et al.	Choi et al.	Ho et al.	Takahashi et al.	Figueroa et al.	Morescalchi et al.
Year	2011	2015	2016	2017	2019	2019	2019	2020
Country	Germany	China	Korea	USA	China	Japan		Italy
Study design	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective	retrospective	prospective
Study period	2008-2010	2009-2013	2011-2014	2009-2015	2013-2016	2010-2016	2010-2017	2015-2017
Surgery	Vitrectomy	Vitrectomy	Vitrectomy	Vitrectomy	Vitrectomy	Vitrectomy	Vitrectomy	Vitrectomy
	ILM/ERM peeling	ILM/ERM peeling	ILM/ERM peeling	ILM/ERM peeling	ILM/ERM peeling	ILM peeling LHEP embedding	ILM/ERM peeling	ILM/ERM peeling
Follow-up	6 months	> 12 months	> 6 months	> 6 months	> 19 months	> 12 months	> 6 months	6 months
	Without LHEP							
Number	6	24	58	11	-	-	77	-
Age (Y)	67.7 ± 12.9	59.8 ± 8.9	64.4 ± 9.5	68.6 ± 8.8	-	-	67 ± 8.9	-
Gender (M/F)	1/5	9/15	9/16	-	-	-	-	-
FT (µm)	-	146.9 ± 51.2	154.0 ± 24.7	166.7 ± 62.0	-	-	279.1 ± 108	-
DLMHI (µm)	-	-	450.4 ± 201.8	308.2 ± 121.2	-	-	-	-
AL (mm)	-	-	23.66 ± 1.59	-	-	-	-	-
	With LHEP							
Number	13	19	15	11	31	34	26	24
Age (Y)	73.9 ± 12.9	60.2 ± 11.2	67.4 ± 9.5	69.9 ± 13.6	67.7 ± 8.7	69.6 ± 10.1	67 ± 8.9	72.1 ± 8.3
Gender (M/F)	8/5	9/10	4/11	-	6/25	12/22	-	15/9
FT (µm)	-	98.4 ± 35.0	116.7 ± 38.1	96.3 ± 33.2	-	-	224 ± 66	-
DLMHI (µm)	-	-	613.5 ± 197.3	334.1 ± 139.8	-	-	-	-
AL (mm)	-	-	24.12 ± 1.84	-	-	24 (< 26), 10 (26≤)	-	-

Abbreviations: AL, Axial Length; DLMHI, Diameter of Lamellar Macular Hole at the ILM level (pre-operation); ERM, Epiretinal Membrane; FT, Foveal Thickness (pre-operation); ILM, Internal Limited Membrane; LHEP, Lamellar Hole-Associated Epiretinal Proliferation; M/F, male/female.

Table 2. Ophthalmic information of involved studies

Author		Parolini et al.	Lai et al.	Ko et al.	Choi et al.	Ho et al.	Takahashi et al.	Figueroa et al.	Morescalchi et al.
BCVA (pre-operation)	Without LHEP	0.40 ± 0.20	0.72 ± 0.32	0.30 ± 0.26	0.48 ± 0.18	-	-	0.38 ± 0.19	-
	With LHEP	0.40 ± 0.20	0.79 ± 0.37	0.38 ± 0.38	0.50 ± 0.25	0.37 ± 0.27	0.31 ± 0.25	0.56 ± 0.19	0.44 ± 0.16
BCVA (post-operation)	Without LHEP	0.20 ± 0.30	0.43 ± 0.44	0.10 ± 0.10	0.16 ± 0.16	-	-	0.18 ± 0.17	-
	With LHEP	0.20 ± 0.20	0.45 ± 0.39	0.33 ± 0.40	0.40 ± 0.29	0.17 ± 0.21	0.10 ± 0.25	0.39 ± 0.28	0.17 ± 0.13
EZD (pre-operation)	Without LHEP	-	9 (24)	0 (42)	3 (11)	-	-	11 (77)	-
	With LHEP	-	13 (19)	2 (10)	10 (11)	10 (33)	15 (34)	13 (26)	-
EZD (post-operation)	Without LHEP	-	8 (24)	2 (42)	2 (11)	-	-	6 (77)	-
	With LHEP	-	7 (19)	2 (10)	8 (11)	4 (33)	8 (34)	12 (26)	-
CRT (pre-operation) (µm)	Without LHEP	-	-	-	166.7 ± 62.0	-	-	-	-
	With LHEP	-	-	-	96.3 ± 33.2	-	123.2 ± 42.6	-	146 ± 34
CRT (post-operation) (µm)	Without LHEP	-	-	-	230.6 ± 103.3	-	-	-	-
	With LHEP	-	-	-	205.6 ± 112.9	-	191.2 ± 45.3	-	272 ± 24

Abbreviations: BCVA, Best corrected visual acuity; CRT, Central Retinal Thickness; EZD, Ellipsoid zone destruction; LHEP, Lamellar hole-associated epiretinal proliferation.

