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# Comparison of femtosecond laser-assisted cataract surgery and conventional phacoemulsification on corneal impact: A meta-analysis and systematic review

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## Abstract

This meta-analysis aims to compare corneal injuries and function after femtosecond laserassisted cataract surgery (FLACS) and conventional phacoemulsification surgery (CPS). A comprehensive literature search of PubMed, EMBASE, and the Cochrane Controlled Trials Register was conducted to identify randomized controlled trials (RCT) and high-quality prospective comparative cohort studies comparing FLACS with CPS. Endothelial cell loss percentage (ECL%), central corneal thickness (CCT), endothelial cell density (ECD), endothelial cell loss (ECL), percentage of the hexagonal cell (6A), and coefficient of variance (CoV) were used as an indicator of corneal injury and function. Totally 42 trials (23 RCTs and 19 prospective cohort studies), including 3916 eyes, underwent FLACS, and a total of 3736 eyes underwent CPS. ECL% is significantly lower in the FLACS group at 1–3 days (P = 0.005), 1 week (P = 0.004), 1 month (P<0.0001), 3 months (P = 0.001), and 6 months (P = 0.004) after surgery compared to CPS. ECD and ECL appeared no statistically significant difference between the two groups, except for the significant reduction of ECD at 3 months in the CPS group (P = 0.002). CCT was significantly lower in the FLACS group at 1 week (P = 0.05) and 1 month (P = 0.002) early postoperatively. While at 1–3 days (P = 0.50), 3 months (P = 0.18), and 6 months (P = 0.11), there was no difference between the FLACS group and the CPS group. No significant difference was found in the percentage of hexagonal cells and the coefficient of variance. FLACS, compared with CPS, reduces corneal injury in the early postoperative period. Corneal edema recovered faster in the FLACS group in the early postoperative period. In addition, FLACS may be a better option for patients with corneal dysfunction.

## Introduction

Cataract is one of the most common eye diseases and the major cause of vision loss worldwide [1]. Surgically removing the opacity lens and replacing it with an intraocular lens is currently

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the only treatment for cataracts [2]. Since its invention in the 1960s, phacoemulsification has continued to improve and remained the best therapy for cataracts [3]. Femtoseconds were first applied to promote the key steps of phacoemulsification in 2008 [4], such as corneal incision, lens fragmentation, and anterior capsulotomy [5]. Ever since the discussion on the comparison of femtosecond-laser assisted cataract surgery (FLACS) with conventional phacoemulsification surgery (CPS) has never ceased. Many studies these years have suggested the optimization of FLACS for cataract surgery, including enhancing the circularity of capsulotomy [6], reducing the effective phacoemulsification time (EPT) [7], and providing better IOL placement [8].

The transparency and barrier function of the cornea is mainly sustained by the corneal endothelium [9], composed of a single layer of the endothelial cell. The corneal endothelium has no regenerative capacity [10]. Once suffering from an injury, endothelial cells cannot proliferate [11], and the loss of endothelial cells is irreversible. The healing procedures occurred as the remaining surrounding endothelial cells enlarged and migrated to cover the damaged area [12]. As a result, the endothelial cells will increase in size and alter in shape from hexagonal to pleomorphic [13]. This leads to a change in the percentage of hexagonal cells (6A) and coefficient of variance (CoV), which illustrate the function of the residual endothelial cells. During cataract surgery procedures, phacoemulsification may increase the risk of endothelial cell loss [9]. It has long been shown that phacoemulsification results in approximately 4%-25% of endothelial cell loss [14, 15]. The negative effect of phaco cataract surgery on endothelium is multifactorial and largely due to thermal [16] and mechanical injury [17]. It has been proven to be associated with surgical instruments, phacoemulsification time, ultrasound energy, and contact with lens fragments during surgery [17–19]. Since femtosecond lasers are thought to modify the surgery procedure and lessen the usage of ultrasound, the effect of this technique on the endothelium is of concern.

The corneal indicators used in previous meta-studies were inadequate, and the included articles were not rigorous enough. A recently published meta-analysis selected endothelial cell loss (ECL) and central corneal thickness (CCT) as indicators to evaluate corneal damage. Kolb, et al., in the meta-analysis, noted a significant ECL decline in the FLACS group 1-3 months postoperatively, while there was no significant difference within 1 week and over 6 months. CCT was significantly higher in the CPS group in the early time. Later in the 6 months, the difference decrease [20]. It was worth mentioning that this paper not only included prospective but also retrospective studies, which are not as reliable as prospective studies and may lead to greater bias. In contrast, Chen et al. proposed in 2021 [21] that ECL was consistently significantly lower than CPS in the FLACS group in the first week after surgery. The study analyzed RCTs only, but there were multiple mistakes in the inclusion of the article. So, we supposed it is not credible enough. Besides ECL and CCT, there are other corneal indicators. As early as 2016, Chen et al. [22] used the endothelial cell loss rate (ECL%) to measure the damage to the corneal endothelium and concluded that the difference persists after surgery from 1 week to 3 months. ECL% is the ratio of the number of endothelial cells loss to preoperative endothelial cells, which eliminates the difference from baseline and therefore may be more statistically significant. However, the sample size was small at the time, and new related studies have been published in recent years. In addition, the morphology of the remaining corneal endothelial cells was also of our interest. It is represented by 6A and CoV, indicating the function of the residual endothelial cells. Corneal injury is an important effect of cataract surgery and is closely related to postoperative visual quality. Former studies had only discussed 1-2 corneal indicators. In our study, a variety of corneal indicators were selected to comprehensively evaluate the postoperative corneal condition. This meta-analysis aimed to compare corneal impact and function after FLACS and CPS to provide a reference for clinical application.

## Materials and methods

## Search strategy and inclusion criteria

The study followed the PRISMA guidelines (Preferred Reporting Item for Systematic Reviews and Meta-Analysis). PubMed, EMBASE, and Cochrane Library were searched by keywords: "femtosecond" OR "Femtolaser" AND "cataract" in full text. Complete and published clinical prospective trials comparing FLACS and CPS up to date December 31, 2021, were included. Reviews, conference abstracts, case reports, letters, correspondence articles, and editorials were excluded. The researches that combined with other ophthalmic surgery were excluded. Involved studies should meet the criteria as follow: 1) prospective randomized control trials or high-quality comparative cohort studies; 2) published in English or Chinese; 3) compared clinical indicators of patients undergoing simple cataract surgery with and without femtosecond laser assistant; 4) contains at least one indicator of ECD, ECL, ECL %, CCT, CoV, 6A.

## Screening process

Studies screening were carried out by two authors (HL. W and JJ. X) independently. Titles and abstracts were read to screen for qualified studies, and full-text reading was performed when necessary to determine eligibility for inclusion criteria. Articles in disagreement were confirmed by a third author (XY. C) after discussion.

## Quality assessment

The cohort studies were assessed by Newcastle-Ottawa Scale (NOS) [23]. The NOS is an 8-stars scale based on patient selection (four stars), comparability (one star), and outcomes (three stars). Cochrane Collaboration's tool for risk of bias [24] was applied to evaluate the quality of included RCTs by two independent authors (HL. W, JJ. X), which had random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

## Data extraction and outcome measurements

A standard data form was used in the extraction process, including the basic information such as title, authors, years, experimental design, sample size, clinical indicators, etc. All the disagreements were discussed and solved before data analysis and all of the data was double-checked by a second reviewer. Corneal endothelium-related clinical indicators at different postoperative time points were recorded with mean and standard deviation. When standard deviation was not reported, data were ruled out. Data expressed as medians and quartiles were converted to mean and standard deviation by Luo's formula [25]. Data containing subgroups in FLACS or CPS were combined.

