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Review Article

Previous intravitreal injection as a risk factor of posterior capsule rupture in cataract surgery: a systematic review and meta-analysis

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ABSTRACT

Purpose: **Intravitreal injections and cataract surgery are two common procedures in the elderly. Posterior capsular rupture (PCR) is a rare but important complication of cataract surgery. We systematically reviewed the literature on previous intravitreal injections as a risk factor of PCR and performed meta-analyses to provide pooled summary risk estimates.**

Methods: **We searched 13 literature databases on 1 June 2021 for studies evaluating the risk of PCR in eyes undergoing cataract surgery with data on previous intravitreal injections. Data extraction was made independently by two authors and discussed afterwards until reaching consensus. Random effects meta-analyses on the pooled odds ratio (OR) of PCR in eyes with previous intravitreal injections were made using MetaXL 5.3.**

Results: **Six studies on 1 051 097 eyes undergoing cataract surgery were eligible for the qualitative and quantitative review. Previous history of intravitreal injections was present in 7034 eyes (majority was anti-VEGF). Our meta-analyses revealed that any previous intravitreal injection was a risk factor for PCR with an OR of 2.30 (95% CI 1.39–3.81). For each previous intravitreal injection, the risk of PCR was OR 1.04 (95% CI 1.01–1.08) (equivalent of relative risk ~1.04). In other words, risk of PCR increases by 4% for each previous intravitreal injection.**

Conclusions: **Previous intravitreal injection is a risk factor for PCR and should be taken into account when planning cataract surgery. However, to be regarded as a clinically significant risk of PCR, a substantial number of previous intravitreal injection (*e.g.* ≥10) should have been administered, considering that the *a priori* risk of PCR is very low (~1%).**

Key words: anti-VEGF – cataract – intravitreal injection – meta-analysis – posterior capsular rupture – systematic review

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Introduction

Cataract surgery is the most frequently performed surgical procedure worldwide with an estimated 20 million surgical cases in 2016 (Allen & Vasavada 2006; Rossi et al. 2021). Cataract surgery rates are at a global increase and are expected to continue to increase due to global improvements of life expectancies and improvements in developing countries (Ianchulev et al. 2016; Wang et al. 2017). Although cataract surgery is generally a safe procedure, one dreaded complication is posterior capsular rupture (PCR), which occurs in approximately 1% (Gogate et al. 2005; Jaycock et al. 2009; Lundström et al. 2011; Day et al. 2015). PCR may lead to a more complicated procedure as anterior vitrectomy is often needed, potentially substituting the planned posterior chamber intraocular lens with a sulcus fixated lens, an iris-claw lens or an anterior chamber lens (Vajpayee et al. 2001; Chakrabarti & Nazm 2017). PCR may even cause the nucleus to drop, which will require a more complicated surgical procedure and clinical course (Arbisser et al. 2006). PCR is associated with retinal detachment (Petousis et al. 2016; Kim et al. 2019), endophthalmitis (Haripriya et al. 2019) and reduced postoperative visual outcomes

(Sparrow et al. 2012). Therefore, identifying risk factors of PCR is of great interest for surgical planning (Sparrow et al. 2012; Lee et al. 2016). Several risk factors have been reported for PCR, including male gender, high age, cataract grade, surgeon experience and the presence of ocular comorbidities (Lundström et al. 2011; Narendran et al. 2009; Hård Af Segerstad 2020).

In developed countries, mean patient age at the time of cataract surgery is approximately 74 years (Behndig et al. 2011; Gollogly et al. 2013; Daien et al. 2015; Ianchulev et al. 2016). This is an age at which many patients also have age-related retinal comorbidities, which may necessitate intravitreal injections using either inhibitors of vascular endothelial growth factor (anti-VEGF) or corticosteroids. The use of intravitreal anti-VEGF injections is increasing globally, and in the United States, their annual number has surpassed that of cataract surgeries (Williams 2014; Lee et al. 2016). Intravitreal injections with anti-VEGF or corticosteroids have drastically improved visual outcomes in patients with various exudative retinal diseases (Bloch & Larsen 2015). Mean age of patients receiving intravitreal injections is reported to be at approximately 70 years in many developed countries (Schmidt-Erfurth et al. 2014; Xu & Tan 2017; Ziemssen et al. 2017). This demographical coincidence leads to a substantial number of eyes with cataract surgery having a history of previous intravitreal injections. This leads to the clinically important question with an important impact on surgical preparation and staffing: is history of previous intravitreal injections a risk factor of PCR?

Our aim with this study was to answer this question through a systematic review of the literature and to provide summary estimates through meta-analyses to provide the best evidence on this subject.

