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Recurrence risk of myopic choroidal neovascularisation: a systematic review of current study

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ABSTRACT

Introduction The rising prevalence of myopia is a concern in ophthalmology, with myopic choroidal neovascularisation (m-CNV) significantly affecting vision. However, long-term outcomes of m-CNV management have been unsatisfactory, leading to high recurrence rates. These studies aim to identify risk factors for m-CNV recurrence.

Methods Comprehensive review followed a pre-registered plan in the International Prospective Register of Systematic Reviews (PROSPERO). The search strategy used various databases including PubMed, Cochrane Library, Embase, Scopus and ScienceDirect using the keywords 'Myopic Choroidal Neovascularization', 'Recurrence' and 'Risk'. Eligible studies were identified and analysed based on predetermined criteria. This study was registered on PROSPERO (CRD4202343461).

Results The systematic review included three retrospective studies investigating risk factors associated with m-CNV recurrence. These factors are: (1) requiring three or more injections for initial disease control, (2) older age, (3) larger myopic macular neovascularisation, (4) juxtafoveal CNV, (5) larger height of hyper-reflective foci (HRF) and (6) destruction or absence of the ellipsoid zone (EZ) and retinal pigment epithelium (RPE).

Conclusion Risk factors for m-CNV recurrence include a greater number of required injections, older age, large macular CNV, juxtafoveal location, increased HRF height and changes in EZ and RPE structure. Understanding these factors can inform personalised treatment approaches and improve patient outcomes by identifying individuals at higher risk of recurrence and implementing proactive measures to mitigate the impact of m-CNV recurrence and progression. Further investigation is needed to enhance our understanding of the underlying mechanisms and develop innovative therapeutic approaches for effective m-CNV management.

PROSPERO registration number CRD4202343461.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myopic choroidal neovascularisation (m-CNV) can rapidly progress and cause severe vision impairment.

⇒ Long-term outcomes regarding the interventions of m-CNV have been unfavourable, with a notable recurrence rate.

WHAT THIS STUDY ADDS

⇒ This systematic review identified the risk factors associated with the recurrence of m-CNV, including a greater number of required injections, older age, large macular CNV, juxtafoveal location, hyper-reflective foci height and alteration in ellipsoid zone and retinal pigment epithelium structure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Personalised treatment plans, guided by the recurrence risk factors, regular follow-up care and proactive measures, are essential in slowing the progression, minimising m-CNV recurrence and improving long-term visual health.

INTRODUCTION

Globally, the prevalence of myopia is steadily on the rise, and it has become a significant concern in the field of ophthalmology.[1 2] This ocular condition, characterised by the elongation of the axial length of the eyeball, has led to the emergence of various complications, one of which is myopic choroidal neovascularisation (m-CNV). The incidence of m-CNV in high myopic eyes is alarmingly high, affecting approximately 4–10% of individuals with pathological myopia.[3–6] If left untreated, m-CNV can rapidly progress and cause severe vision impairment, posing a considerable threat to the affected individuals' quality of life. The consequences of m-CNV are particularly pronounced in middle-aged individuals, who face the burden of compromised vision and grapple with the economic, social and emotional challenges associated with this condition.[3–6] Over the years, numerous therapeutic approaches have been explored to manage m-CNV and mitigate its detrimental effects. However, the long-term outcomes of these interventions have been unfavourable, with a notable recurrence of the condition in many cases. This recurrence undermines the effectiveness of the initial treatment and