Figures

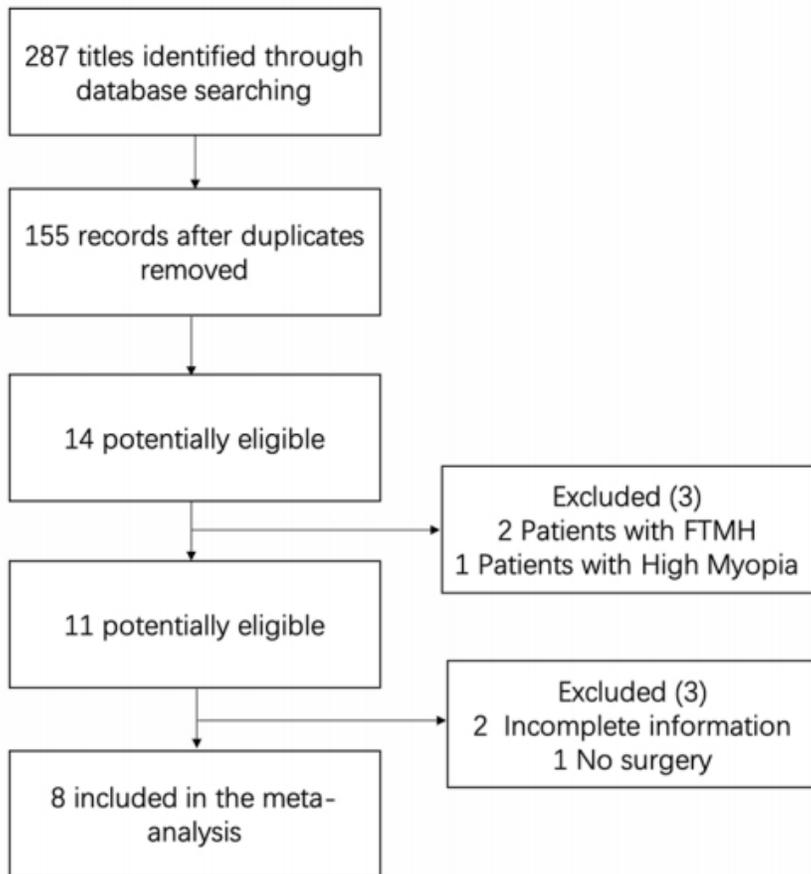


Figure 1

The flow diagram of the screening of the literatures.

