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Carotid endarterectomy versus carotid stenting for asymptomatic carotid stenosis: Evaluating the overlapping meta-analyses of randomized controlled trials

Ahmed Y. Azzam [a,*,1], Sherief Ghozy [b,c,1], Adam Elswedy [d], Mohammed A. Azab [h], Kevin M. Kallmes [a,e], Adam A. Dmytriw [f], Ramanathan Kadirvel [b,g], David F. Kallmes [b]

[a] *Nested Knowledge, St. Paul, MN, USA*
[b] *Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[c] *Nuffield Department of Primary Care Health Sciences and Department for Continuing Education (EBHC program), Oxford University, UK*
[d] *Biomedicinskt Centrum BMC, Uppsala University, Husargatan 3, 752 37 Uppsala, Sweden*
[e] *Superior Medical Experts, St. Paul, MN, USA*
[f] *Neuroendovascular Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[g] *Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA*
[h] *Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, Salt Lake City, UT, 84132, USA*

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ABSTRACT

Background: Asymptomatic carotid stenosis is associated with increased risk of ischemic stroke. The management of asymptomatic carotid stenosis ranges from open surgical approaches, minimally invasive endovascular interventions, and medical therapeutics. However, the research synthesis comparing these interventions, as shown by the scattered and overlapping published meta-analysis, has been inconsistent and non-comprehensive.
Methods: Using previously-employed methods, we searched for and compared published meta-analyses comparing carotid endarterectomy and carotid stenting. A comprehensive search was conducted for all relevant studies published until November 13th, 2021, using the following databases: PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, OVID, and Google Scholar.
Results: Five meta-analysis studies were included in this review. In summary, clinical findings were: carotid endarterectomy reduced the rate of ischemic stroke and stroke-related mortality, but led to a higher rate of intraoperative cranial nerve injury. There was no significant difference between carotid endarterectomy and carotid stenting in ipsilateral stroke and myocardial infarction events.
Conclusions: The clinical findings favor the carotid endarterectomy over the carotid stenting in terms of stroke incidence (overall and minor events) and stroke-related mortality rates. However, the carotid stenting was superior to the carotid endarterectomy in the events of cranial nerve injury during the intervention.

1. Introduction

Asymptomatic carotid stenosis is among the significant causes of ischemic stroke. The management of asymptomatic carotid stenosis ranges from open surgical approaches, minimally invasive endovascular interventions, and medical therapeutics [4]. Over the past two decades, it has been proven that surgical intervention is superior to medical therapeutics to prevent disease progression and induce ipsilateral ischemic stroke [2]. With the advances in the neurosurgical field within the last decade, various surgical interventions have emerged, including minimal invasive intervention to access and stent carotid stenosis. However, to date, the literature evidence regarding the interventional strategies for asymptomatic carotid stenosis is controversial and discordant.

To date, several meta-analyses have analyzed the safety and efficacy of carotid endarterectomy compared to carotid stenting for asymptomatic carotid stenosis [3,5,8,9,12]. However, the reviews and meta-analyses on this topic—comparing carotid endarterectomy against

* Corresponding author.
E-mail address: Ahmedyazzam@gmail.com (A.Y. Azzam).
[1] Equal Contribution.

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carotid stenting—do not present consistent findings for these interventions and thus lead to discordant interpretations. Overlapping but non-confirmatory meta-analyses on the same research question are common and may lead to conflicting results. Hence, it is challenging to draw conclusions from the existing literature until the meta-analyses comparing these interventions are harmonized.

This systematic review aims to evaluate all published meta-analyses comparing carotid endarterectomy and carotid stenting for asymptomatic carotid stenosis and highlight the gaps in the current evidence.

2. Materials and methods

This study was designed in line with prior published studies using the same approach to aggregate and compare meta-analytical findings [1,6,7].

