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REVIEW

Current Understanding of Retinal Vein Thrombosis in Older Adults: A Review of the Literature

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Background: Retinal vein thrombosis (RVT) represents a global public health problem, ranking as the second position in prevalence among all retinal vascular pathologies and becoming an "epidemic" with the advanced age of patients. The prevalence of this pathology increases 20 times in patients aged over 80 years, compared to the age of 40–49 years. This pathology can lead to visual impairment, blindness and causes disability, but it is reversible within the first 7 days with timely diagnosis and treatment. The response to anti-VEGF treatment is better with earlier initiation. VEGF suppression not only improves macular edema but also reopens some closed retinal vessels, prevents the progression of vessel closure, and improves retinopathy. Consequently, early diagnosis, competent treatment and rehabilitation, especially in older adults with retinal vascular pathology, are necessary to prevent vision loss and disability. However, there is a lack of studies on mechanisms of RVT development in this demographic group.

Purpose of the Study Was: To provide a synthesis of the literature regarding the evaluation risk factors and pathogenesis of ocular vascular pathology, with special emphasis on examination methods, clinical characteristics, complications and modern treatment strategies in older adults with retinal vein thrombosis.

Materials and Methods: PubMed, Web of Science and Cochrane Library were searched for studies, systematic reviews or meta-analyses reporting the relationship between the central retinal vein (CRV) or its branches thrombosis and patient age in the period from 2015 to 2024. Population-based or cohort studies with maximum population inclusion were selected.

Results: Analysis of modern methods examination – fluorescence angiography of the ocular fundus (FA), an angio-optical coherence tomography (Angio-OCT) study of the retina and Fluorescence angiography allows revealing important pathogenetic aspects of retinal vein occlusion. Understanding all epidemiological, pathogenetic and diagnostic aspects in older adults is paramount for RVT timely effective prevention, clinical intervention and rehabilitation.

Conclusion: The prevalence of retinal vein occlusion increases significantly with age. It is associated with an increase in stroke, cardiovascular events, and mortality. This requires monitoring and treating vascular risk factors.

Keywords: retinal vein thrombosis, occlusion, ocular vascular pathology, epidemiology, pathogenesis, risk factors, clinic, geriatrics

Introduction

Retinal vein thrombosis (RVT) is an acute vascular disease resulting in complete or partial occlusion of patency in the cavity of the central retinal vein (CRV) or its branches due to thrombus. Depending on the occlusion location, RVT can be generally classified as the Central Retinal Vein Occlusion (CRVO) or its branches – Branch Retinal Vein Occlusion (BRVO).

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According to population studies, thrombosis of the CRV or CRVO is the second most common retinal vascular disease worldwide.[1]

The association of ocular vascular pathology with somatic diseases (arterial hypertension, hyperglycaemia, hyperlipidaemia, atherosclerosis) and cerebrovascular pathology was indicated. AH and age are significant risk factors for RVT. In comparison to age, AH is a correctable risk factor. Therefore, timely detection and correction of AH in the older adults is required. Both routine methods of examination (visometry, ophthalmoscopy, tonometry) and specialized methods (fluorescent angiography of the ocular fundus, optical coherence tomography of the retina, Transcranial Doppler) are important in early diagnosis strategy.

The study was designed to identify differences in the prevalence, comorbidity, clinic and medication management of RVT in the older adults compared to general population.

Purpose of the study was: to provide a synthesis of the literature regarding the evaluation risk factors and pathogenesis of ocular vascular pathology, with special emphasis on examination methods, clinical characteristics, complications and modern treatment strategies in older adults with retinal vein thrombosis.

Materials and Methods

Search Strategies

PubMed, Web of Science and Cochrane Library were searched for studies, systematic reviews or meta-analyses reporting the relationship between the central retinal vein or its branches thrombosis and patient age in the period from 2015 to 2024. All searches were performed in English. Keywords included “retinal vein occlusion” or and “ocular vascular pathology” or “epidemiology” or “pathogenesis” or “prevalence” or “risk factors”. Population-based or cohort studies with maximum population inclusion were selected. The study objectives were to examine this condition prevalence in various regions, the gender and age impact, and hypertension presence.

A total of 375 articles on the relevant topic were retrieved from the database searches. Following the initial screening and removal of duplicates, 66 articles remained.

Study Selection

The articles underwent screening and assessment for quality and eligibility.