Methods

Study design

This was a systematic review with meta-analysis and meta-regression, which was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al. 2000; Moher et al. 2009). We followed the recommendations of the Cochrane Handbook (Higgins et al. 2021). According to Danish law, institutional review board approval is not required for such studies. Our protocol was registered in the PROSPERO database (Appendix S1).

Eligibility criteria

Studies were considered when fulfilling the following criteria:

- *Population:* Adult (18+ years of age) human eyes who underwent cataract surgery. No restrictions were made on cataract type or severity, any ocular comorbidity, cataract surgery or type of intraocular lens.
- *Exposure*: Intravitreal injection therapy. We did not include intravitreal injections with antibiotics, as eyes in need of such therapy may have other intraocular aspects potentially affecting the fragility of the posterior capsule and the surgical difficulty, and therefore cannot be reasonably representative of the large majority of eyes in intravitreal injection therapy. If the study did not outline that the intravitreal injection therapy was of either anti-VEGF or corticosteroids, we evaluated whether, based on the study design or presented data, one could assume that ≥95% of the intravitreal injections in the study were performed using any anti-VEGF agents or corticosteroids. This could be done by either looking at numbers reported on actual injections, or indirectly by looking at numbers of various conditions treated. We did not restrict to any practical aspects of the intravitreal injection, such as the setting (*e.g.* operating theatre or office), the personnel (*e.g.* doctor or nurse), the device (*e.g.* prefilled syringes, injection assisting devices or gauge-size), the underlying retinal condition or the injected agent within the categories of anti-VEGF or corticosteroids.
- *Comparator*: Eyes in the study undergoing cataract surgery without any history of previous intravitreal injection.
- *Outcome*: Incidence of PCR.
- *Study types*: No restrictions on study design were enforced, but we anticipated that studies would be of retrospective cross-sectional design. We included relevant abstracts, but not studies without original data or case reports. We did not restrict studies based on geography or journal. We only considered studies disseminated in the English language.

Information sources and search strategy

We searched the following literature databases: the Cochrane Central, PubMed/MEDLINE, EMBASE, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index, SciELO Citation Index and ClinicalTrials.gov. All database searches were conducted on 9 August 2021 with database specific details outlined in Appendix S2.

Study selection

One author (Y.S.) examined titles and abstracts from the literature search and removed duplicates and obviously irrelevant reports. Two authors (J.B. and E.H.C.D.) then independently examined the full text of the remaining references for eligibility and reviewed references from these studies for any additional relevant studies. Afterwards, consensus on study selection was attempted through discussion in between the two authors (J.B. and E.H.C.D.). In case of further disagreement, the third author (Y.S.) was involved for further discussion and to reach a final consensus.

Outcome measures, data collection and risk of bias assessment

Primary outcome of interest was the risk of PCR in eyes with any number of prior intravitreal injections. Secondary outcome of interest was the risk of PCR for each prior intravitreal injection. Data regarding study design, characteristics, methods and results were extracted from eligible studies using extraction forms. As we anticipated that studies primarily would be cohort studies, the quality of eligible studies was assessed using the Newcastle-Ottawa Assessment Scale for Cohort Studies which is the recommended assessment tool for cohort studies (Zeng et al. 2015). Two authors (J.B. and E.H.C.D.) worked

independently in data extraction and risk of bias assessment. Results were compared and discussed afterwards with the third author (Y.S.) until consensus was reached.

Data analysis and synthesis

All studies were reviewed qualitatively in the text and in tables. Meta-analyses were performed with MetaXL. We used the random effects model for our meta-analyses. Heterogeneity was assessed with Cochran's Q and quantified with I^2 (Higgins et al. 2003). A funnel plot was used to evaluate risk of bias across studies (Egger et al. 1997). The final results were pooled odds ratio (OR) estimate of the risk of PCR in eyes with previous intravitreal injections compared with eyes without any previous intravitreal injection. We also calculated 95% confidence intervals (95% CI) for these estimates. The unit of analysis of all data was per eye, and where possible, we used the OR from adjusted analyses for the meta-analysis. We also explored the pooled OR estimate of the risk of PCR per previous intravitreal injection. Sensitivity analyses were made to explore robustness of the estimates. P values below 0.05 were considered statistically significant.

Results

Study selection

Our literature search identified 163 records. From these, eight records remained for full-text review after removing duplicates and obviously irrelevant records. We identified one further record after screening reference lists. Finally, six records remained after excluding records deemed irrelevant, which were all included for the qualitative and the quantitative review. Details of the study selection process are shown in Fig. 1.