2.1. Literature search

A comprehensive search was conducted for all relevant studies published before November 13th, 2021, using the following databases: PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, OVID, and Google Scholar using The relevant keywords included "Carotid Endarterectomy AND Carotid Stenosis", "Carotid Endarterectomy AND Asymptomatic Carotid Stenosis", "Carotid Stenting AND Carotid Stenosis", "Carotid Stenting AND Carotid Stenosis", "Carotid Stenting AND Asymptomatic Carotid Stenosis", "Carotid Endarterectomy AND Carotid Stenting AND Carotid Stenosis", "Carotid Endarterectomy AND Carotid Stenting AND Asymptomatic Carotid Stenosis". We filtered the search results to include only meta-analyses. Screening of the search results was conducted by two authors independently. Titles and abstracts were first screened, followed by full texts. Disagreements between authors were resolved by group discussion and through the help of a third author. Study metadata and abstracts were uploaded to the AutoLit platform (Nested Knowledge, St. Paul, MN) for screening and extraction.

2.2. Eligibility criteria

We included meta-analyses of randomized controlled trials (RCTs) comparing Carotid Endarterectomy and Carotid Stenting for Asymptomatic Carotid Stenosis. Non-RCT meta-analyses, systematic reviews without meta-analyses, review articles, editorials, case reports, and case series were excluded.

2.3. Data extraction

Data extraction was conducted by two authors independently for the following data: author, year/month of publication, study design, number of included RCTs in each meta-analysis, number of patients in both the Carotid Endarterectomy and Carotid Stenting groups, percent heterogeneity, and the results of the studies. The following outcomes were compared among different studies; overall stroke rate, ipsilateral stroke, major stroke, minor stroke, myocardial infarction, mortality, cranial nerve injury, overall complications.

2.4. Quality assessment

We used the Assessment of Multiple Systematic Review (AMSTAR) [10] and Oxford Levels of Evidence [11] to evaluate the methodological quality of the studies. AMSTAR is widely used to assess the quality of systematic reviews and meta-analyses with good reliability [10]. Two authors conducted the quality assessment criteria; a third author resolved any conflicts.

3. Results

3.1. Literature search

The PRISMA flowchart for the study selection process is shown in Fig. 1. Database search retrieved overall number of 1020 searching results. After applying the filter of meta-analysis inclusion only, 975 articles were excluded. 45 articles were eligible to the next phase of screening, of which we excluded 30 due to the fact that these studies reported symptomatic cases only. 15 articles were sought for final (full-text) screening, ten out of them were excluded because they were non-RCT meta-analysis. Overall number of five studies were included in this systematic review. The flowchart illustrated the selection criteria for the included studies in this systematic review, and also mentioned the exclusion reasons.

3.2. Baseline characteristics

The characteristics of the included studies are highlighted in Table 1. We highlighted details about the published journal name, number of included patients within each intervention and date of publication. Last database search for the included meta-analyses ranged between April 2016 and July 2017. The number of included RCTs in each meta-analysis ranged between five to up nine studies.

The included studies were published between August 2017 and May 2019. A total of 16 RCTs were published between 2001 and 2016 (Table 2).

3.3. Assessment of heterogeneity

The Q-statistics and I^2 values were used to quantify heterogeneity (Table 3). Four studies used sensitivity analysis and only one study Kakkos et al. [6] neglected to conduct sensitivity analysis. Galyfos G et al. [3] used funnel plot and Habbord-Egger test. Yuan G et al. [4] used the leave-one-out approach. Cui L et al. [5] used manual exclusion of studies as the only method for limiting heterogeneity. Moresoli P et al.