## Data analysis

RevMan software (version 5.4; Cochrane Collaboration, Oxford, United Kingdom) was used in statistical analyses. The corneal indicators were recorded in continuous data presented by weighted mean differences (WMDs) with 95% CIs. Statistical heterogeneity was calculated using the chi-square test and I2 statistics, with I2 measures more than 50% being attributed to strong heterogeneity. When heterogeneity was demonstrated, random-effects models were used, otherwise fixed-effect models. It was regarded as a statistically significant difference between FLACS and CPS when the P value was less than 0.05. Sensitivity analysis assessed how the results would have changed if a single study had been omitted by a single-study deletion analysis.

## Results

## Literature research and trails characteristics

A total of 3281 studies were identified originally. One thousand six hundred ten duplicates were discarded. One thousand six hundred seventy-one left studies were screened by title and abstract. A full-text examination was conducted when necessary. After excluding all research that did not meet the criteria, 42 [26–67] trials remained (Fig 1). Of the included studies, 23 were RCTs, and 19 were comparative cohort studies. Totally 3916 eyes underwent FLACS, and 3736 eyes underwent CPS. Characteristics of all the trials are recorded in Table 1. The quality assessment of RCTs is presented in <u>S1</u> and <u>S2</u> Figs, while that of the comparative cohort is in <u>S1 Table</u>.





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Image         Image <t< th=""></t<>
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Kanellopoulos2016cohortLenSxGreece $67.3\pm11.99$ $69.92\pm11.73$ $27:40$ $29:37$ $67$ $66$ $12m$ Kelkar2020cohortCatalysIndia $64.5\pm9.7$ $65.4\pm8.4$ $56:33$ $57:41$ $89$ $98$ $6m$ Khan2017RCTLenSXPakistanNANA $23:25$ $25$ $25$ $1m$ Krarup2019RCTLensARDenmarkNANA $52:56$ $81$ $81$ $6m$ Krarup2021RCTLensARDenmarkNANANA $47$ $47$ $3m$ Liu2016cohortNAChina $50.1\pm3.3$ $49.6\pm2.6$ $15:6$ $14:7$ $21$ $21$ $12m$ Liu2021RCTLDV Z8Singapore $69.5\pm6.9$ $48:37$ $78$ $78$ $12m$
Kelkar2020cohortCatalysIndia $64.5\pm9.7$ $65.4\pm8.4$ $56:33$ $57:41$ $89$ $98$ $6m$ Khan2017RCTLenSXPakistanNANA $23:25$ $25$ $25$ $1m$ Krarup2019RCTLensARDenmarkNANA $52:56$ $81$ $81$ $6m$ Krarup2021RCTLensARDenmarkNANA $52:56$ $81$ $81$ $6m$ Krarup2014cohortLensARDenmarkNANANA $A7$ $47$ $3m$ Liu2016cohortNAChina $50.1\pm3.3$ $49.6\pm2.6$ $15:6$ $14:7$ $21$ $21$ $12m$ Liu2021RCTLDV Z8Singapore $69.5\pm6.9$ $48:37$ $78$ $78$ $12m$
Khan2017RCTLenSXPakistanNANA $23:2 \cdot$ 25251mKrarup2019RCTLensARDenmarkNANA $52:5 \cdot$ 81816mKrarup2021RCTLensARDenmark $7 \cdot$ $7 \cdot$ 31316mKrarup2014cohortLensARDenmarkNANANA47473mLiu2016cohortNAChina $50:1\pm3.3$ $49.6\pm2.6$ $15:6$ $14:7$ $21$ $21$ $12m$ Liu2021RCTLDV Z8Singapore $69.5\pm6.9$ $48:37$ $78$ $78$ $12m$
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Krarup2021RCTLensARDenmark $75$ $17:17$ 31316mKrarup2014cohortLensARDenmarkNANANAA7473mLiu2016cohortNAChina $50.1\pm3.3$ $49.6\pm2.6$ $15:6$ $14:7$ $21$ $21$ $12m$ Liu2021RCTLDV Z8Singapore $69.5\pm6.9$ $48:37$ $78$ $78$ $12m$
Krarup         2014         cohort         LensAR         Denmark         NA         NA         NA         47         47         3m           Liu         2016         cohort         NA         China         50.1±3.3         49.6±2.6         15:6         14:7         21         21         12m           Liu         2021         RCT         LDV Z8         Singapore         69.5±6.9         48:37         78         78         12m
Liu         2016         cohort         NA         China         50.1±3.3         49.6±2.6         15:6         14:7         21         21         12m           Liu         2021         RCT         LDV Z8         Singapore         69.5±6.9         48:37         78         78         12m
Liu 2021 RCT LDV Z8 Singapore 69.5+6.9 48:37 78 78 12m
Mencucci         2020         cohort         LenSx         Italy         73.9±7.7         74.5±5.8         NA         NA         20         20         6m
Mursch-Edlmayr         2017         RCT         Victus         Germany         72±6         31:19         50         50         6m
Niu         2018         cohort         LenSx         China         67.12±5.64         66.39±5.23         32:38         35:47         107         126         3m
Oka         2021         RCT         LenSx         Japan         73.4±6.5         20:33         53         53         7m
Pisciotta 2018 cohort LDV Z8 Italy 74.07±8.48 75.72±9.16 10:20 8:22 30 30 3m
Ranjini         2017         cohort         LenSx         India         NA         NA         NA         55         55         1m
Reddy         2021         cohort         Catalys         India         59.5±9.5         58.25±10.1         11:9         22:18         20         40         5w
Roberts         2019         RCT         LenSx         UK         69.9±10.9         70.5±9.8         100:100         82:118         200         200         1m
Schargus         2015         RCT         Catalys         Germany         71.8         15:22         37         37         6m
Schroeter         2021         RCT         LenSx         Switzerland         70.5±8.3         69.6±8.1         31:34         27:38         65         65         3m
Shi         2020         RCT         LenSx         China         61.09±10.87         144:134         150         150         3m
Takacs         2012         RCT         LenSx         Hungary         65.81±12.42         66.93±10.99         10:28         15:23         38         38         1m
Vasavada         2019         RCT         LenSx         India         67.21±11.11         63.70±11.84         NA         NA         91         91         6m
Wu         2017         RCT         NA         China         62.9±4.8         61.7±5.2         NA         NA         85         105         3m
Yang         2019         cohort         LenSx         China         60.51±3.41         61.43±3.46         25:22         24:23         47         47         3m
Yu         2015         cohort         LensAR         China         62.3±11.6         56.5±16.6         NA         NA         25         29         3m
Yu         2016         cohort         LenSx         China         69.66±9.27         72.74±8.83         33:37         23:31         70         54         6m

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## Endothelial cell loss rate (ECL%)

Fifteen studies reported postoperative ECL%. FLACS group demonstrated significantly lower ECL% at 1–3 days (WMD: -3.95, 95%CI: -6.70, -1.21, P = 0.005), 1 week (WMD: -3.09, 95%CI:

-5.19, -0.98, P = 0.004), 1 month (WMD: -3.14, 95%CI: -4.17, -1.57, P<0.0001), 3 months (WMD: -4.72, 95%CI: -7.62, -1.82, P = 0.001) and 6 months (WMD: -1.60, 95%CI: -2.70, -0.50, P = 0.004) postoperatively (Fig 2).