Study characteristics

The six studies summarized data on 658 076+ patients with cataract (number of patients was not clearly outlined in three studies), where data on 1 051 097 eyes undergoing cataract surgery were presented (Table 1). All were retrospective registry-based studies. Five studies were cohort studies of patients undergoing cataract surgery (Lee et al. 2016; Shalchi et al. 2017; Hård Af Segerstad 2020; Nagar et al. 2020; Miller et al. 2021), and one was a case–control study of patients who either had or had not received intravitreal therapy (Hahn et al. 2016). Study populations were from the United Kingdom (Lee et al. 2016; Shalchi et al. 2017; Nagar et al. 2020), the United States of America (Hahn et al. 2016; Miller et al. 2021) and from Sweden (Hård Af Segerstad 2020). Mean age of patients ranged between 69 and 74 years, and females constituted 55–60% of all eyes. Further study characteristics are summarized in detail in Table 1.

Cataract type and severity were outlined in three studies with different definitions (Hahn et al. 2016; Nagar et al. 2020; Miller et al. 2021). In two of these studies, the percentage of advanced/brunescent/hypermature cataracts was reported, and in both cases, these cataracts constituted a small percentage of the overall sample (Nagar et al. 2020; Miller et al. 2021). Surgeons were both experienced consultants and trainee surgeons/residents (Hahn et al. 2016; Lee et al. 2016; Shalchi et al. 2017; Hård Af Segerstad 2020; Nagar et al. 2020; Miller et al. 2021). Four studies outlined details regarding the surgery, and all four studies declared that all surgeries were phacoemulsification surgery (Lee et al. 2016; Hård Af Segerstad 2020; Nagar et al. 2020; Miller et al. 2021). Further details of the cataracts and surgical aspects are summarized in Table 2.

A total of 7034 eyes with cataract had previously received any intravitreal injections. Neovascular age-related macular degeneration and proliferative diabetic retinopathy/diabetic macular oedema were the most prevalent reasons for the intravitreal injections. The vast majority of the injections were constituted by anti-VEGF therapy. Mean or median number of intravitreal injections prior to cataract surgery ranged between 5 and 10.4 across the four studies reporting on this parameter (Hahn et al. 2016; Lee et al. 2016; Hård Af Segerstad 2020; Nagar et al. 2020). Further details regarding

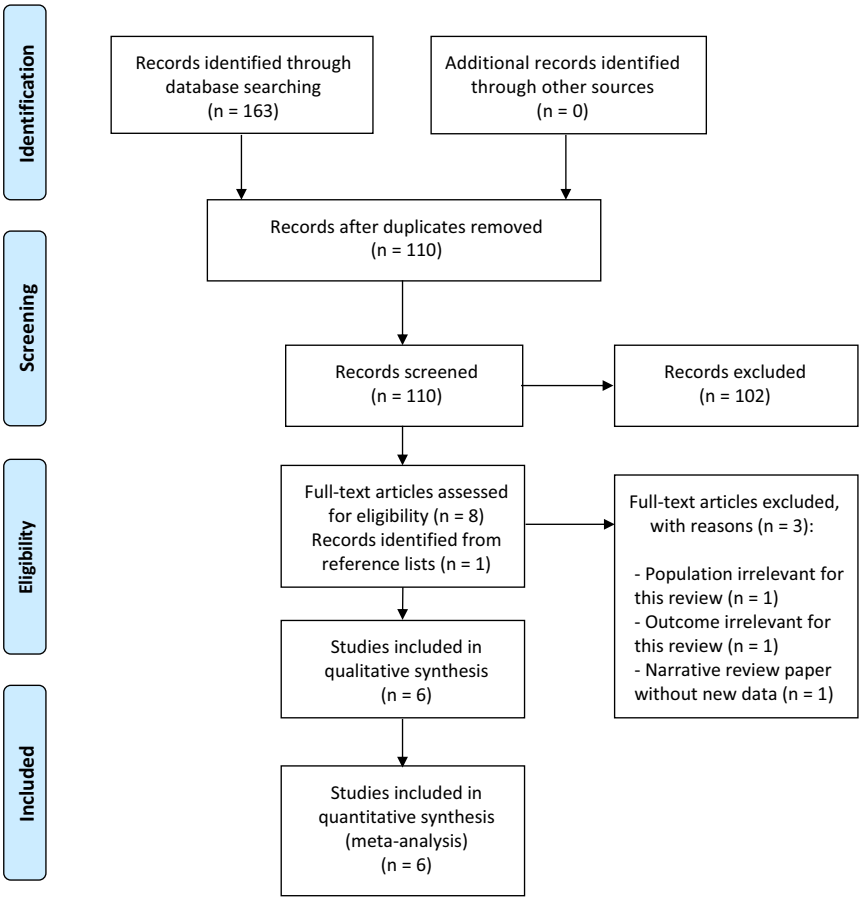

Fig. 1. Flow diagram of study selection process.