The following were excluded from the study during the initial screening:

- Studies with an unknown number of subjects,
- Studies with age-restrictions (only a certain age),
- Studies, examining the RVT prevalence in patients with specific pathologies (eg, patients with chronic kidney disease, diabetes, metabolic syndrome, post-vascular accidents, sleep apnea, etc),
- Studies, examining the RVT prevalence in patients reporting bad habits (smoking, alcohol, drug addiction),
- Studies examining the RVT prevalence in patients with other ophthalmologic diseases or injuries (ophthalmic hypertension, cataracts, retinopathy).

The remaining articles then were screened for compliance with the following criteria:

- large studies (over 100 participants) conducted in various regions of the world,
- epidemiological data on age and the impact of hypertension.

Results

World prevalence, based on global epidemiological study data is shown for comparison. We selected five large-scale regional studies conducted over the past 10 years, with maximum number of subjects and without restrictions on age, ethnicity, comorbidities, or lifestyle habits for placement on the map. CRV prevalence was divided into ranges: 0.50–0,65%,[2,3] 0.65–0,80%,[4] and above 0.8%.[5,6] These ranges are represented by different colors.

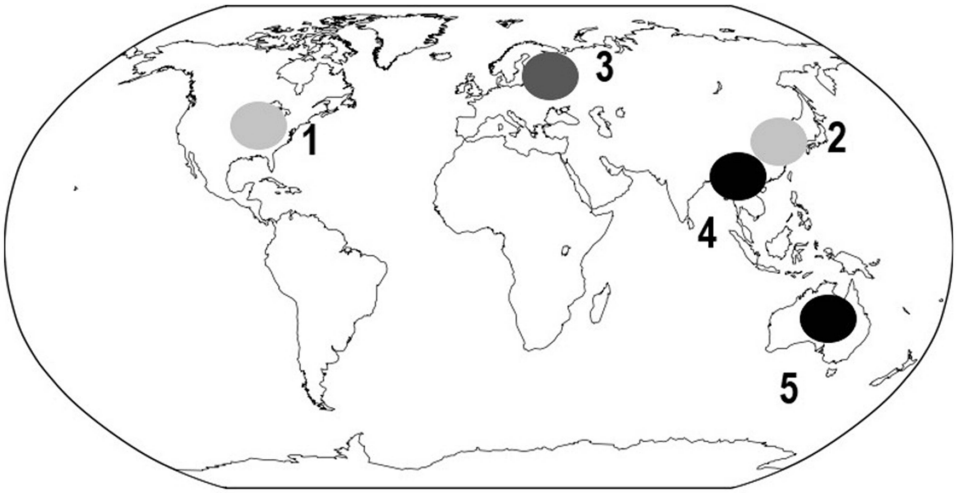

Figure 1 Prevalence of thrombosis of CRV and its branches in the world and different countries, where n – is the volume of the sample; % – is the incidence of RVT. The following regions are marked with numbers: 1. USA (n=4926) – 0.60%. 2. Korea (n=37982) – 0.60%. 3. Europe (n=25002) – 0.70%. 4. China (n=208758) – 0.99%. 5. Australia (n=1738) – 0.91%. Global study (n=120771) – 0.77%. In the figure, regions with thrombosis of CRV prevalence in the range of 0.50–0.65% are shown in light gray[4,5], 0.65–0.80% are shown in gray,[6] and above 0.8% – in black[7,8] World prevalence, based on global epidemiological study data is shown for comparison. Large regional studies with the largest number of subjects and without restrictions on age, ethnicity, or comorbidities were selected for comparison.

The global prevalence of this pathology is presented in Figure 1[1–8] (see Figure 1).

Next, the eight studies we identified that were most indicative, providing data on the influence of both age and hypertension on the RVT prevalence. The eight studies, providing data on the influence of both age and hypertension on the RVT prevalence, are presented in the Table 1 (see Table 1). World prevalence, based on global epidemiological study data, is shown for comparison.[1]

According to Song et al, the prevalence of RVT increases significantly with age rise: in the age group of 40–49 years the prevalence of RVT is in the range of 0.2–0,25 per 1000 population,[1] in the age group of 60–69 years it is 2,1 per 1000 population, in the age group over 80 years this indicator increases to 4,6 cases per 1000 population;[12] thus, the incidence doubles after 50 years old.[13] Researchers indicate, that older age is a prior risk factor for any RVT, with regression coefficient is 1,60 (95% confidence interval [CI]: 1,38–1,84, $p<0.001$) for each decade of increase,[1] while younger age conversely increases the rate of better outcome.[14]

With the global tend to increase in older population, it is expected the RVT may become a growing burden for all countries.