## Endothelial cell density (ECD) and Endothelial cell loss (ECL)

There was no significant difference in ECD at 1–3 days (WMD:-12.40, 95%CI:-109.56, 84.76, P = 0.80), 1 week (WMD:10.58, 95%CI:-64.10, 85.26, P = 0.78), 1 month (WMD:21.14, 95% CI:-77.01, 119.29, P = 0.67), 6 months (WMD:-1.23, 95%CI:-68.27, 65.81, P = 0.97) and 12 months (WMD:6.80, 95%CI:-52.86, 66.47, P = 0.82) after surgery between two groups, and significant difference at 3 months (WMD: 84.49, 95%CI:31.25, 137.73, P = 0.002, Fig 3).

Similarly, there was no significant difference in ECL at 1–3 days (WMD: 50.95, 95%CI: -24.92, 126.82, P = 0.19), 15–40 days (WMD: 11.49, 95%CI: -67.40, 90.38, P = 0.78), 2–3 months (WMD:2.81, 95%CI: -32.61, 38.23, P = 0.88), and 6 months (WMD: -19.72, 95%CI: -85.63, 46.19, P = 0.56) after surgery between two groups (Fig 4).

## Central corneal thickness (CCT)

Fifteen studies reported postoperative CCT. No statistically significant difference was found between FLACS and CPS at 1–3 days (WMD: -3.98, 95%CI: -15.61, 7.64, P = 0.50) after surgery. Significantly lower CCT was observed in FLACS compared to CPS at 1 week (WMD: -6.17, 95%CI: -12.29, -0.06, P = 0.05) and 1 month (WMD: -6.86, 95%CI: -10.15, -2.04, P = 0.002). Whereas, later at 3 months (WMD: -4.99, 95%CI: -12.28, 2.30, P = 0.18) and 6 months (WMD: -3.44, 95%CI: -7.70, -0.82, P = 0.11), there was no statistically significant difference between two groups (Fig 5).

## Percentage of hexagonal cells (6A)

As was reported by seven researches, no significant difference was found between FLACS and CPS group at 1 month (WMD: -0.36, 95%CI: -3.04, 2.32, P = 0.79), 3 months (WMD: 0.25, 95%CI: -1.42, 1.92, P = 0.77) and 6 months (WMD: -0.58, 95%CI: -1.79, -0.62, P = 0.34, Fig 6).

## Coefficient of variance (CoV)

Five researches reported CoV were enrolled. No significant difference was found between the two groups at 1 month (WMD: -0.76, 95%CI: -1.99, 0.48, P = 0.23), 3 months (WMD: 0.47, 95%CI: -0.78, 1.73, P = 0.46) and 6 months (WMD: 0.35, 95%CI: -0.64, 1.34, P = 0.48, Fig 7).

## Discussion

This meta-analysis study showed the impact of FLACS on postoperative corneal endothelial injury compared to CPS. FLACS reduced ECL% significantly at each time point postoperatively. And CCT favored FLACS at 1 week and 1 month early after surgery.

The ECL% of the FLACS group was significantly lower than that of the CPS group at each time point during 6 months postoperatively, indicating that FLACS has reduces the injury of corneal endothelial cells. This was consistent with previously published meta-analysis [22]. Cataract surgical injury may result in a decrease in corneal endothelial cells, thus affecting the function of the cornea, and leading to corneal edema. Several factors had been reported to be involved in endothelial cell loss, such as ultrasound energy, phacoemulsification time, irrigation time, and usage of balanced salt solution during operation [68–70]. In FLACS, the nucleus of the lens is pre-fragmented by a femtosecond laser instead of manipulation. This allows less

	FLACS				CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen 2017	17.18	16.28	47	30.81	21.8	48	9.5%	-13.63 [-21.36, -5.90]	
Chlasta-Twardzik 2019	8.93	2.54	26	11.4	2.69	61	36.2%	-2.47 [-3.66, -1.28]	+
Fan 2018	12.9	9.3	16	16.8	4.4	15	16.7%	-3.90 [-8.97, 1.17]	
Liu 2016	1.66	5.62	21	6.17	5.92	21	23.8%	-4.51 [-8.00, -1.02]	
Yu 2016	14.247	15.805	70	14.518	17.352	54	13.8%	-0.27 [-6.20, 5.66]	
Total (95% CI)			180			199	100.0%	-3.95 [-6.70, -1.21]	
Heterogeneity: Tau <sup>2</sup> = 5.0	15; Chi <sup>2</sup> = 1		-20 -10 0 10 20						
Test for overall effect: Z =	2.82 (P =	Favours [FLACS] Favours [CPS]							

#### B.1 week postoperative

	FLACS CPS						Mean Difference Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen 2017	13.1	13.13	47	26.44	20.79	48	7.1%	-13.34 [-20.32, -6.36]	
Chlasta-Twardzik 2019	9.42	2.45	26	12.41	2.76	61	30.4%	-2.99 [-4.16, -1.82]	+
Conrad-Hengerer 2013	7.9	7.8	73	12.1	7.3	73	23.0%	-4.20 [-6.65, -1.75]	
Mencucci 2020	4.65	1.94	20	5.94	1.72	20	30.5%	-1.29 [-2.43, -0.15]	-
Yu 2016	16.399	16.827	70	14.872	17.105	54	8.9%	1.53 [-4.50, 7.56]	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 3.4	4; Chi² = 1	17.79, df	236 = 4 (P =	0.001);	l²= 78%	256	100.0%	-3.09 [-5.19, -0.98]	-20 -10 0 10 20
Test for overall effect: Z =	2.88 (P =	0.004)							Favours [FLACS] Favours [CPS]

#### C.1 month postoperative

		F	LACS			CPS			Mean Difference	Mean Difference	
Ļ	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
	Al-Mohtaseb 2017	6	8.02	60	9.06	8.77	60	11.5%	-3.06 [-6.07, -0.05]		
	Chen 2017	11.42	12.1	47	25.67	18.87	48	4.7%	-14.25 [-20.61, -7.89]		
	Chlasta-Twardzik 2019	9.53	2.45	26	12.94	2.76	61	17.9%	-3.41 [-4.58, -2.24]	+	
	Dzhaber 2020	10.7	20	67	6.8	18	67	4.6%	3.90 [-2.54, 10.34]		
	Fan 2018	21.3	9.7	16	27.2	4.2	15	6.3%	-5.90 [-11.11, -0.69]	<u> </u>	
	Mencucci 2020	5.38	1.82	20	7.97	2.02	20	17.9%	-2.59 [-3.78, -1.40]	*	
	Niu 2018	3.81	1.24	107	8.56	2.05	126	19.6%	-4.75 [-5.18, -4.32]	•	
	Roberts 2019	10.2	13.7	200	9.7	13.7	200	12.6%	0.50 [-2.19, 3.19]		
	Yu 2016	17.359	17.052	70	17.163	17.204	54	5.0%	0.20 [-5.89, 6.28]		
										•	
	Total (95% CI)			613			651	100.0%	-3.14 [-4.71, -1.57]	•	
	Heterogeneity: Tau <sup>2</sup> = 3.2	4; Chi <sup>2</sup> = -	45.37, df	= 8 (P <	< 0.00001	l); I <sup>2</sup> = 82	%			-20 -10 0 10 20	
	Test for overall effect: Z =	3.91 (P <	0.0001)							-20 -10 0 10 20	