Table 1. Study characteristics.

Reference	Country	Design	Population	Demographics	Patients with cataract, *N*	Eyes with cataract, *N*
Hahn et al. (2016)	USA	Retrospective, registry-based, single-centre, case–control study	Patients aged ≥18 years who had cataract surgery from 2005 to 2012. Patients were excluded where history of prior intraocular surgery, penetrating ocular trauma or absence of baseline records. From the resulting sample of 10,105 surgeries, 197 cases (previous intravitreal injection) and 197 controls (no intravitreal injection, matched according to surgeon and age) were selected.	• Age 71 ± 14 years • Females 56%	Unclear	394
Hård Af Segerstad (2020)	Sweden	Retrospective, registry-based, multi-centre, cohort study	Patients aged >20 years who had cataract surgery between 2010 and 2018.	• Age 74 years (range 20–109) • Females 60%	572,536	907,499
Lee et al. (2016)	UK	Retrospective, registry-based, multi-centre, cohort study	Patients aged ≥18 years who had cataract surgery across 20 centres.	Not reported	44,635	65,836
Miller et al. (2021)	USA	Retrospective, registry-based, single-centre, cohort study	Patients aged ≥18 years who had cataract surgery from 2014 to 2018. Patients were excluded where history of traumatic cataracts, patients in intravitreal injection treatment at another clinic and surgeries combined with vitrectomy.	• Age 69 ± 10 years • Females 59%	Unclear	10,327
Nagar et al. (2020)	UK	Retrospective, registry-based, single-centre, cohort study	Patients aged ≥18 years who had cataract surgery from 2016 to 2018. Patients were excluded where non-phacoemulsification cataract surgery was performed, or if surgery was combined with any other intraocular procedure.	• Age 72 ± 11 years • Females 55%	4,047	4,047
Shalchi et al. (2017)	UK	Retrospective, registry-based, multi-centre, cohort study	Patients aged ≥18 years who had cataract surgery from 2012 to 2015. Patients were excluded if intravitreal injections were made with antibiotics, ocriplasmin or gas injections.	• Median age 73 years (mean ± SD not reported) • Females 56%	Unclear	62,994

Abbreviations: UK = the United Kingdom, USA = the United States of America.
Continuous data are presented in mean ± SD unless otherwise noted.

Table 2. Details of the cataracts and its surgery.

Reference	Cataract type and severity	Details regarding the surgeons	Details regarding the surgery
Hahn et al. (2016)	Cataract grading: • NS 2.1 ± 0.8 • CS 0.3 ± 0.7 • PSC 0.7 ± 1.2	Surgery was performed by four experienced cataract surgeons performing >250 cataract surgeries per year.	N/A
Hård Af Segerstad (2020)	N/A	Surgeon's experience in number of previous surgeries was mean 3,670 (range 1–20,874)	Phacoemulsification surgery. No further details.
Lee et al. (2016)	Advanced (defined as brunescent, hypermature or white cataract) and non-advanced cataract. Their distribution was not reported.	Surgeons were categorized into trainee surgeon years 1–2, 3–6 and 7+; as well as independent non-consultant and consultant. Their distribution was not reported.	Phacoemulsification surgery. No further details.
Miller et al. (2021)	Cataract grading: • Mature 2.3% • Non-mature 97.7%	Primary surgeon: • Attending/Fellow 95% • Resident 5%	Standard phacoemulsification using either Alcon Infiniti or Centurion and with clear corneal incisions. The vast majority of cases were performed under topical anaesthesia.
Nagar et al. (2020)	Brunescent/white cataract in 6.7%.	Surgery was performed by 10 consultants and 12 junior surgeons of different grades.	Phacoemulsification surgery. No further details.
Shalchi et al. (2017)	N/A	Surgeon: • Consultants 41% • Junior surgeon 59%	N/A

Abbreviations: CS = cortical spokes, NS = nuclear sclerosis; PSC = posterior subcapsular cataract.
Continuous data are presented in mean ± SD unless otherwise noted.

the intravitreal injections are outlined in Table 3.

Results of individual studies and risk of bias within studies

Hahn et al. (2016) extracted data from patients undergoing cataract surgery at the Duke Eye Center and compared 197 eyes with prior intravitreal injection to an equal number of eyes without any prior intravitreal injection who were matched by age and surgeon. Here, the authors found that a history of intravitreal injection was associated with a statistically significant higher rate of intraoperative complications, which in all cases were PCR (Hahn et al. 2016).