Table 1 Dependence of RVT Incidence Risk from Patients' Age and Presence of Arterial Hypertension

	Number of People in the Study	Study Country	OR, Age	OR, Presence of AH	Reference in the List
1	120771	Global	1,6	2,82	Study[1]
2	10033	Singapore	1,03	3,65	Study[7]
3	203	Italy	1,109	6,632	Study[8]
4	3098	Australia	1,64	–	Study[6]
5	37982	Korea	1,72	2,56	Study[3]
6	5559	USA	1,93	1,47	Study[9]
7	92	Germany	–	1,81	Study[10]
8	1369	Japan	–	1,51	Study[11]

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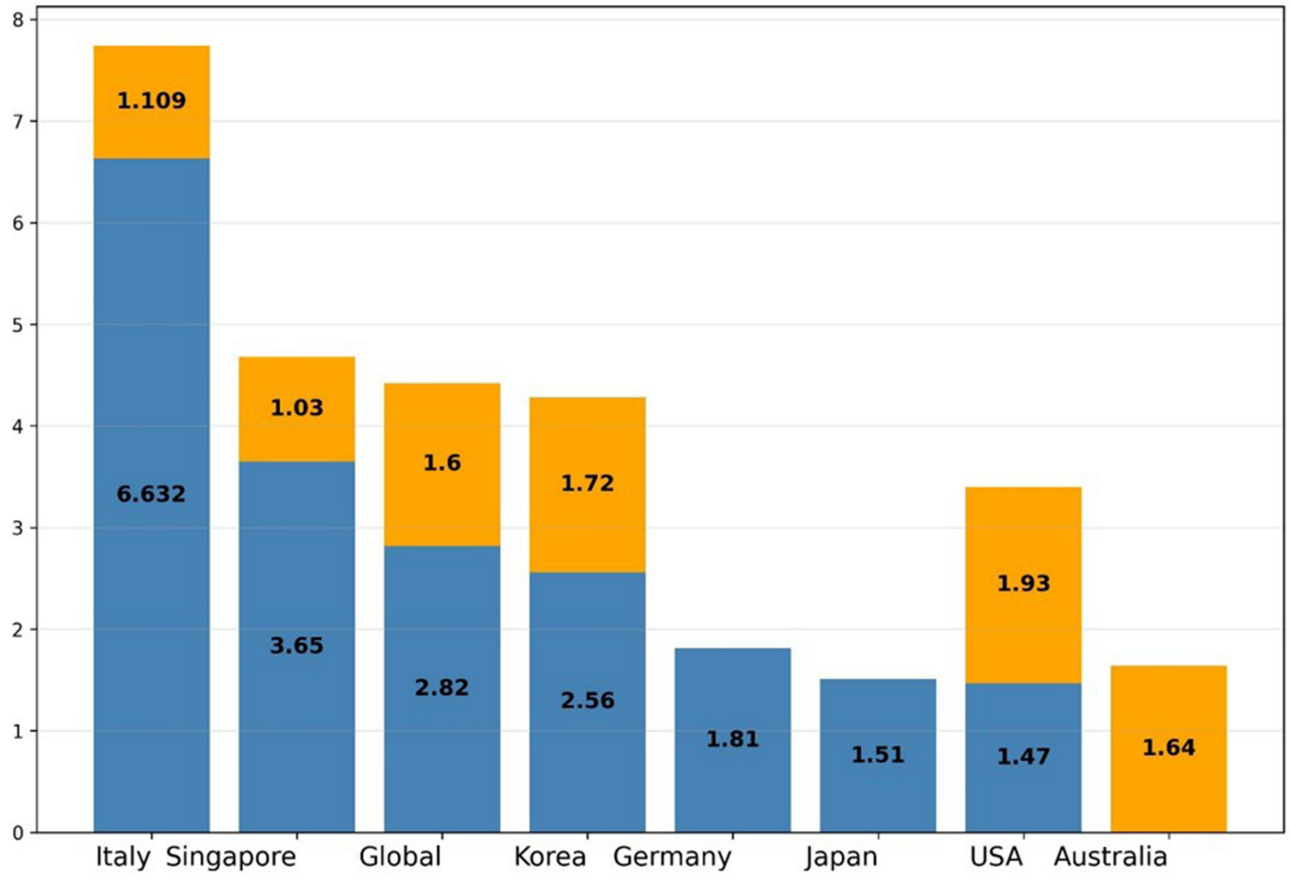

Figure 2 Epidemiological distribution of risk factors (AH and age) across countries. Epidemiological studies from various regions were selected for inclusion in the diagram. These studies considered not only the TBC overall prevalence in the population but also the influence of age and the presence of hypertension. The odds ratio (OR) for the TBC overall incidence in relation to blood pressure is shown in blue, and the odds ratio (OR) for age is shown in Orange. The diagram shows that the blood pressure contribution (OR) to TBC incidence varies across regions, while the age contribution (OR) is less significant and relatively constant across all countries.