#### D.3 months postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Chen 2017	7.85	8.59	47	19.96	16.81	48	10.9%	-12.11 [-17.46, -6.76]	
Conrad-Hengerer 2013	8.1	8.1	73	13.7	8.4	73	15.2%	-5.60 [-8.28, -2.92]	
Dzhaber 2020	11.2	17.9	67	8	18.5	67	9.7%	3.20 [-2.96, 9.36]	
Fan 2018	23.6	7.2	16	30.9	5.4	15	12.3%	-7.30 [-11.76, -2.84]	
Liu 2021	1.5	0.3	78	7	2.4	78	17.3%	-5.50 [-6.04, -4.96]	•
Niu 2018	6.58	2.16	107	12.35	3.12	126	17.2%	-5.77 [-6.45, -5.09]	•
Vasavada 2019	9.76	1.6	91	9.85	1.1	91	17.3%	-0.09 [-0.49, 0.31]	1
Total (95% CI)			479			498	100.0%	-4.72 [-7.62, -1.82]	•
Heterogeneity: Tau <sup>2</sup> = 12.	60; Chi²	= 370.	76, df=	= 6 (P <	0.00001	);  ² = 9	98%		
Test for overall effect: Z =	3.19 (P =	= 0.00	1)						Favours [FLACS] Favours [CPS]

#### E.6 months postoperative

		FLACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Bascaran 2018	6.4	11.6	92	6.33	9	92	8.1%	0.07 [-2.93, 3.07]	-
Chlasta-Twardzik 2019	9.32	2.51	26	13.44	3.28	61	16.2%	-4.12 [-5.39, -2.85]	+
Fan 2018	23.9	7.9	16	29.8	5.9	15	4.1%	-5.90 [-10.79, -1.01]	
Liu 2021	7.2	1.9	78	8.2	2.6	78	19.0%	-1.00 [-1.71, -0.29]	•
Mencucci 2020	5.85	1.77	20	8.23	2.11	20	16.5%	-2.38 [-3.59, -1.17]	+
Oka 2021	1.5	5.6	53	2.7	5.2	53	12.0%	-1.20 [-3.26, 0.86]	
Vasavada 2019	7.55	1.8	91	8.2	0.87	91	20.0%	-0.65 [-1.06, -0.24]	-
Yu 2016	17.06	15.197	70	13.089	12.542	54	4.1%	3.97 [-0.91, 8.86]	
Total (95% CI)			446			464	100.0%	-1.60 [-2.70, -0.50]	•
Heterogeneity: Tau <sup>2</sup> = 1.5 Test for overall effect: Z =	3; Chi² = 2.84 (P	-20 -10 0 10 20							

# Fig 2. Forest plot of postoperative ECL% between FLACS and CPS at A. 1–3 days, B. 1 week, C. 1 month, D. 3 months, and E. 6 months.

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application of ultrasound energy and irrigating solution during cataract surgery [29], thereby reducing its damage to endothelial cells. As was reported by Abell [27] and Oshika [71], the effect of FLACS may be due to the lower requirement of effective phacoemulsification time (EPT), ultrasound energy, and irrigation fluid compared to CPS.

	FL	ACS		C	PS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Chlasta-Twardzik 2019	2,098.5	361.5	26	2,242.24	288.57	61	18.3%	-143.74 [-300.43, 12.95]	
Conrad-Hengerer 2013	2,147	328	73	2,174	330	73	24.5%	-27.00 [-133.73, 79.73]	
Fan 2018	1,821	559	16	1,727	480	15	5.9%	94.00 [-272.10, 460.10]	
Krarup 2014	2,409	499	47	2,369	500	47	13.9%	40.00 [-161.95, 241.95]	
Takacs 2012	2,860	217	38	2,719	350	38	21.3%	141.00 [10.07, 271.93]	
Yu 2016	2,216.086	419.845	70	2,343.444	548.02	54	16.2%	-127.36 [-303.53, 48.82]	
Total (95% CI)			270			288	100.0%	-12.40 [-109.56, 84.76]	-
Heterogeneity: Tau <sup>2</sup> = 707	2.10; Chi# =	10.25, df =	5 (P =	0.07); I* = 5	1%				£00 250 0 250 500
Test for overall effect: Z =	0.25 (P = 0.8	0)							Favours [FLACS] Favours [CPS]

#### B.1 week postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chlasta-Twardzik 2019	2,087.38	361.15	26	2,216.64	291.05	61	12.0%	-129.26 [-286.12, 27.60]	
Conrad-Hengerer 2013	2,208	248	73	2,155	254	73	19.5%	53.00 [-28.43, 134.43]	
Gao 2018	2,256.34	110.57	59	2,148.26	128.26	47	23.2%	108.08 [61.81, 154.35]	
Mencucci 2020	2,110.15	286.32	20	2,178.9	347.2	20	9.2%	-68.75 [-265.98, 128.48]	
Reddy 2021	2,484	261	20	2,445	305	40	12.7%	39.00 [-109.38, 187.38]	
Takacs 2012	2,730	205	38	2,669	377	38	13.8%	61.00 [-75.44, 197.44]	
Yu 2016	2,169	479.025	70	2,336.722	565.033	54	9.7%	-167.72 [-355.62, 20.17]	
Total (95% CI)			306			333	100.0%	10.58 [-64.10, 85.26]	+
Heterogeneity: Tau <sup>2</sup> = 571	12.72; Chi2:	= 17.08, df	= 6 (P	= 0.009); l <sup>2</sup> =	65%				-500 -250 0 250 500
Test for overall effect: Z =	0.28 (P = 0.	78)							Favours [FLACS] Favours [CPS]

C.1 month postoperative

	FI	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Al-Mohtaseb 2017	2,254.84	264.46	60	2,255.53	262.93	60	7.8%	-0.69 [-95.05, 93.67]	
Cavallini 2019	2,233.91	460.15	80	2,095.54	391.23	80	7.3%	138.37 [6.02, 270.72]	
Chee 2021	2,239.33	418	45	2,513	358	48	6.9%	-273.67 [-432.33, -115.01]	
Chlasta-Twardzik 2019	2,084.58	359.49	26	2,204.03	296.81	61	6.9%	-119.45 [-276.43, 37.53]	
Dzhaber 2020	2,370	580	67	2,467	564	67	6.3%	-97.00 [-290.72, 96.72]	
Fan 2018	1,665	571	16	1,517	452	15	3.9%	148.00 [-213.39, 509.39]	
Khan 2017	2,712	218	25	2,240	238	25	7.4%	472.00 [345.48, 598.52]	
Mencucci 2020	2,093.55	323.7	20	2,133.85	353.58	20	6.1%	-40.30 [-250.39, 169.79]	
Niu 2018	2,328	416.4	107	2,229	413.7	126	7.6%	99.00 [-7.97, 205.97]	
Ranjini 2017	1,975.6	323.7	55	2,073.7	236.6	55	7.6%	-98.10 [-204.06, 7.86]	
Reddy 2021	2,357	318	20	2,409	339	40	6.6%	-52.00 [-226.53, 122.53]	
Schroeter 2021	2,096	513.3	65	1,961	516.5	65	6.6%	135.00 [-42.02, 312.02]	
Takacs 2012	2,738	245	38	2,542	466	38	6.7%	196.00 [28.61, 363.39]	
Yu 2015	2,120	430.4	25	2,192.1	382.3	29	5.9%	-72.10 [-290.79, 146.59]	
Yu 2016	2,146.657	488.999	70	2,274.241	553.488	54	6.4%	-127.58 [-314.44, 59.27]	
Total (95% CI)			719			783	100.0%	21.14 [-77.01, 119.29]	+

Heterogeneith, Tau<sup>#</sup> = 29934.67; Chi<sup>#</sup> = 86.63; df = 14 (P < 0.00001); i<sup>#</sup> = 84% Test for overall effect Z = 0.42 (P = 0.67) Favours (FLACS) Favours (CPS)