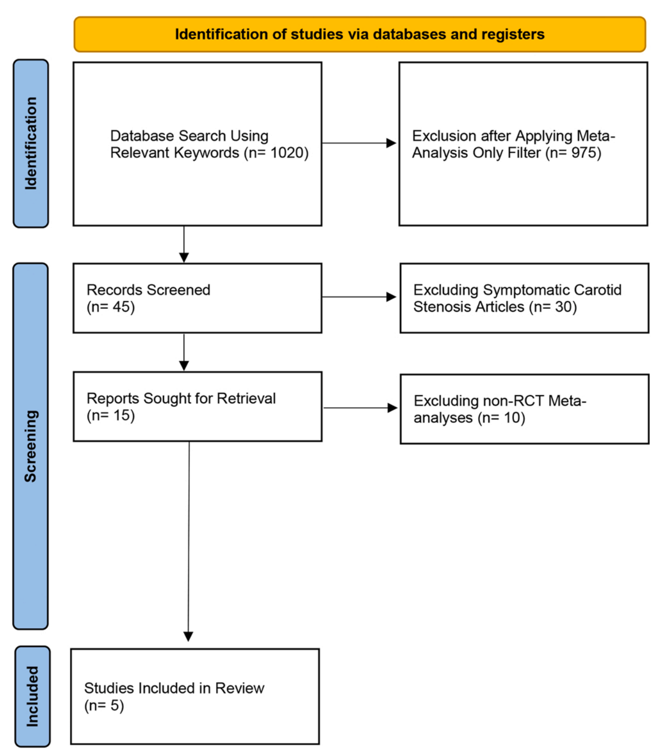

Fig. 1. PRISMA Flow Diagram.

Table 1
Characteristics of the Included Studies.

Author	Publication Date	Journal	Number of Included Studies	Last Literature Search Date	Number of Carotid Endarterectomy patients	Number of Carotid Stenting Patients
Galyfos G et al. [3]	May 2019	Cardiovascular Revascularization Medicine	7	July 2017	4147	4827
Yuan G et al. [4]	May 2018	International Heart Journal	5	March 2016	1833	2581
Cui L et al. [5]	May 2018	European Journal of Vascular and Endovascular Surgery	6	May 2017	1585	2316
Kakkos SK et al. [6]	August 2017	Journal of Vascular Surgery	9	March 2017	1479	2230
Moresoli P et al. [7]	August 2017	Stroke	5	April 2016	1138	1881

Table 2
Included Primary Studies.

Author	Galyfos G et al. [3]	Yuan G et al. [4]	Cui L et al. [5]	Kakkos SK et al. [6]	Moresoli P et al. [7]
Year	2019	2018	2018	2017	2017
CREST 2010 [5]	**Yes**	No	**Yes**	**Yes**	**Yes**
Brooks et al. 2004 [2,3]	**Yes**	**Yes**	**Yes**	No	**Yes**
SAPPHIRE 2004 [14,28]	**Yes**	No	No	**Yes**	**Yes**
CAVATAS 2001 [6,12]	**Yes**	No	No	**Yes**	No
SPACE-2 2016 [11]	**Yes**	No	No	**Yes**	No
ACT-1 2016 [24]	**Yes**	No	**Yes**	**Yes**	**Yes**
Kuliha 2015 [19]	**Yes**	No	No	**Yes**	**Yes**
Rosenfield 2016 et al. [25]	No	**Yes**	No	No	No
Brott 2010 et al. [4]	No	**Yes**	No	No	No
Liu 2009 et al. [21]	No	**Yes**	No	No	No
Yadav 2004 et al. [29]	No	**Yes**	No	No	No
Brooks 2014 et al. [1]	No	No	**Yes**	No	No
Kougias 2015 et al. [18]	No	No	**Yes**	No	No
Mannheim 2016 et al. [22]	No	No	**Yes**	**Yes**	No
Kentucky 2004 (non-published data)	No	No	No	**Yes**	No
Li 2014 et al. [20]	No	No	No	**Yes**	No

[7] used the fixed-effects model with applying the inverse-variance weighting.

3.4. Jadad decision algorithm results

There was heterogeneity among studies regarding the included rials, selection criteria, and methodology. This led to discordant results across the meta-analyses. The results of each meta-analysis are shown in Fig. 2.

3.5. Research question and primary trials

All the included studies investigated the same research question: Carotid Endarterectomy versus Carotid Stenting for Asymptomatic Carotid Stenosis. However, the meta-analyses did not have the same primary trials, meaning the underlying set of data differed across meta-analyses. The included primary trials of each meta-analysis are listed in Table 2.