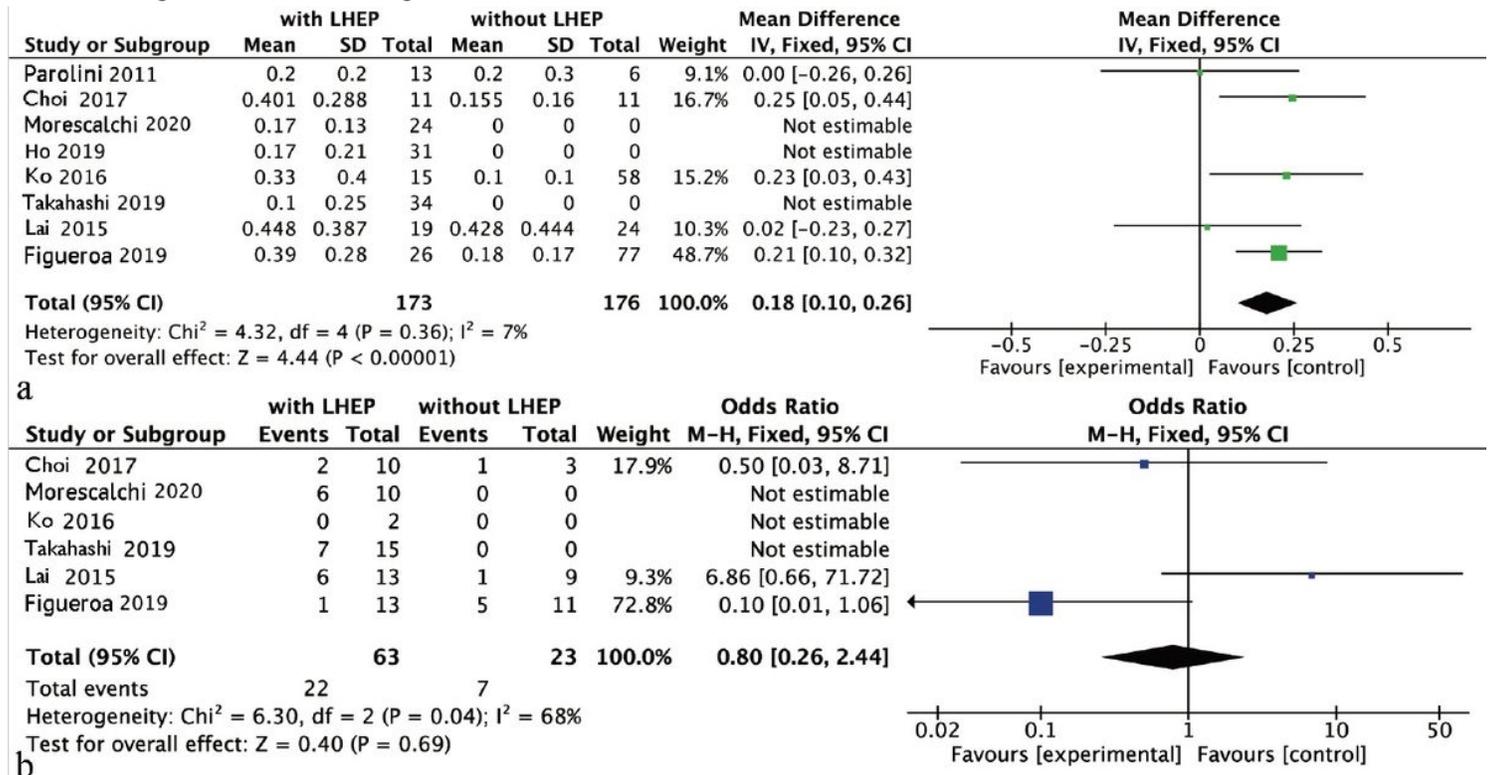


Figure 2

(a) Meta-analysis of the best corrected visual acuity in patients between eyes with or without lamellar hole-associated epiretinal proliferation (LHEP), (b) Meta-analysis of the ellipsoid zone restoration rate in patients between eyes with or without LHEP.

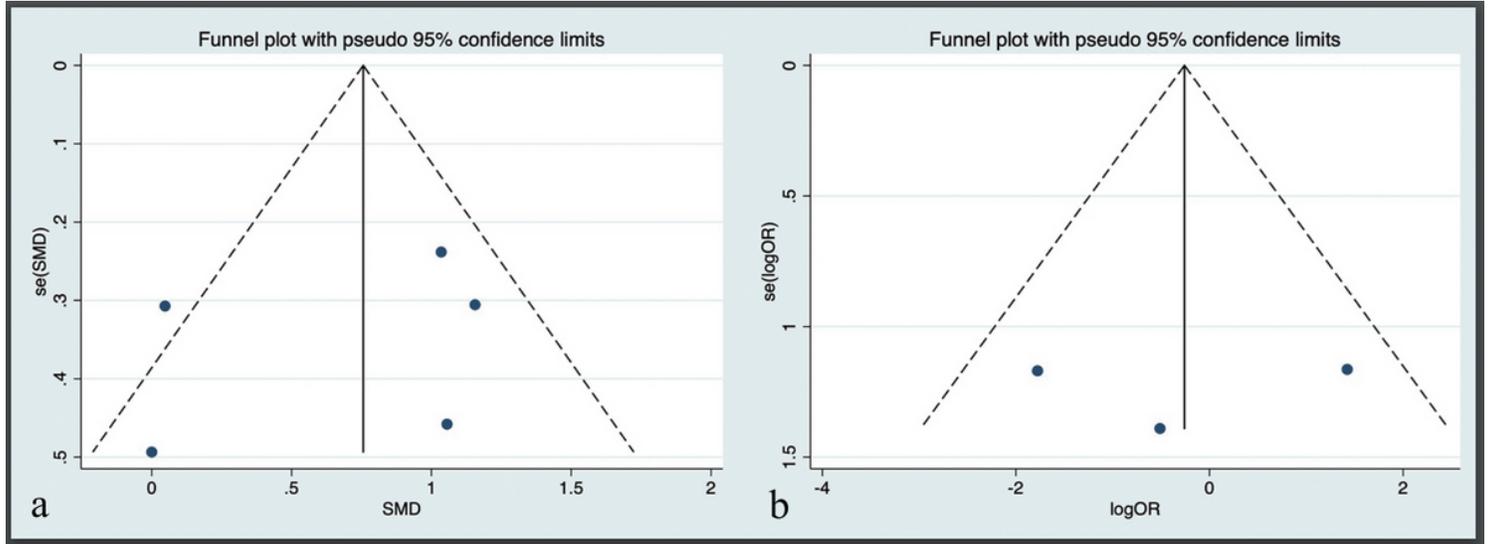


Figure 3

(a) The funnel plot of studies included in the analysis of BCVA, (b) the funnel plot of studies included in the analysis of ellipsoid zone restoration rate.