Hård Af Segerstad (2020) extracted phacoemulsification cataract surgery data from the Swedish National Cataract Register for an eight-year period (from year 2010 to 2018). Data were obtained for 907 499 eyes in 572 536 patients with cataract, of whom 3451 eyes of 3168 patients had previously received any intravitreal injection (Hård Af Segerstad 2020). This data set was obtained through cross-referencing the Swedish National Cataract Register with the Swedish Macula Register (Hård Af Segerstad 2020). Intraoperative complications were defined as any communication between the anterior and posterior segment, which could be PCR, zonular dehiscence and dropped nucleus (Hård Af Segerstad 2020). Reported data did not differentiate between these intraoperative complications (Hård Af Segerstad 2020). In this study, the authors found previous intravitreal injection to be a statistically significant risk factor of such intraoperative complications (Hård Af Segerstad 2020).

Lee et al. (2016) extracted data from electronic medical records from 20 centres in the United Kingdom and evaluated data on 65 836 eyes of which 1935 had a history of intravitreal injection. This study was specifically designed to evaluate the effect of previous intravitreal injection on PCR, and the authors found a statistically significant relationship (Lee et al. 2016).

Miller et al. (2021) evaluated records of eyes who had undergone phacoemulsification cataract surgery at the UCHealth Sue Anschultz-Rodgers Eye Center during a four-year period (from 2014 to 2018) and extracted data on 10 327 eyes of which 308 had previously received intravitreal anti-VEGF injection. Eyes with previous intravitreal injection had a statistically significant odds of experiencing PCR (Miller et al. 2021).

Nagar et al. (2020) evaluated data from electronic medical records from patients (4047 eyes) who had undergone phacoemulsification surgery between 2016 and 2018 at the Whipps Cross University Hospital Eye Treatment Center and extracted data on intravitreal anti-VEGF injection therapy (108 eyes). This study found that previous intravitreal injection significantly correlated with an increased risk of PCR (Nagar et al. 2020).

Shalchi et al. (2017) evaluated electronic databases of the Moorfields Eye Hospital and its satellite clinics and extracted data on all cataract surgeries between 2012 and 2015 (62 994 eyes) including any data on previous intravitreal injection (650 eyes). The authors found that the history of previous intravitreal injection increased the risk of PCR (Shalchi et al. 2017).

Taken together, all studies found a statistically significant association between a history of intravitreal injection and PCR, and in studies with multivariable adjustment of the

Table 3. Details of the retinal diseases and their intravitreal injection therapy.

Reference	Retinal diseases	Eyes with cataract who had previous intravitreal injections, *N* (%)	Details of the intravitreal injections	Number of intravitreal injections prior to cataract surgery, mean (SD)
Hahn et al. 2016	In those with intravitreal injection: • nAMD 45% • DME 30% • Other 25%	197 (50.0%)	Bevacizumab was used in the majority of cases, and the rest received ranibizumab, aflibercept, pegaptanib and triamcinolone. Any anti-VEGF injection constituted 84% of the intravitreal injections. No further details were reported on the setting, the personnel or the device.	5.6 (7.0)
Hård Af Segerstad (2020)	Overall: • AMD 15% • DR 4%	3,451 (0.4%)	Data were extracted from the Swedish Macula Register, which only registers neovascular AMD. No details were reported on the setting, the personnel, the device or the injected agent.	10.4 (N/A)
Lee et al. (2016)	In those with intravitreal injection: • nAMD 80% • PDR/DME 18% • Other 2%	1,935 (2.9%)	99% of all intravitreal injections were made using anti-VEGF, and the rest was corticosteroid therapy. Consultants, trainee surgeons at various experience levels and nurse practitioners performed the intravitreal injection. No further details were reported on the setting or the device.	Median 5 (IQR: 3–9)
Miller et al. (2021)	In those with intravitreal injection: • nAMD 35% • PDR/DME 47% • RVO 11% • Other 7%	308 (3.0%)	All intravitreal injections were anti-VEGF and performed by or under the supervision of a vitreoretinal specialist. Tetracaine was used for analgesia, betadine for antisepsis and injection 3.5-4 mm behind the limbus. No further details were reported on the setting or the device.	N/A
Nagar et al. (2020)	In those with intravitreal injection: • AMD 38% • DR 41%	108 (2.7%)	All intravitreal injections were made with anti-VEGF agents. No details were reported on the setting, the personnel or the device.	10.4 (8.1)
Shalchi et al. (2017)	In those with intravitreal injection: • nAMD 59% • DME 22% • RVO 14% • Other 6%	1,035 (1.6%)	Intravitreal injections were constituted by anti-VEGF in the vast majority (91%), and the remaining were triamcinolone intravitreal injections, dexamethasone intravitreal implant and fluocinolone acetonide intravitreal implant. No further details were reported on the setting, the personnel or the device.	N/A

Abbreviations: AMD = age-related macular degeneration, DME = diabetic macular oedema, DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, RVO = retinal vein occlusion, nAMD = neovascular age-related macular degeneration, VEGF = vascular endothelial growth factor.

association (Lee et al. 2016; Shalchi et al. 2017; Hård Af Segerstad 2020; Miller et al. 2021), this risk remained statistically significant.