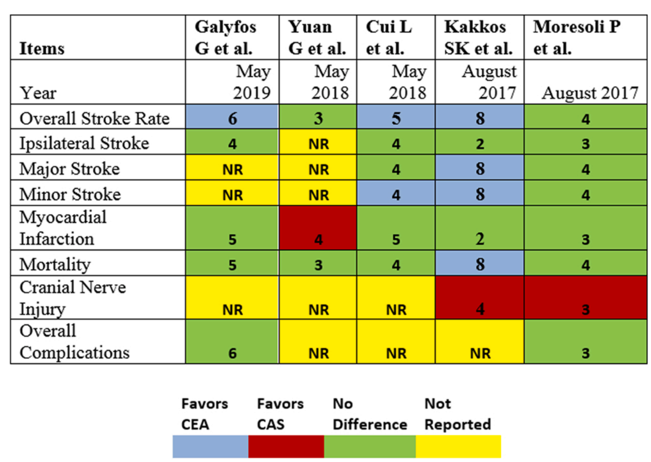

Fig. 2. Results of the Included Meta-analyses. Numbers within each cell reflect the number of pooled primary studies in each analysis.

Table 3
Heterogeneity or Subgroup Analysis for the Variables in Meta-analyses.

Items	Galyfos G et al. [3]	Yuan G et al. [4]	Cui L et al. [5]	Kakkos SK et al. [6]	Moresoli P et al. [7]
Year	May 2019	May 2018	May 2018	August 2017	August 2017
Overall Stroke Rate	**Yes**	**Yes**	No	**Yes**	**Yes**
Ipsilateral Stroke	**Yes**	N/A	No	**Yes**	**Yes**
Major Stroke	N/A	N/A	No	**Yes**	**Yes**
Minor Stroke	N/A	N/A	No	**Yes**	**Yes**
Myocardial Infarction	**Yes**	**Yes**	No	**Yes**	**Yes**
Mortality	**Yes**	**Yes**	No	**Yes**	**Yes**
Cranial Nerve Injury	N/A	N/A	N/A	**Yes**	**Yes**
Overall Complications	**Yes**	N/A	N/A	N/A	**Yes**

3.6. Selection criteria and methodology

The included meta-analyses did not have the same selection criteria. Galyfos G et al. [3] included RCTs up to July 2017 with no lower limit for searching of results. The authors excluded trials with less than 50 total patients, trials reporting symptomatic patients, trials with unequal distribution of medical therapy, and trials published in a language other than English. Yuan G et al. [4] included RCTs up to March 2016 with no lower limit for searching of results. The authors excluded non-RCT trials, but they did not set language restrictions to their exclusion criteria. The study by Cui L et al. [5] included RCTs from 1994 up to May 2017. The authors excluded non-RCT trials and non-English trials without indicating another criterion. The study by Kakkos et al. [6] included RCTs up to March 2017 with no lower limit for searching of results. The authors excluded non-English RCTs. However, the authors requested unpublished data to be included in their study from investigators of unpublished trials. Moresoli P et al. [7] included all RCTs without lower limit in the date up to April 2016 and limited their results to English and French Language only. In addition to that, they did not include non-published materials in their analysis. Each study's language restriction and methodological details are listed in Supplementary Table 1.

Studies that reported fewer outcomes than expected were deemed of lower quality. According to this criteria, Kakkos et al. [6] study had the highest-quality evidence among the present meta-analyses (Fig. 3).

3.7. Quality assessment

According to Oxford Levels of Evidence, all the primary studies were RCTs and considered level II evidence (Table 4). Only one study by Kakkos et al. [6] used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) for quality assessment. A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) results are presented in Table 5. The lowest AMSTAR score (Moderate) was given for Galyfos G et al. [3] and Moresoli P et al. [7], while the highest AMSTAR score (High) was given for the other three studies [3,8,12].