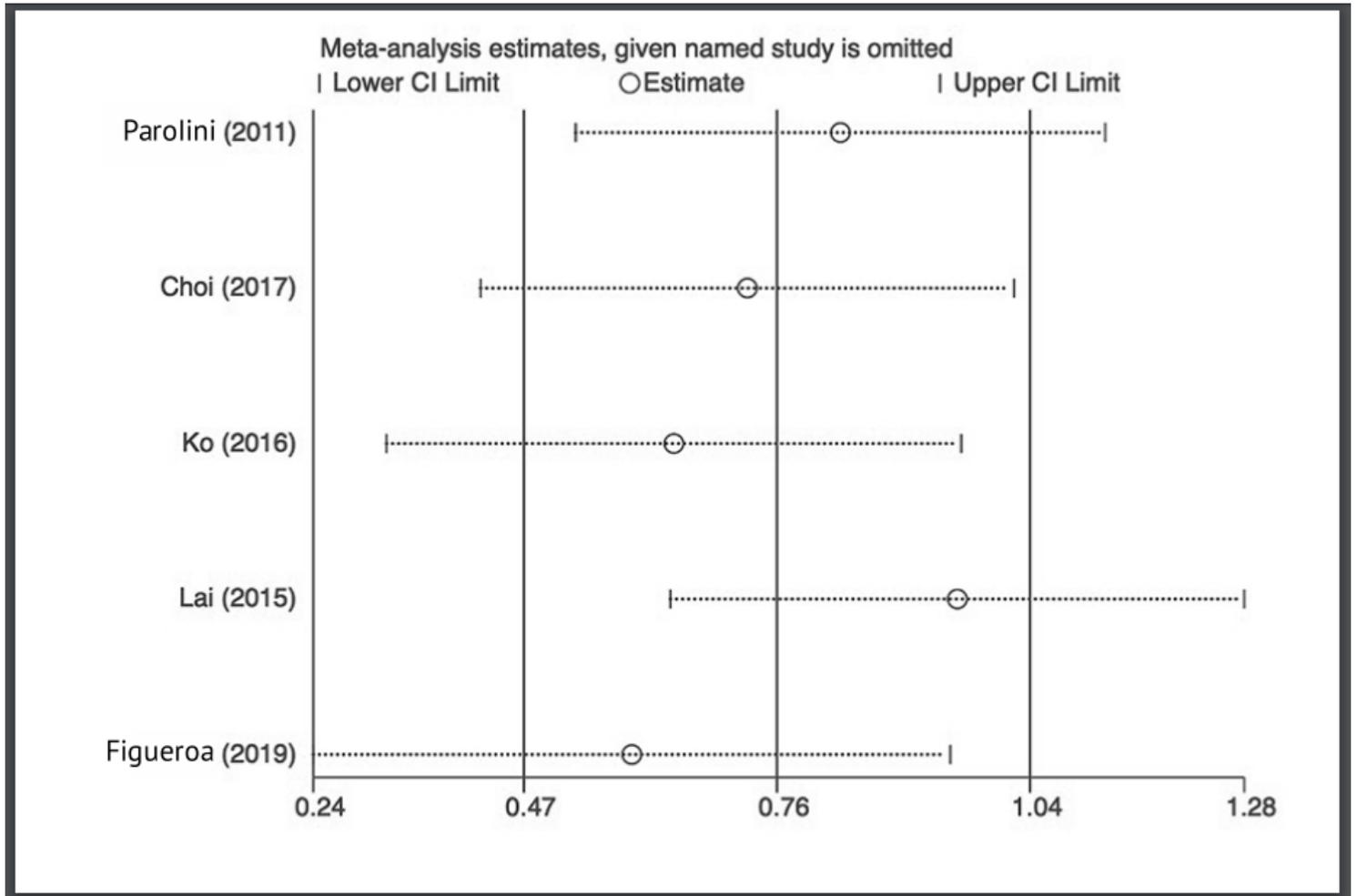


Figure 4

The sensitivity analysis on the pooled results of the best corrected visual acuity (BCVA).

Supplementary Files

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- [PRISMA2009checklist.doc](#)