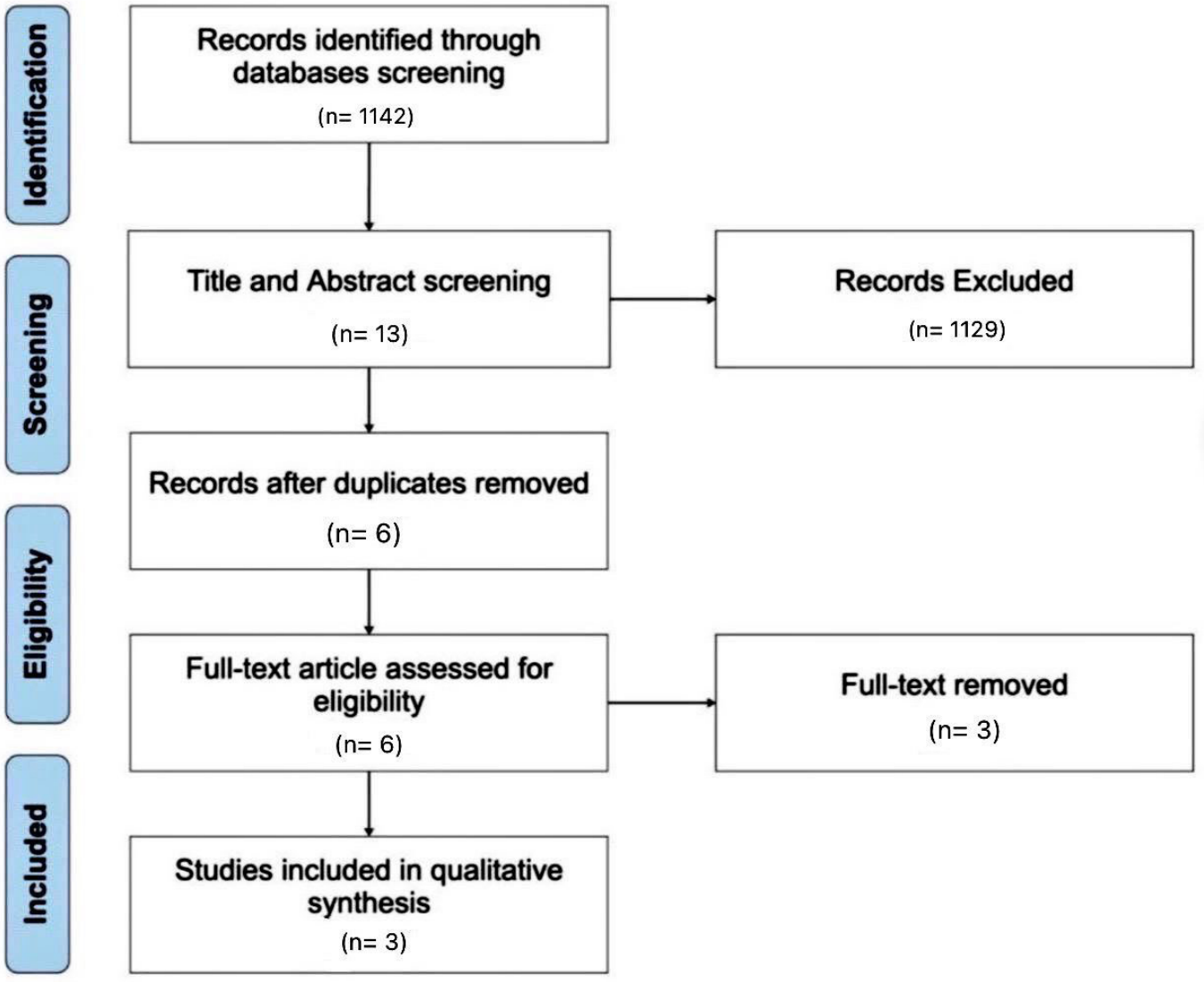

Figure 1 Literature search and selection flow chart.

imposes additional burdens on the patients, necessitating further medical intervention and potentially resulting in prolonged suffering.

Due to the seriousness of the situation, it is imperative to promptly identify the factors that contribute to the recurrence of m-CNV, to develop more targeted and successful treatment strategies. Among the current therapeutic modalities, anti-vascular endothelial growth factors (anti-VEGFs) have emerged as the gold standard of therapy for m-CNV.These agents, which act by inhibiting the abnormal growth of blood vessels in the choroid, have shown promising results in clinical trials and have become the cornerstone of treatment for m-CNV. However, despite their effectiveness in the short term, there have been concerns regarding their long-term efficacy and the associated recurrence rates. Consequently, recent studies have focused on investigating various factors that may contribute to the recurrence of m-CNV following anti-VEGF therapy. The analysis of these recent studies aims to shed light on the complex nature of m-CNV recurrence and the underlying mechanisms. Recently, several potential factors were considered to influence the likelihood of recurrence, including patient demographics, genetic predisposition, ocular characteristics, treatment regimens and the presence of other ocular comorbidities.[7–16] By comprehensively examining these factors, this study seeks to obtain a deeper perception of the multifaceted nature of m-CNV and to provide valuable insights into personalised treatment approaches. Understanding the factors associated with m-CNV recurrence is of paramount importance for clinicians and researchers alike. By identifying high-risk individuals and implementing appropriate preventive measures, it may be possible to reduce the burden of this condition and improve long-term outcomes for patients. Moreover, unravelling the underlying mechanisms of m-CNV recurrence could open avenues for the creation of novel therapeutic strategies that target these mechanisms directly, thereby offering a more effective and sustainable solution for individuals with m-CNV. In this study, we will

Table 1 Search results[17–19]