4. Discussion

To the best of our knowledge, this is the first systematic review of the overlapping meta-analyses investigating Carotid Endarterectomy versus Carotid Stenting for Asymptomatic Carotid Stenosis. According to the Jadad decision algorithm, the study by Kakkos et al. [6] represents the highest quality meta-analysis comparing Carotid Endarterectomy versus Carotid Stenting for Asymptomatic Carotid Stenosis. Moreover, the identified discordant findings across studies show the need for higher-quality and better-coordinated meta-analyses. Although the findings of Kakkos et al. are the highest quality, they may require further assessment since the authors did not include 8 + studies found by other searches. Furthermore, the underlying studies support endarterectomy on major clinical outcomes other than risk of cranial nerve injury.

Kakkos et al. [6] concluded that Carotid Endarterectomy is superior to Carotid Stenting in most clinical outcomes, including overall stroke rate, significant stroke incidence, minor stroke incidence, and mortality risk. However, the risk of cranial nerve injury was favoring the carotid stenting group over the carotid endarterectomy. Meanwhile, there were no significant differences between both interventions regarding the risk of developing ipsilateral stroke and the risk of myocardial infarction. Major stroke was defined as a stroke-inducing disability or morality, while minor stroke was defined as non-disabling (Fig. 2).

We found conflicting results among different meta-analyses in the literature. The study by Galyfos et al. [3] demonstrated that the overall stroke rate favored the carotid endarterectomy group, while the risk of developing ipsilateral stroke, myocardial infarction, mortality rate, and the overall complications was similar between carotid endarterectomy and carotid stenting. Yuan G et al. [4] reported only three outcomes; the overall stroke rate and the mortality rate were similar between both groups, while the risk of myocardial infarction favored the carotid stenting group. The study by Cui L et al. [5] favored carotid endarterectomy regarding the overall stroke rate and minor stroke incidence. However, the risk of developing ipsilateral stroke, significant stroke incidence, myocardial infarction, and mortality rate were all comparable between carotid endarterectomy and carotid stenting. The study by Moresoli P et al. [7] did not favor an intervention regarding all clinical outcomes, except the risk of cranial nerve injury. It favored the carotid stenting over the carotid endarterectomy. The potential reasons for these discordant results are different eligibility criteria by authors and different databases for the search strategy. Some studies did not perform a comprehensive search in all available scientific databases.

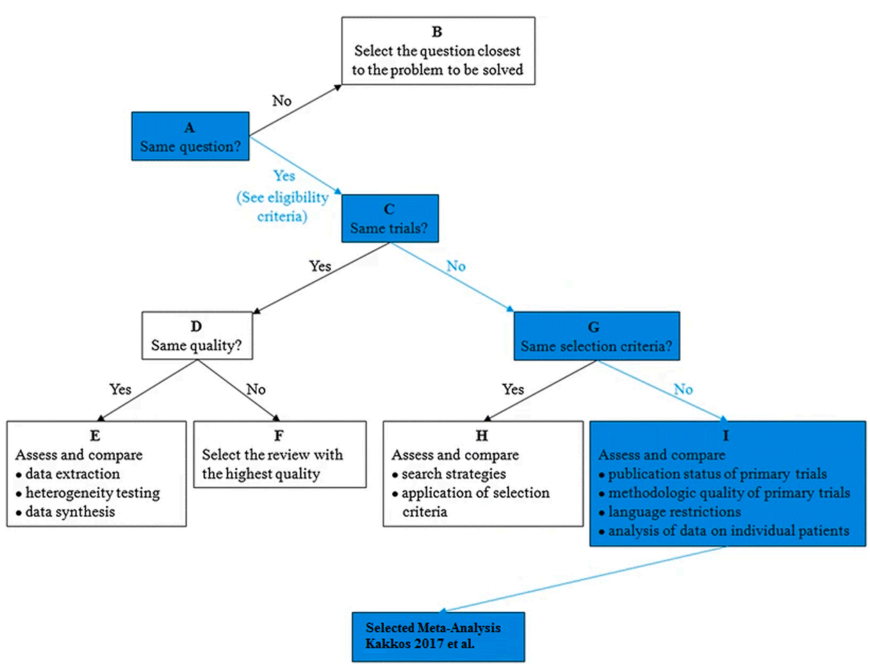

Fig. 3. Jadad Decision Algorithm Figure.