#### D.3 months postoperative

		LHOU						medir binerenee	medit birter energy
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Cavallini 2019	2,172.79	396.73	80	2,037.62	405.49	80	7.9%	135.17 [10.86, 259.48]	
Conrad-Hengerer 2013	2,207	264	73	2,115	290	73	9.9%	92.00 [2.04, 181.96]	
Day 2021	2,398	492	346	2,376	500	311	10.8%	22.00 [-54.00, 98.00]	
Duan 2017	2,317.8	512.8	74	2,091.3	492.8	74	6.1%	226.50 [64.46, 388.54]	
Dzhaber 2020	2,374	527	67	2,433	526	67	5.4%	-59.00 [-237.29, 119.29]	
Fan 2018	1,606	518	16	1,440	445	16	2.1%	166.00 [-168.61, 500.61]	
Kanellopoulos 2016	2,325.33	487.79	67	2,348.12	286.63	66	7.3%	-22.79 [-158.53, 112.95]	
Krarup 2014	2,230	536	47	2,170	603	47	3.8%	60.00 [-170.65, 290.65]	
Liu 2021	2,583	624	78	2,462	589	78	5.0%	121.00 [-69.43, 311.43]	
Niu 2018	2,260	408.3	107	2,038	403.6	126	9.0%	222.00 [117.35, 326.65]	
Schroeter 2021	2,130	450.3	65	1,966	567.7	65	5.5%	164.00 [-12.15, 340.15]	
Shi 2020	1,918.6	507	150	1,942.9	419.2	150	9.0%	-24.30 [-129.58, 80.98]	
Wu 2017	2,243.2	584.2	85	2,216.7	583.9	105	5.8%	26.50 [-140.53, 193.53]	
Yang 2019	2,243.64	253.48	47	2,047.91	264.47	47	9.0%	195.73 [91.00, 300.46]	
Yu 2015	2,044.1	485.5	25	2,166.6	426	29	3.5%	-122.50 [-367.97, 122.97]	
Total (95% CI)			1327			1334	100.0%	84.49 [31.25, 137.73]	◆
Heterogeneity: Tau <sup>2</sup> = 535	54.44: Chi <sup>2</sup> :	= 30.56. 0	if = 14	(P = 0.006)	: I <sup>2</sup> = 54%	5			to to to to to
Test for overall effect Z =	3.11 (P = 0.	002)							-500 -250 0 250 500

#### E.6 months postoperative

FLACS UPS										Mean Difference		Mean Difference
	Study or Subgroup	Mea	n	SD T	otal	Mean		D Total	Weight	IV, Random, 95	% CI	IV, Random, 95% Cl
	Bascaran 2018	2,246.3	1 403	.48	92	2,211.88	392.	19 92	11.3%	34.43 [-80.59, 149	3.45]	
	Chlasta-Twardzik 2019	2,089.4	6 360	.01	26	2,191.36	298.	78 61	8.7%	-101.90 [-259.29, 55	5.49]	
	Fan 2018	1,59	9 5	520	16	1,457	4:	23 15	3.3%	142.00 [-190.78, 474	1.78]	
	Kelkar 2020	2,61	4 3	379	89	2,448	2	74 98	12.6%	166.00 [70.38, 261	.62]	
	Krarup 2019	2,30	8 4	195	81	2,258	5:	31 81	8.7%	52.00 [-106.09, 210	0.09]	
	Liu 2021	2,43	4 4	48	78	2,433	5	32 78	8.9%	1.00 [-153.35, 155	5.35]	
	Mencucci 2020	2,083.4	5 279	.77	20	2,127.75	353.	25 20	6.8%	-44.30 [-241.79, 153	3.19]	
	Oka 2021	2,58	3 2	215	53	2,561	21	30 53	12.9%	22.00 [-68.83, 112	2.83]	
	Schargus 2015	2,75	8 3	870	37	2,736	3:	25 37	8.7%	22.00 [-136.68, 180	0.68]	
	Vasavada 2019	2,157	8 39	2.7	91	2,246.8	570	.3 91	9.6%	-88.80 [-231.07, 53	3.47]	
	Yu 2016	2,155.88	6 453.8	861	70 2	2,382.519	448.0	03 54	8.6%	-226.65 [-386.60, -66	5.71]	
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 69 Test for overall effect: Z =	10.43; Chi <sup>a</sup> 0.04 (P = 1	= 23.80, 0.97)	df = 1	653 0 (P =	0.008); I²	= 58%	100.0%	-1.23 [-68.27, 65	.81] _	-500 -250 0 250 500 Favours [FLACS] Favours [CPS]	
	F.12 months	posto	pera	tive	e							
		FL	ACS			CPS			Mea	n Difference		Mean Difference
	Study or Subgroup	Mean	SD T	otal	Mear	1 SD	Total	Weight		IV, Fixed, 95% CI		IV, Fixed, 95% CI
	Day 2020a	2.404	434	311	2.413	3 406	292	79.2%	-9.	00 [-76.05. 58.05]		
	Fan 2018	1 560	519	16	1 41	5 434	15	3 2%	145.00	I-191 02 481 021		
	Liu 2021	2 406	496	70	2 261	416	70	17 7%	52.0	0 1.00 07 104 071		
	LIG 2021	2,400	400	10	2,000	410	10	17.7 20	55.0	0[00.57, 154.57]		
	T-4-LIOFN OD			105			205	400.00		001 50 00 00 171		<b>_</b>
	Total (95% CI)		'	405			365	100.0%	0.3	00[-32.00, 00.47]		· · · · ·
	Heterogeneity: Chi <sup>2</sup> =	1.27, df=	= 2 (P =	0.53)	); I* = I	0%					500	-250 0 250 500
	Test for overall effect:	Z = 0.22	(P = 0.8	32)							500	Favours [FLACS] Favours [CPS]
												· · · · · · · · · · · · · · · · · · ·



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Lacking regenerative ability, the total amount of cells was no longer compensated after endothelial cell loss. Instead, migration and enlargement of residual cells occur as a corneal repairing procedure [9]. The remaining cells migrate to the injured area, resulting in a gradual increase in endothelial cell density when measuring at the center of the cornea [12]. This process takes months [72], therefore, lower ECL% on the first day after surgery indicated less

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Krarup 2014	249	744	47	235	681	47	6.9%	14.00 [-274.35, 302.35]	·
Mursch-Edimayr 2017	48	188	50	-5.7	212.5	50	93.1%	53.70 [-24.94, 132.34]	
Total (95% CI)			97			97	100.0%	50.95 [-24.92, 126.82]	
Heterogeneity: Chi² = 0.1 Test for overall effect: Z :	07, df = 1 = 1.32 (F	P = 0.1	0.79); I 9)	*=0%					-200 -100 0 100 200 Favours (FLACS) Favours (CPS)

#### B.15-40 days postoperative

		FLACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Abell 2013	224.9	188.95	150	143.8	208.3	51	14.6%	81.10 [16.43, 145.77]	
Abell 2014	103	208	405	138	189	215	15.7%	-35.00 [-67.38, -2.62]	
Chee 2021	270	179	45	173	162	48	14.4%	97.00 [27.46, 166.54]	
Kelkar 2020	193	240	89	187	156	98	14.8%	6.00 [-52.65, 64.65]	
Krarup 2019	344	99	81	497	117	81	15.7%	-153.00 [-186.38, -119.62]	
Krarup 2021	550	220	31	450	35	31	13.9%	100.00 [21.58, 178.42]	
Mursch-Edlmayr 2017	128.8	403	50	124.64	285	50	10.9%	4.16 [-132.65, 140.97]	
Total (95% CI)		0.17	851			574	100.0%	11.49 [-67.40, 90.38]	
Heterogeneity: Tau* = 10 Test for overall effect: Z :	= 0.29 (F	Cni <sup>2</sup> = 8 P = 0.78)	r.51, di	т= 6 (P <	0.00001	l); l* = {	93%		-200 -100 0 100 200 Favours [FLACS] Favours [CPS]