However, analysis of epidemiological studies has shown that age is a less important risk factor than a hypertension (Table 1, Figure 2) (See Figure 2).

The risk of vision loss in the older adults due to RVT requires targeted attention to the arterial hypertension (AH) correction.

The limited number of studies worldwide has narrowed our opportunity to perform a complete analysis across different regions. Due to the lack of statistically sufficient data, we considered only potential risk factors: age and AH, but did not consider the effect of AH correction on the RVT development.

Study of gender differences revealed no sex preference for the disease development. However, all authors agreed that the risk of RVT developing increases with age in all genders.[1,13,15] An analysis of the risk factors for RVT development with the patients' age revealed a strong positive correlation with hyper-glycaemia,[16] hyper-lipidaemia,[1,16] and high level of creatinine.[17] Retrospective study has shown that among older adults with retinal vein thrombosis, one in five (26%) dies of acute myocardial infarction and one in eighteen (5,3%) dies of cerebrovascular disease within the next 12 years.[1,17–19] According to Rogers et al, RVT patients have a recurrent thrombotic episode within four years in 7% of cases; also both re-thrombosis and thrombosis in the paired, healthy eye can occur.[13] However, for all listed comorbid pathologies, AH is one of the leading risk factors.

Clinical Features and Examination of Retinal Vein Thrombosis in Older Adults

Usual Biological micro-ophthalmoscopic RVT signs are: low visual acuity, relative afferent pupillary defect, multiple deep intraretinal haemorrhages and cotton-wool spots. The most frequent and serious RVT complication is ischaemic

macular oedema, the incidence of which increases with age.[17,20] Classification of the RVT includes the Central Retinal Vein Occlusion (CRVO), Branch Retinal Vein Occlusion (BRVO). Both states can manifest themselves with non-ischemic (NI-CRVO) and ischemic CRVO (I-CRVO) eyes. Occlusion of retinal veins with ischemic component often form neovascularization in the retina and front segment of the eye.

Much attention in scientific publications is given to the use of a multidisciplinary diagnostic approach to older adults with retinal vascular pathology.[15] First of all, attention is paid to the disease history and comorbid pathology (atherosclerosis, arterial hypertension, diabetes mellitus, vasculitis, blood diseases, systemic diseases, ophthalmic hypertension) identification. When collecting anamnesis, it is important to identify whether the patient has had a stroke, myocardial infarction, thrombosis of deep and superficial veins of the lower limbs. An important aspect of history-taking is also to clarify information about long-term medication use. All these data are more important in older adults with retinal vascular pathology, because of the potential for polypragmasis.

Currently, the main modern methods of retinal vascular disease examination are fluorescence angiography of the ocular fundus (FA) and an angio-optical coherence tomography (Angio-OCT) study of the retina.[15,21–23] Fluorescence angiography is used primarily to determine: localization, duration, degree of thrombosis; the state of venous wall, pathological changes in the arterial channel, condition of capillary perfusion; anastomoses and neovascularization presence or absence; condition of the macular zone (assessment of the perifoveolar capillary network preservation degree), blood circulation in the choroidea vessels. An Angio-OCT study determines: height and size of macular oedema, structural characteristics of oedema, formation of vitreoretinal tractions, presence of epiretinal fibrosis and position of the vitreous body posterior hyaloid membrane. An Angio-OCT allows also to monitor the effectiveness of macular oedema treatment.

These modern examination methods have helped to clarify important pathogenetic aspects of retinal vein occlusion – it is caused by a combination of three main factors: vein compression at the arteriovenous crossing, degenerative changes in the vascular wall, and abnormal blood rheology. Thus, the following play an important role in the pathogenesis of retinal vein occlusion: 1. narrowing of the venous lumen due to external compression of the vein by a rigid artery. Causes: arteriosclerosis, atherosclerosis, vein wall diseases, inflammation (vasculitis, phlebitis), endothelial degeneration (diabetes, arterial hypertension) with intravascular detachment and proliferation. 2. Decreased perfusion pressure play important role as well. Causes: increased arteriolar resistance (arteriosclerosis, arterial hypertension), increased intraocular pressure (glaucoma) and increased blood viscosity (diabetes, blood diseases).