Table 4
Methodological Information about the Included Studies.

Authors	Publication Year	Included Studies Design	Evidence Level of Included Studies	Software	Cochrane Handbook Guidelines use	GRADE use	Sensitivity analysis	PRISMA use
Galyfos G et al. [3]	2019	RCT	Level II	StatsDirect	No	No	Yes	Yes
Yuan G et al. [4]	2018	RCT	Level II	Comprehensive Meta-Analysis	Yes	No	Yes	Yes
Cui L et al. [5]	2018	RCT	Level II	R	Yes	No	No	Yes
Kakkos SK et al. [6]	2017	RCT	Level II	RevMan	Yes	Yes	No	Yes
Moresoli P et al. [7]	2017	RCT	Level II	R	Yes	No	No	Yes

Table 5
AMSTAR Assessment for the Included Studies. Moderate= More than one non-critical weakness (the meta-analysis has more than one weakness but no critical flaws), High= No or one non-critical weakness (the meta-analysis provides am accurate and comprehensive presentation of the results).

Items	Galyfos G et al. (2019) [3]	Yuan G et al. (2018) [4]	Cui L et al. (2018) [5]	Kakkos SK et al. (2017) [6]	Moresoli P et al. (2017) [7]	Total, N (%)
Was an a priori design provided?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was a comprehensive literature search performed?	Yes	Yes	No	No	No	2, (40)
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was a list of studies (included and excluded) provided?	Yes	No	Yes	Yes	No	3, (60)
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was the scientific quality of the included studies assessed and documented?	No	Yes	Yes	Yes	Yes	4, (80)
Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes	Yes	4, (80)
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was the likelihood of publication bias assessed?	Yes	Yes	Yes	Yes	Yes	5, (100)
Was the conflict of interest stated?	Yes	Yes	Yes	Yes	Yes	5, (100)
Overall Methodological Quality (L= Low, M= Moderate, H= High)	M	H	H	H	M	

Furthermore, the different timeframe of the conducted searches is a possible contributing reason.

There are several reasons why the study by Kakkos et al. [6] was found to have the highest quality of evidence. At first, this meta-analysis included nine studies, making it the most extensive meta-analysis in the current literature. Second, the authors followed the Cochrane Handbook for Systematic Reviews of Interventions to conduct their study. Nevertheless, Kakkos et al. [6] acknowledged several limitations influencing their results. First, the GRADE assessment method for stroke and myocardial infarction outcomes showed insufficient and moderate evidence levels. Second, the number of myocardial infarction events was low to provide significant evidence. Third, the results suggested that the carotid endarterectomy is superior to the carotid stenting.

The strengths of this study include the focus on reviewing the highest evidence quality and determination of the best results based on specific decision algorithms. According to Oxford Levels of Evidence, our study was limited to level I evidence. However, our results are limited by the quality of the included meta-analyses and their inherent limitations.

5. Conclusions

The clinical findings favor the carotid endarterectomy over the carotid stenting in terms of stroke incidence (overall and minor events) and stroke-related mortality rates. There was no significant difference between carotid endarterectomy and carotid stenting in ipsilateral stroke and myocardial infarction events. However, the carotid stenting was superior to the carotid endarterectomy in the events of cranial nerve injury during the intervention. Further meta-analytical studies investigating the safety and efficacy of carotid endarterectomy versus carotid stenting should draw from the findings of Kakkos et al. but ensure that a comprehensive search is undertaken of all subsequent evidence to continue updating the research synthesis on this clinical question.

Ethical statement

This work was completely free from involving human subjects.

Funding

None.

CRediT authorship contribution statement

KMK works for and holds equity in Nested Knowledge, Inc., works for Conway Medical LLC, and holds equity in Superior Medical Experts, Inc. DK has the following conflicts: Ownership in Nested Knowledge, Inc., Superior Medical Experts, Inc., Conway Medical LLC; Research support from: Microvention, Balt USA, Medtronic.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejro.2022.100460.

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