The risk of bias within studies revealed overall strong study quality score (range 8–9 in a scale from 0 to 9) according to the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. Patient selection, comparability and nature of the outcomes were representative and relevant in all studies. For comparability, we evaluated whether comparisons were made within comparable age (most important factor, which qualified for one star), and any other relevant demographical or clinical aspects (which qualified for a separate star). This could be done by using a matched comparison group or by performing adjusted analyses. This approach led to all studies receiving at least one star, and four studies receiving two stars (Lee et al. 2016; Shalchi et al. 2017; Hård Af Segerstad 2020; Miller et al. 2021). Risk of bias evaluation within studies is summarized in Table 4.

Meta-analysis of intravitreal injection as a risk factor of PCR

All six studies of 1 051 097 eyes with cataract were eligible for the quantitative analysis and provided data eligible for our primary outcome meta-analysis. When looking at risk of PCR based on any previous intravitreal injection, the summary estimate was OR 2.30 (95% CI: 1.39–3.81; p = 0.001) (Table 5). Heterogeneity statistics (I^2 = 87.4; Cochran's Q = 39.7) showed sign of substantial heterogeneity. Funnel plot showed that study estimates were right skewed, which may indicate some publication bias; however, this should be interpreted with caution due to the small number of studies available (Appendix S3). Sensitivity analysis showed robustness of the results as omitting any single study neither changed the effect size nor the direction, nor the conclusion of the analysis (Appendix S4).

For our secondary outcome, which was the risk of PCR for each prior intravitreal injection, only three studies provided eligible data (Lee et al. 2016; Shalchi et al. 2017; Nagar et al. 2020). Here, the summary estimate was OR 1.04 (95% CI: 1.01–1.08; p = 0.02) (Table 5). Heterogeneity statistics (I^2 = 70.5; Cochran's Q = 6.7) showed sign of substantial heterogeneity; however, this should be interpreted with caution because only three studies were available for this analysis. For the same reason, we refrained from performing Funnel plot analysis and sensitivity analysis for this secondary analysis.

Discussion

Our systematic review analysed six eligible studies with a total of more than one million cataract surgeries. Individual studies in review unanimously reported a significant relationship between the history of previous intravitreal injection and PCR. Using meta-analyses, we calculated that any previous intravitreal injection was associated with an OR of 2.30 for PCR. Compared with other known risk

Table 4. Risk of bias within individual studies included in the review.

	Selection				Comparability	Outcome			Quality score
Reference	#1	#2	#3	#4	#1	#1	#2	#3	
Hahn et al. (2016)	★	★	★	★	★	★	★	★	8
Hård Af Segerstad (2020)	★	★	★	★	★★	★	★	★	9
Lee et al. (2016)	★	★	★	★	★★	★	★	★	9
Miller et al. (2021)	★	★	★	★	★★	★	★	★	9
Nagar et al. (2020)	★	★	★	★	★	★	★	★	8
Shalchi et al. (2017)	★	★	★	★	★★	★	★	★	9

Newcastle-Ottawa Quality Assessment Scale for Cohort Studies evaluates categories within three domains: Selection, Comparability and Outcome. Categories within Selection are (#1) representativeness of the exposed cohort, (#2) selection of the non-exposed cohort, (#3) ascertainment of exposure and (#4) demonstration that outcome of interest was not present at the start of study. For Comparability, one category evaluated is (#1) comparability of cohorts on the basis of the design or analysis. Categories within Outcome are (#1) assessment of outcome, (#2) was follow-up long enough for outcomes to occur and (#3) adequacy of follow-up of cohorts. The quality score is a summary of number of stars across all categories within each study.

Table 5. Meta-analysis of previous intravitreal injection therapy as a risk for posterior capsular rupture.