#### C.2-3 months postoperative

	1	FLACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Day 2020	242	416	392	200	369	393	41.5%	42.00 [-13.02, 97.02]	
Hansen 2020	209	427	64	225	534	71	4.8%	-16.00 [-178.40, 146.40]	
Kelkar 2020	203	248	89	199	168	98	33.4%	4.00 [-57.33, 65.33]	_ <b>_</b>
Krarup 2014	274	358	47	333	422	47	5.0%	-59.00 [-217.21, 99.21]	
Mursch-Edimayr 2017	68.6	258.4	50	97.7	323.5	50	9.5%	-29.10 [-143.86, 85.66]	
Pisciotta 2018	162.27	225.11	30	322.52	339.93	30	5.9%	-160.25 [-306.14, -14.36]	
Total (95% CI)			672			689	100.0%	2.81 [-32.61, 38.23]	+
Heterogeneity: Chi <sup>2</sup> = 7.8	68, df = 5	(P = 0.17)	); I <sup>2</sup> = 3	5%					-200 -100 0 100 200
Test for overall effect: Z =	= 0.16 (P =	= 0.88)							Favours [FLACS] Favours [CPS]

#### D.6 months postoperative

	I	LACS			CPS			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, Random, 95% C	1	
Abell 2014	150	244	405	149	233	215	23.2%	1.00 [-38.18, 40.18]				
Kelkar 2020	219	260	89	214	195	98	20.1%	5.00 [-61.40, 71.40]				
Krarup 2019	362	88	81	465	88	81	24.3%	-103.00 [-130.10, -75.90]				
Krarup 2021	606	166	31	559	131	31	19.1%	47.00 [-27.44, 121.44]				
Mursch-Edimayr 2017	39.4	298.3	50	76.8	338.6	50	13.2%	-37.40 [-162.48, 87.68]			-	
Total (95% CI)			656			475	100.0%	-19.72 [-85.63, 46.19]				
Heterogeneity: Tau <sup>2</sup> = 44 Test for overall effect: Z =	468.96; ( = 0.59 (F	Chi <sup>2</sup> = 3 P = 0.56)	0.30, df )	′= 4 (P <	< 0.000	01); I² =	87%		-200	-100 0	100	200
										ravouis (rEACO) ravouis	[01:0]	

# Fig 4. Forest plot of postoperative ECL between FLACS and CPS at A. 1–3 days, B. 15–40 days, C. 2–3 months, and D. 6 months.

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damage to the corneal endothelium in the FLACS group. The long-term follow-up (3 months, 6 months) in the general population subgroup (S3 Fig) showed no significant difference between the two groups. It meant that the corneal endothelium can be repaired to a similar level in the FLACS and CPS groups. And the low ECL% in the FLACS group at 1 week and 1 month after surgery indicated that the corneal endothelial repair was faster in the FLACS group.

Differences in ECL% at 3 and 6 months after surgery proposed a persistent effect of FLACS and CPS on the cornea, but we found that the main impact may come from studies targeted to a specific population. Subgroup analysis of the general population revealed that ECL% at 1–3 days, 1 week, and 1 month in the FLACS group was still significantly lower than the CPS group, while no significant difference was found at 3 months and 6 months after surgery. Fuch's syndrome or hard nuclear patients were not included in the subgroup. This result suggested that differences in ECL% in long-term follow-up are mainly caused by special populations. Fuchs' endothelial corneal dystrophy patients were in a state of corneal decompensation

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Abell 2014	601	46	405	618	48	215	13.2%	-17.00 [-24.83, -9.17]	
Chen 2017	570.98	51.4	47	599.21	59.4	48	9.2%	-28.23 [-50.55, -5.91]	
Chlasta-Twardzik 2019	578.69	47.79	26	575.37	44.61	61	9.5%	3.32 [-18.19, 24.83]	
Conrad-Hengerer 2013	626	47	73	639	45	73	11.4%	-13.00 [-27.93, 1.93]	
Dzhaber 2020	607	59	67	574	45	67	10.6%	33.00 [15.23, 50.77]	
Kanellopoulos 2016	601.68	69.22	67	579.45	54.23	66	9.6%	22.23 [1.11, 43.35]	
Schargus 2015	591	50	37	590	52	37	9.0%	1.00 [-22.24, 24.24]	
Takacs 2012	580	42	38	607	91	38	6.8%	-27.00 [-58.87, 4.87]	
Vasavada 2019	540.4	49.4	91	556	12.5	91	12.6%	-15.60 [-26.07, -5.13]	
Yu 2016	587.229	81.122	70	585.556	68.888	54	8.1%	1.67 [-24.76, 28.11]	<del></del>
Total (95% CI)			921			750	100.0%	-3.98 [-15.61, 7.64]	
Heterogeneity: Tau <sup>2</sup> = 250	0.65; Chi <sup>2</sup> =	42.36, dt	'= 9 (P	< 0.00001	); l <sup>2</sup> = 79	%		-	-50 -25 0 25 50
Test for overall effect: Z =	0.67 (P = 0	.50)							Favours [FLACS] Favours [CPS]

### B.1 week postoperative

	FL	ACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Chlasta-Twardzik 2019	561.96	35.24	26	574.1	79.64	31	3.9%	-12.14 [-43.28, 19.00]	
Conrad-Hengerer 2013	580	44	73	582	49	73	16.4%	-2.00 [-17.11, 13.11]	
Dzhaber 2020	595	63	67	604	57	67	9.0%	-9.00 [-29.34, 11.34]	
Kanellopoulos 2016	553.89	57.98	67	551.96	43.2	66	12.4%	1.93 [-15.43, 19.29]	
Mencucci 2020	553	30.97	20	548.6	40.21	20	7.6%	4.40 [-17.84, 26.64]	
Takacs 2012	554	36	38	559	52	38	9.3%	-5.00 [-25.11, 15.11]	
Vasavada 2019	535.5	44.3	91	551	40.8	91	24.4%	-15.50 [-27.87, -3.13]	
Yu 2016	539.986	40.66	70	545.185	42.565	54	17.0%	-5.20 [-20.02, 9.62]	
Total (95% CI)			452			440	100.0%	-6.17 [-12.29, -0.06]	•
Heterogeneity: Chi <sup>2</sup> = 4.4	3, df = 7 (P	= 0.73);	I <sup>2</sup> = 0%	, ,					-50 -25 0 25 50
Test for overall effect: Z =	1.98 (P = 0	.05)							Favours [FLACS] Favours [CPS]

## C.1 month postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Yu 2016	529.914	43.699	70	534.759	38.671	54	7.1%	-4.85 [-19.38, 9.69]	
Vasavada 2019	532.3	40.9	91	530.1	39.6	91	11.0%	2.20 [-9.50, 13.90]	
Takacs 2012	545	31	38	557	42	38	5.5%	-12.00 [-28.60, 4.60]	
Ranjini 2017	575.45	49.24	55	571.04	32.48	55	6.2%	4.41 [-11.18, 20.00]	
Mencucci 2020	546.8	30.68	20	540.65	36.39	20	3.5%	6.15 [-14.71, 27.01]	
Kanellopoulos 2016	539.5	51.15	67	541.05	38.54	66	6.4%	-1.55 [-16.93, 13.83]	
Dzhaber 2020	593	50	67	590	57	67	4.6%	3.00 [-15.16, 21.16]	
Conrad-Hengerer 2013	552	37	73	553	36	73	10.7%	-1.00 [-12.84, 10.84]	
Chlasta-Twardzik 2019	548.69	28.76	26	563	29.14	61	8.6%	-14.31 [-27.56, -1.06]	
Chen 2017	537.45	35.96	47	558.71	48.82	48	5.1%	-21.26 [-38.48, -4.04]	
Cavallini 2019	544.14	50.92	80	573.31	58.11	80	5.3%	-29.17 [-46.10, -12.24]	
Abell 2014	548	34	405	556	51	215	26.2%	-8.00 [-15.58, -0.42]	
Total (95% CI)			1039			868	100.0%	-6.28 [-10.15, -2.40]	◆
Heterogeneity: Chi <sup>2</sup> = 19.3	35. df = 11 (	(P = 0.06)	$ ^2 = 4$	3%					
Test for overall effect: Z =	3.17 (P = 0	002)							-50 -25 0 25 50
		/							Favours [FLACS] Favours [CPS]