Author (year)	Research design	Location	Study population	Results
Jain *et al*[17] (2022)	Retrospective cohort study	India	A total of 167 individuals with m-CNV therapy participated in the study, resulting in the inclusion of 167 eyes. Among these, 59 eyes were treated with intravitreal ranibizumab monotherapy, while 108 eyes received bevacizumab monotherapy.	The only notable factor that predicted recurrence was the number of injections administered to treat the disease in the initial episode (Cox proportional HR 2.89–3.07, 95% CI 1.28–7.45; p=0.005). Following 12 months, eyes that received a single injection during the first episode exhibited a recurrence rate of 12%, while eyes that necessitated three or more injections in the initial episode experienced a recurrence rate of 45%.
Cicinelli *et al*[18] (2023)	Retrospective cohort study	Italy	The study included a total of 310 eyes with active myopic macular neovascularisation and the median duration of follow-up was 3.5 years.	Multiple recurrences were predicted by advanced age (HR=1.13 (95% CI 1.04–1.27) for every 10-year increase, p=0.006), larger size of myopic macular neovascularisation (HR=1.06 (95% CI 1.01–1.13) for every 1 mm² increase, p=0.04) and a juxtafoveal location (HR=1.88 (95% CI 1.28–2.77) compared with extrafoveal, p=0.001).
Jing *et al*[19] (2022)	Retrospective cohort study	China	A total of 48 patients with pathologic myopia choroidal neovascularization (PM-CNV) who received conbercept treatment and underwent a period of monitoring for at least 6 months were included in the study, comprising 48 eyes in total.	The binary logistic regression analysis demonstrated a significant correlation between PM-CNV recurrence and various factors, including the height of hyper-reflective foci, CNV area, as well as the presence of ellipsoid zone and retinal pigment epithelium abnormalities (p<0.05).

m-CNV, myopic choroidal neovascularisation; PM-CNV, pathologic myopia choroidal neovascularisation.

look at various factors associated with m-CNV recurrence based on various recent studies.

METHODS

Protocol and registration

We filed a guideline prior to authoring this review and meta-analysis, and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 24 June 2023 (CRD4202343461).

Eligibility criteria

The following criteria were used to determine whether a study met the inclusion standards: (a) original research study type; (b) topic suitability (recurrence risk in patients with m-CNV); (c) presence of at least one control group and one exposure group; and (d) use of a transparent extraction and statistical analysis method. The studies included are limited to studies published in English with full-text availability.

Search strategy

This study was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Systematic literature research is done in five primary databases: PubMed, Cochrane Library, Embase, Scopus and ScienceDirect. We used the term '((*Myopic Choroidal Neovascularization*) AND (*Recurrence*) AND (*Risk*))'.

Study selection and data extraction

Five reviewers (AAV, GA, AD, ARY, MMH) independently screened the title and abstract and excluded the irrelevant studies. The final retrieved studies were screened for duplicates and systematically evaluated according to the inclusion and exclusion criteria. Two reviewers (SHA and KAS) obtained data from qualified studies, including characteristics of the study (author, year of publication, study methodology), subject characteristics (patients with m-CNV), outcome of the study (recurrence risk) and other relevant information. The first reviewer (AAV) reviewed and checked all the extracted data.

Quality assessment

The quality of the studies was assessed by using the Tool to Assess Risk of Bias in Cohort Studies by CLARITY Group at McMaster University, consisting of eight questions with four potential responses. Two authors (KAS and SHA) conducted an independent assessment of the quality of the studies. Any disagreement was resolved with a third author (AAV).

RESULT

Study selection

Collectively, 1142 studies were derived using the keywords from PubMed (n=101), ScienceDirect (n=537), Scopus (439), Embase (64) and Cochrane Library (1). After

screening for title and abstract, 51 studies were excluded. The studies were then compared for duplicates and no studies were excluded. The remaining five studies were screened for the inclusion and exclusion criteria, and two were removed. The final screening resulted in three studies that met the inclusion and exclusion criteria. (Figure 1 visualises the study selection flow chart.)

Study characteristics and outcomes

In this systematic review, three retrospective studies that met the inclusion criteria were obtained. A summary of data from these three studies is provided in table 1.

Risk of bias assessment

The full risk of bias assessment is presented in online supplemental appendix 1. All studies appropriately selected cohorts from the same population, assessed exposure and outcomes effectively and had a proper follow-up of cohorts. All studies reported the statistical analysis adjusted for the prognostic variables. Overall, these studies are categorised as 'low risk' in terms of study quality due to their adherence to most risk of bias criteria.

Summary of main results

The first study by Jain *et al*[17] described the number of injections in patients as a predictor of recurrence. The recurrence was outlined as the reappearance of CNV activity, which was verified through optical coherence tomography (OCT) on a minimum period of 3 months following the discontinuation of anti-VEGF therapy. Follow-up of the patients was carried out after 3 months.