	Risk of posterior capsular rupture from any history of previous intravitreal injection			Risk of posterior capsular rupture for each previous intravitreal injection		
Reference	OR	95% CI	Weight	OR	95% CI	Weight
Hahn et al. (2016)	13.41	0.75–239.63	2.24%	–	–	0.00%
Hård Af Segerstad (2020)	1.45	1.09–1.93	23.17%	–	–	0.00%
Lee et al. (2016)	1.21	1.02–1.44	24.58%	1.04	1.00–1.08	32.43%
Miller et al. (2021)	4.69	2.12–10.38	14.17%	–	–	0.00%
Nagar et al. (2020)	5.33	3.19–8.91	15.99%	1.09	1.04–1.14	27.53%
Shalchi et al. (2017)	1.66	1.03–2.69	19.85%	1.02	1.00–1.04	40.04%
Pooled estimates	2.30	1.39–3.81	100.00%	1.04	1.01–1.08	100.00%
Heterogeneity statistics	I^2 = 87.4	Cochran's Q = 39.7		I^2 = 70.3	Cochran's Q = 6.7	

Abbreviations: 95% CI = confidence interval; OR = odds ratio.

factors for PCR, previous intravitreal injection seems to be a risk factor of greater importance than axial length > 26 mm (OR 1.47), small pupil size (OR 1.45) or patient taking doxazosin (OR 1.51); however, it seems to be a less important risk factor than surgeon training year 1–2 (OR 2.83), pseudoexfoliation or phacodonesis (OR 2.92), or brunescent or white cataract (OR 2.99) (Narendran et al. 2009; Lee et al. 2016). However, when considering these numbers, it is also important to realize that the risk from previous intravitreal injections is highly dependent on the number of previously performed injections. For each previous intravitreal injection, our meta-analysis found an OR of 1.04 for PCR. This OR can be converted to a relative risk for easier interpretation (relative risk~1.04), which allows a more practical interpretation: a 4% increase in the risk of PCR for each number of previous intravitreal injection. Considering that the *a priori* risk of PCR is very low (~1%), clinically significant risk of PCR should be considered when the history reveals a substantial number of previous intravitreal injections (*e.g.* ≥10).

Among the eligible studies in review, anti-VEGF agents comprised the overwhelming majority of the intravitreal injections given—84 to 99% in three studies (Hahn et al. 2016; Lee et al. 2016; Shalchi et al. 2017) and 100% in the three other studies (Hård Af Segerstad 2020; Nagar et al. 2020; Miller et al. 2021). The exact mechanisms behind the increased risk of PCR after intravitreal injection remain elusive, but explanations may fall into four categories: (i) iatrogenic physical trauma caused by the injection needle, (ii) changes in the mechanical properties of the lens capsule resulting from exposure to anti-VEGF or corticosteroids, (iii) accelerated cataractogenesis related to either anti-VEGF exposure or corticosteroids resulting in denser cataracts and (iv) denser cataracts because cataractous patient, who have concurrent retinal diseases that require intravitreal injection treatment, may have limited visual potential and are therefore perhaps referred for cataract surgery later compared with others. For the latter, however, it can also be argued that surgeons proceed to cataract surgery faster in subjects in an intravitreal injection treatment regimen due to earlier diagnosis of cataract, as patients are continuously monitored (Lee et al. 2016).

Postinjection traumatic cataracts and visible signs of physical, iatrogenic damage to the lens and surrounding structures caused by intravitreal injection are known adverse effects to injection treatment (Saeed & Prasad 2009; Khalifa & Pantanelli 2011). It can therefore also be assumed that intravitreal injection can lead to subclinical, mechanical damage to the lens capsule, which may render the capsule more likely to tear during surgery. Possible mechanisms may include inadvertent zonular trauma either directly or due to local scleral deformation at the time of injection or inadvertent crystalline lens capsule trauma (Lee et al. 2016; Miller et al. 2021). Hård Af Segerstad (2020) speculated that the increased risk of PCR is most likely due to iatrogenic damage to the lens or zonulae, presumably mechanical in nature, following poor injection technique. Hahn et al. (2016) found that three of the four eyes in which PCR occurred in those with previous intravitreal injection had posterior subcapsular cataract at the preoperative evaluation. This led the investigators to suggest that a needle-induced trauma during injection had resulted in violation of the posterior capsule and secondary PSC formation (Hahn et al. 2016). Anterior OCT may have utility in discerning otherwise invisible damage to the posterior capsule in preoperative evaluation of patients with previous intravitreal injection (Martinez-Enriquez et al. 2016; Shalchi et al. 2017).