## D.3 months postoperative

	F	ACS			CPS			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV, Fixed, 95% Cl	
Kanellopoulos 2016	538.21	49.43	67	537.51	37.22	66	24.1%	0.70 [-14.16, 15.56]			
Dzhaber 2020	578	52	67	578	48	67	18.5%	0.00 [-16.95, 16.95]			
Conrad-Hengerer 2013	551	37	73	553	35	73	38.9%	-2.00 [-13.68, 9.68]			
Cavallini 2019	540.39	59.11	80	564.12	50.02	80	18.5%	-23.73 [-40.70, -6.76]		_ <b>-</b>	
Total (95% CI)			287			286	100.0%	-4.99 [-12.28, 2.30]		· · ·	
Heterogeneity: Chi <sup>2</sup> = 5.83	, df = 3 (F	9 = 0.12	); $ ^2 = 4$	9%					-50	-25 0 25	50
Test for overall effect: Z =	1.34 (P =	0.18)								Favours [FLACS] Favours [CPS]	

### E.6 months postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Abell 2014	541	28	405	550	45	215	41.5%	-9.00 [-15.60, -2.40]	
Bascaran 2018	534.89	33.02	92	532.04	32.19	92	20.4%	2.85 [-6.57, 12.27]	
Chlasta-Twardzik 2019	543.16	29.45	26	552.98	52.48	61	6.0%	-9.82 [-27.19, 7.55]	
Kanellopoulos 2016	537.92	46.6	67	536.72	37.14	66	8.8%	1.20 [-13.11, 15.51]	
Mencucci 2020	546.9	30.44	20	538.1	37.1	20	4.1%	8.80 [-12.23, 29.83]	
Schargus 2015	555	35	37	551	35	37	7.1%	4.00 [-11.95, 19.95]	
Yu 2016	518.7	32.753	70	522.426	36.081	54	12.0%	-3.73 [-16.03, 8.58]	
Total (95% CI)			717			545	100.0%	-3.44 [-7.70, 0.82]	•
Heterogeneity: Chi <sup>2</sup> = 7.5	0, df = 6 (F	P = 0.28)	I <sup>2</sup> = 20	%				+	50 -25 0 25 50
Test for overall effect: Z =	1.58 (P =	0.11)							Favours [FLACS] Favours [CPS]

Fig 5. Forest plot of postoperative CCT between FLACS and CPS at A. 1–3 days, B. 1 week, C. 1 month, D. 3 months, and E. 6 months.

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#### A.1 month postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kelkar 2020	46.4	8.4	89	47.8	9.5	98	33.9%	-1.40 [-3.97, 1.17]	
Krarup 2019	50	11	81	53	13	81	25.3%	-3.00 [-6.71, 0.71]	
Krarup 2021	56	26	31	53	21	31	4.7%	3.00 [-8.77, 14.77]	
Schroeter 2021	41.07	6.27	65	39.03	7.15	65	36.0%	2.04 [-0.27, 4.35]	<b>↓</b> ■
Total (95% CI)			266			275	100.0%	-0.36 [-3.04, 2.32]	-
Heterogeneity: Tau <sup>2</sup> :	= 3.79; C	hi² = 6	.89, df =	= 3 (P =	0.08);	I <sup>2</sup> = 56	%		
Test for overall effect	: Z = 0.26	6 (P = 0	0.79)	1					-10 -5 U 5 10 Favours (FLACS) Favours (CPS)

#### B.3 months postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Kelkar 2020	46.3	8.4	89	47.4	9.8	98	41.0%	-1.10 [-3.71, 1.51]	
Krarup 2014	53	11	47	53	10	47	15.5%	0.00 [-4.25, 4.25]	
Schroeter 2021	43.06	6.58	65	41.46	8.07	65	43.6%	1.60 [-0.93, 4.13]	+=
Total (95% CI)			201			210	100.0%	0.25 [-1.42, 1.92]	•
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	2.13, df Z = 0.29	= 2 (P 9 (P = 0	= 0.34) 0.77)	); I² = 69	6				-10 -5 0 5 10 Favours (FLACS) Favours (CPS)

#### C.6 months postoperative

	F	LACS			CPS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bascaran 2018	55.29	8.59	92	56.62	0.15	92	47.0%	-1.33 [-3.09, 0.43]	
Kelkar 2020	46.1	8.3	89	47.1	9.9	98	21.2%	-1.00 [-3.61, 1.61]	
Krarup 2019	55	11	81	53	11	81	12.6%	2.00 [-1.39, 5.39]	
Krarup 2021	54	26	31	56	26	31	0.9%	-2.00 [-14.94, 10.94]	
Vasavada 2019	54.1	10.2	91	54	9.1	91	18.3%	0.10 [-2.71, 2.91]	-+
Total (95% CI)			384			393	100.0%	-0.58 [-1.79, 0.62]	•
Heterogeneity: Chi2 =	: 3.30, df	= 4 (P	= 0.51)	); I <sup>2</sup> = 09	6			· · · · ·	
Test for overall effect	Z = 0.95	(P = (	0.34)						Favours [FLACS] Favours [CPS]

#### Fig 6. Forest plot of postoperative 6A between FLACS and CPS at A. 1 month, B. 3 months, and C. 6 months.

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#### A.1 month postoperative



#### B.3 months postoperative

	-								
	FLACS			CPS				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Kelkar 2020	34.2	6.6	89	33.6	5.2	98	53.5%	0.60 [-1.11, 2.31]	
Schroeter 2021	38.9	5.28	65	38.57	5.41	65	46.5%	0.33 [-1.51, 2.17]	
Total (95% CI)			154			163	100.0%	0.47 [-0.78, 1.73]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.83); l <sup>2</sup> = 0%									-4 -2 0 2 4
Test for overall effect: $Z = 0.74$ (P = 0.46)								Favours [FLACS] Favours [CPS]	

#### C.6 months postoperative

	FLACS			CPS				Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Bascaran 2018	33.42	8.87	92	31.9	4.66	92	23.3%	1.52 [-0.53, 3.57]		
Kelkar 2020	33.1	5.6	89	33.6	5.2	98	40.5%	-0.50 [-2.05, 1.05]		
Krarup 2021	28	6	31	27	7	31	9.3%	1.00 [-2.25, 4.25]		
Vasavada 2019	30.6	6.6	91	30.2	6.5	91	27.0%	0.40 [-1.50, 2.30]		
Total (95% CI)			303			312	100.0%	0.35 [-0.64, 1.34]	-	
Heterogeneity: Chi <sup>2</sup> = 2.56, df = 3 (P = 0.46); I <sup>2</sup> = 0%										
Test for overall effect: Z = 0.70 (P = 0.48)									Favours [FLACS] Favours [CPS]	

Fig 7. Forest plot of postoperative 6A between FLACS and CPS at A. 1 month, B. 3 months, and C. 6 months.