The second study by Cicinelli *et al*[18] showed various risk factors associated with the recurrence of patients with m-CNV including older age, larger myopic macular neovascularisation (mMNV) for 1 mm^2 increase and juxtafoveal location, all three of which can predict recurrence in patients with m-CNV. Follow-up of the patients was carried out after 3.5 years. In the study, they identified various risk factors correlated with the relapse of m-CNV in subjects with different parameters. For instance, age was considered as a parameter, with a risk increase observed for every 10-year increment. In terms of myopic size, a 1 mm^2 increase was found to be associated with an elevated risk. Lastly, the researchers compared the risk based on the location of the m-CNV lesions. It was determined that subfoveal and juxtafoveal locations posed a higher risk compared with extrafoveal locations, with HRs of 1.89 (1.37–2.63) and 2.06 (1.48–2.87), respectively.

Jing *et al*[19] described several risk factors for m-CNV recurrence, including the larger height of hyper-reflective foci (HRF), the presence or absence of the ellipsoid zone (EZ) and the observed damage to the epithelium of retinal pigment, can be seen using OCT.

DISCUSSION

Individuals whose eyes need three or more injections to initially stabilise their disease are especially prone to experiencing early recurrence. Past research has consistently shown that the majority of recurrences tend to happen early on, primarily within the first 12 months. In a retrospective series by Yang *et al*, it was observed that 72.7% of recurrences took place during the initial year of treatment.[20] Additionally, Jo *et al* discovered a direct correlation between the total amount of injections required for initial therapy and the likelihood of recurrence.[21] Similarly, in the study conducted by Jain *et al*, we also observed a significant association between the total amount of injections required for initial disease control and the prediction of relapse.[17]

Previous researchers have emphasised the correlation between advanced age and poorer visual outcomes in the eyes of individuals with mMNV who undergo anti-VEGF treatment. Although we lack specific information on the duration of mMNV, older age could indicate the presence of long-standing neovascular abnormalities. Conversely, elderly patients with myopia might experience more significant tissue damage resulting from myopic degeneration, as indicated by the characteristics observed in our patient population. The documented recurrence rate of mMNV varies between 23% and 62%.[20–24]

Collectively, these three studies provide valuable insights into the factors linked with recurrence in patients with m-CNV. The study by Jain *et al*[17] highlighted the number of injections received as a significant predictor of recurrence, emphasising the importance of appropriate treatment strategies and follow-up care. Cicinelli *et al* identified older age, larger mMNV and juxtafoveal location as key risk factors for recurrence, emphasising the need for personalised approaches based on individual characteristics. Additionally, Jing *et al*[19] highlighted the significance of specific OCT markers in predicting recurrence, offering potential targets for early intervention and monitoring.

The impact of the number of injections emphasises the need for appropriate treatment strategies and monitoring to effectively manage m-CNV. Furthermore, patient demographics and ocular characteristics, including older age, larger mMNV and juxtafoveal location, play a crucial role in recurrence risk. By considering these factors, personalised treatment plans can be developed, leading to improved management strategies. The presence of specific OCT markers, such as HRF height, the manifestation of the EZ and retinal pigment epithelium (RPE), provides valuable insights for predicting recurrence and guiding early intervention. This underscores the importance of OCT imaging in monitoring patients with m-CNV.

Overall, the identification and understanding of these risk factors enable healthcare professionals to implement tailored treatment plans, targeted interventions and proactive measures to mitigate the burden of m-CNV recurrence. However, further research is warranted to investigate genetic predispositions, evaluate long-term treatment efficacy and develop novel therapeutic strategies targeting underlying mechanisms.

CONCLUSION

This systematic review highlights the significance of identifying risk factors linked with the relapse of m-CNV. A greater number of injections required, older age, large macular CNV, juxtafoveal location, HRF height and alteration in EZ and RPE structure are the risk factors linked to the recurrence of m-CNV. Personalised treatment plans, guided by these factors, along with regular follow-up care and proactive measures, are essential in slowing the progression, minimising m-CNV recurrence and improving long-term visual health. Further research is needed to explore genetic predispositions, assess long-term treatment efficacy and develop novel therapeutic strategies targeting underlying mechanisms.

Contributors In this research project, AAV acts the guarantor. The conceptualisation, data analysis and manuscript writing were primarily undertaken by AAV, SHA and KAS. The remaining authors (GA, AD, MMH and ARY) contributed to the review and refinement of the manuscript.

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Appendix 1. Risk of Bias of All Included Studies

Studies	**Selection of exposed and non-exposed cohorts drawn from the same population**	**Assessment of exposure**	**Outcome of interest was not present at start of study**	**Match variables, adjust analysis.**	**Assessment of the presence or absence of prognostic factors**	**Assessment of outcome**	**Follow-up of cohorts**	**Similar co-interventions**	**Study Quality**
Jain M et al, 2022	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**Low risk**
Cicineli MV et al, 2023	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**Low risk**
Jing R et al, 2022	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**Low risk**

1: Definitely yes; 2: Probably yes; 3: Probably No; 4: Definitely No