Although a mechanical explanation to the increased risk of PCR in eyes with the history of intravitreal injection treatment seems convincing, additive effect of other factors cannot be excluded. There may be a possible effect from changes in lens epithelial viability and morphology after exposure to anti-VEGF agents, as these changes have been reported after bevacizumab exposure (Jun et al. 2016; Miller et al. 2021). Potential effects on the mechanical integrity of the posterior capsule by anti-VEGF remain unclear, but Miller et al. (2021) suggested that the capsule in eyes with previous anti-VEGF therapy may be more sensitive to the usual surgical stress during cataract surgery. This hypothesis is based on the lack of any significant differences in in surgical stage at which PCR occurred between eyes with and without the history of intravitreal anti-VEGF therapy, which may support a notion of a general fragility of the capsule (Miller et al. 2021). This was, however, inferred from a study population with very low occurrences of PCRs (n = 8 in the group with the history of any intravitreal injection and n = 45 in the group without any intravitreal injection) and calls for more further investigation. Nagar et al. (2020) reported that PCR in their study occurred at different steps during cataract surgery with no obvious cause.

So far, little is known on the risk of PCR by specific intravitreal agents. Uncomplicated intravitreal injection of triamcinolone has been associated with cataract formation after injection (Thompson 2006), and zonular dehiscence has been observed in cases with previous ocriplasmin injection (Keller & Haynes 2015; Lee et al. 2016). Miller et al. (2021) found that the type of anti-VEGF agent last used (bevacizumab *versus* other) was not associated with a higher risk of PCR (OR = 0.76, 95% CI 0.19–3.12); however, the number of cases may have been too small for a thorough comparison of this aspect. Miller et al. (2021) also suggested that previous anti-VEGF therapy may lead to denser cataracts. This relationship was based on the finding of a higher cumulative dispatched energy spend during the phacoemulsification stage of surgery in eyes with the previous history of anti-VEGF treatment and in eyes with PCR, suggesting a mediating relationship that could be investigated further (Miller et al. 2021). This could be attributable to either a potential accelerated cataractogenesis related to anti-VEGF exposure, or a later cataract surgery referral pattern for patients in anti-VEGF therapy because of a limited visual potential due to retinal comorbidity. Another possibility is that patients in intravitreal anti-VEGF treatment are at a higher risk of PCR for other reasons, such as difficult positioning for surgery due to back pain or stiffness in those with higher age or harder cataracts in those with diabetic macular oedema (Narendran et al. 2009; Shalchi et al. 2017), or eccentric fixation or fixation difficulties

due to central vision impairment. Investigating these potential influencing factors warrants studies with larger number of cases with previous intravitreal injection to allow meaningful multivariate adjustments and subgroup analyses.

Miller et al. (2021) also studied a possible association between the number of days since the last anti-VEGF injection and the risk of PCR during cataract surgery. The number of days between the most recent intravitreal injection and cataract surgery was not significantly associated with increased risk of PCR (OR = 1.00, 95% CI: 0.99–1.00, p = 0.1803) (Miller et al. 2021). These results are interesting and may suggest that cataract surgery can be planned regardless of the time from the last intravitreal injection, at least in terms of risk of PCR. Considering that timing of surgery is one of the few parameters, which we can control, this topic deserves more attention in future studies.

Limitations should be acknowledged when interpreting the results of this systematic review and meta-analysis. Our study is based on six studies with 1 051 097 eyes undergoing cataract surgery, but any previous history of intravitreal injection was only present in 7034. Considering that PCR is a rare complication, our findings – albeit based on large number of eyes undergoing surgery – remains based on a small number of patients with a history of intravitreal injection and therefore is subject to uncertainty. Furthermore, considering that large number of cases from one study (Hård Af Segerstad 2020) relative to the other studies, there is also an important limitation in that the conclusions heavily relies on the findings of one study. Moreover, considering that anti-VEGF injections constitute the vast majority, generalizability of the conclusions to the risk after corticosteroid injections can be challenging. It is also important to emphasize that it was unclear whether cataract surgery was phacoemulsification surgery in two studies (Hahn et al. 2016; Shalchi et al. 2017), which if not may drastically alter the incidence of PCR. Also, our estimate on the risk of PCR for each prior intravitreal injection is based on three studies which reported such data, which lessens the strength of the calculated summary estimate. Finally, our analyses suggested some publication bias, although the low number of studies should lead to cautious interpretation of this finding. However, it is likely that it may be easier to publish a statistical significantly finding on this topic rather than no association, which should be kept in mind when interpreting the results.

In conclusion, we find that previous intravitreal injection increases the risk of PCR in cataract surgery. Considering the high incidence of both intravitreal injection and cataract surgery and their shared demographics, the history of intravitreal injection is an important aspect for consideration when planning cataract surgery. From a clinical perspective, it is important to take into consideration the number of previous intravitreal injections for a more accurate evaluation of the risk for PCR.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Protocol as registered at PROSPERO.
Appendix S2. Search strategy across different literature databases.
Appendix S3. Funnel plot of the primary meta-analysis.
Appendix S4. Sensitivity analysis of the primary meta-analysis.