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preoperatively, with extremely low basal endothelial cell count [73]. In Fan's study, the ECL% remained a significant difference until the endpoint of follow-up (12 months) [39]. And the mean ECL% in the CPS group (32.2% at 12 months) was also much higher than 4%-25%, which was previously reported in the general population [15]. Additionally, patients with hard nuclear may suffer higher ultrasound energy and prolonged phacoemulsification time to manifest the dens cataract; thus, intraoperative endothelial cells injury was even more severe [32]. In the general population, the ECL% was similar in the long-term follow-up in FLACS and CPS groups. It implied that the long-term effect of FLACS and CPS are comparable. As for the population with dysfunctional cornea, injury caused by surgery will persist [39]. Thus, we strongly recommend that FLACS may be the superior option for corneal dysfunction and hard nuclear patients.

Contrary to previously published meta-analysis [20, 21], ECD and ECL did not show significant differences across periods. It was possibly because that the absolute value of endothelial cells may be affected by the baseline level (preoperative ECD), while the ECL% can rule out the influence. ECL% is the percentage of endothelial cell loss in the preoperative endothelial cell density, calculated by the formula: ECL% = ((preoperative ECD- postoperative ECD)/preoperative ECD) \*100%. Compared with ECD and ECL, ECL% appears to be less affected by interference factors. For example, Al-Mohtaseb [28] reported that baseline ECD in the FLACS group  $(2,408.78 \pm 169.73)$  was significantly lower than that of the CPS group  $(2,486.29 \pm 154.37, P = 0.03)$ . Postoperatively, there was no difference in ECD between the two groups (FLACS: 2,254.84 ± 264.46, CPS: 2,255.53 ± 262.93, P = 0.49). However, ECL% favored the FLACS group (P = 0.04). Although the postoperative ECD was the same, there were differences in the number of endothelial cells loss between the two groups; thus, the ECD may not be an accurate reflection of endothelial cell change. The same is true for ECL, where the same number of ECL accounts for different ratios when the two groups are at different baselines [42]. Given these conditions, ECL% might be a more objective indicator to represent endothelial cell changes because the preoperative variance in ECD was removed.

In addition, different surgical approaches, such as manual or femtosecond-assist corneal incision, can also influence the endothelium. Femtosecond incision was thought to cause further damage to the cornea [74]. Femtosecond laser acts on the capsular bag when pretreating cataracts. While in the step of laser-assisted corneal incision, the laser energy directly conveys to the corneal endothelium [26]. Furthermore, microbubbles arising from laser-induced corneal rupture can influence the surface tension of endothelium and amplify the damage to it [75]. However, some studies lacked a description of this step; thus, it was difficult for us to perform a subgroup analysis of corneal incisions.

Across all time points, ECD at 3 months after surgery differed from the others. We noticed studies that recorded corneal data only at 3 months after surgery [60, 67], which might exert a large impact on the 3 months postoperative outcomes of ECD. Although the ECD in the FLACS group was significantly higher than that in the CPS group, the difference disappeared when only RCTs were included (S4 Fig). Meanwhile, the heterogeneity in the RCT subgroup decreased significantly ( $I^2 = 4\%$ ). RCT studies reduce bias due to randomized grouping and are considered more reliable than cohort studies. We, therefore, supposed that the subgroup results of the RCT were more convincing at this time point. At other time points, there was no significant difference in ECD between the two groups when considering the RCT studies only (S4 Fig).

CCT represents the degree of corneal edema and is also an evaluation index of corneal endothelial function [76]. Our study demonstrated no significant difference in CCT 1–3 days after FLACS and CPS, which indicated similar corneal edema caused by two types of cataract surgery. This was in contrast to earlier meta-analyses. However, we performed a subgroup analysis of the femtosecond platform and found that in studies using the Catalys (Johnson &

Johnson Vision Care, Inc.) femtosecond platform, CCT was significantly smaller in the FLACS group (S5 Fig). It may be caused by different docking modes. In Catalys femtosecond platform, a liquid optical immersion interface (LOI) [77] is applied to the docking phase. Correspondingly, LenSx platforms use curved contact lens interface [78]. Since LOI does not directly compress the cornea, it exerts less pressure, and consequently, induces less damage to the shape of the cornea [79]. Because of the fact above, we supposed Catalys performs a better protective effect on corneal endothelium since there is no direct contact with the cornea during the femtosecond-laser period. Currently, there was no study proposing that Catalys laser platform has better endothelium protection than LenSx. And subgroup analyses of platforms at more time postoperatively had no significant results due to the limited number of studies across different platforms. We look forward to more studies on the corneal effects of femtosecond platforms in the future. CCT was significantly smaller than CPS at 1 week and 1 month in the FLACS group, while there was no significant difference at 3 months and 6 months. This implied that corneal edema resolved faster in the FLACS group, and the long-term effects of FLACS and CPS on corneal edema were similar.

CoV and 6A demonstrated that neither proved significant differences at any time point, indicating a similar morphological change of endothelial cells after surgery. Alteration in cell shape and size occurs during corneal repairment, and these two indicators represent endothelial functional capacity. It suggested that there was no difference in the effect of the two surgeries on the function of the residual endothelial cells. Interestingly, a subgroup analysis of Schroeter's study [55] showed that CoV decreased when EPT lessened. Although the results were highly consistent, the number of studies and the follow-up time points on these two indicators were not rich enough. Therefore, more follow-up articles and subgroup analyses are necessary.

In addition, we should also note that some reports have followed up on the long-term effects of FLACS and CPS for one year. The results showed that there was no significant difference in a long-term vision, complications, and corneal effects between the two groups [36, 80]. It is worth noting that FLACS has a higher economic cost, which may also be a problem to be considered when selecting surgical methods [81].

Unavoidably, there were limitations to this meta-analysis. Firstly, the postoperative followup time was only 6 months, which was due to insufficient follow-up data beyond 6 months. We look forward to more long-term follow-up articles. Secondly, the included studies were from different regions, using different CPS platforms, implemented by doctors of varying proficiency, making it difficult to unify patients' preoperative baselines, resulting in increased heterogeneity. This meta-analysis was restricted to data from published studies, so information bias could not be fully ruled out if studies with small sample-size or unpublished data exist. And we only included clinical studies published in Chinese and English, which may lead to language bias.

## Conclusions

In conclusion, FLACS reduced corneal injury in the early postoperative period. Early postoperative corneal edema recovered faster than CPS. For patients with fewer endothelial cells, it is strongly recommended to consider FLACS first.

## Supporting information

S1 Fig. Risk of bias graph: Based on researchers' opinions about each risk of bias item, percentages are presented for all included studies. (TIF) **S2 Fig. Assessment of the risk of bias in the included RCTs.** Green circle (+): Low risk, Red circle (-): High risk,?: Unclear.

(TIF)

S3 Fig. Forest plot of postoperative ECL% in general population between FLACS and CPS at A. 1–3 days, B. 1 week, C. 1 month, D. 3 months, and E. 6 months. (TIF)

S4 Fig. Forest plot of postoperative ECD between FLACS and CPS that only included RCTs at A. 1–3 days, B. 1 week, C. 1 month, D. 3 months, and E. 6 months. (TIF)

S5 Fig. Subgroup analysis of postoperative CCT between FLACS and CPS at 1–3 days. (TIF)

**S1 Table.** The Newcastle-Ottawa Scale (NOS) of cohort studies. (PDF)

**S1 Checklist. PRISMA 2020 checklist.** (DOCX)

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