To receive objective criteria for assessing the functional state of the visual organ and the dynamics of the pathological process in RVT, electroretinographic examination is most often used. According to the literature, in retinal vein thrombosis the amplitude of the a-wave may not change, while the amplitude of the b-wave decreases and the b/a ratio changes. The lower the b-wave amplitude, the more severe the retinal ischaemia is and the worse the prognosis in terms of visual acuity and neovascular complications in the patient.[15]

Treatment and Medical Rehabilitation of Older Adults with Retinal Vein Thrombosis

There are several management strategies for retinal vein thrombosis interventions. One of them is antithrombotic treatment.[24] Laser photocoagulation: macular retinal laser was the "gold standard" for the treatment of macular oedema in older adults with RVT before the intravitreal therapy introduction; however, its application may result in the sectoral scotomas development. Currently, intravitreal drugs injection is used specifically for the post-thrombotic macular oedema treatment;[25–28] however, there is no intervention that can safely and reliably eliminate actual RVT. Therefore, the intervention is aimed at preventing or treating the vision-threatening complications.[29,30]

According to Zeng et Liu, another strategy for the treatment of macular oedema in RVT patients is the use of intravitreal injection of an implant with dexamethasone (Ozurdex).[31] But Cornish et al found that dexamethasone high efficacy has been observed in the treatment of the basic disease, but complications have been reported with its application: increased intraocular pressure and the occurrence or progression of cataract.[32] Intravitreal injection of vascular endothelial growth factor (anti-VEGF) inhibitors seems to be a perspective direction. Several drugs are currently available for the treatment of RVT with macular oedema: ranibizumab, aflibercept, faricimab and bevacizumab.[17,21–28,33] They are infused separately or in certain combinations that reduce the number of injections,[29,30,34] but, according to

Galvez-Olortegui et al, indicated combinations that are unequivocally recognized, have not been developed and more studies are needed.[35–37] Liang et al described that anti-VEGF drugs and retinal photocoagulation combination may also be important and safety intervention.[38,39]

Discussion

Analysis of global RVT prevalence data revealed different rates across regions: it is lower than global rates in regions 1 and 2, while it is higher in regions 4 and 5 (see Figure 1). Data for region 3 are consistent with global rates. Assuming equal quality of all the studies, this difference may indicate different levels of preventive measures across regions.

It was shown that the prevalence of this pathology increases 20 times in patients aged over 80 years, compared to the age of 40–49 years. Sex differences in prevalence were not significant.

Figure 2 and Table 1 show that hypertension and age are significant risk factors for RVT; however, the AH presence contributes most to the RVT prevalence in the older adults. Furthermore, the very RVT occurrence in older adults is an important biomarker for cardiovascular disease and stroke, and preventive efforts are needed to reduce mortality. Although this concept has been accepted by some authors, it is not well balanced and requires further research.

The classical scheme of drug rehabilitation in the RVT acute phase consists of dis-aggregants, corticosteroids, antioxidants and vasodilators.

Often to increase the concentration of angiogenesis inhibitors at the site of thrombus formation, specialists carry out the application of these drugs sub-tentorially, epi-retinally or intravitreally. This type of injection is relevant in older adults, but it is associated with an increased risk of intraoperative or postoperative complications.

Intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF) or their combination with retinal photocoagulation seems to be a more perspective strategy for effective intervention. Intravitreal administration of a dexamethasone implant is also described. The response to anti-VEGF treatment is better with earlier initiation. VEGF suppression not only improves macular edema but also reopens some closed retinal vessels, prevents the progression of vessel closure, and improves retinopathy.

Side effects of such type of treatments include lens damage, subconjunctival hemorrhages, inflammation of the ocular structures (post-injection endophthalmitis), and others. Increased intraocular pressure and the development or progression of cataracts have been reported in the older adults after using Ozurdex. If conservative therapy is ineffective, laser photocoagulation of the ocular fundus tissues is used, but this method of intervention may result in the appearance of sectoral scotomas.

It is important indicate that this review had described treatment for retinal vein occlusion with local strategies: antiangiogenics, laser, and intravitreal corticosteroids. But associated vascular pathology or general comorbidity requires general treatment approach, especially for AH.

Limitations

There are several Limitations of this review that should be mentioned. First, the lack of studies from many regions precludes an adequate analysis of global prevalence. Second, many studies were limited to certain age groups, comorbidities, or the presence of harmful habits. Third, other ophthalmologic conditions were not taken into account. Fourth, drug therapy, particularly for hypertension, was not considered. Future studies should improve the quantity and quality of studies where possible, and provide clear and detailed results. In this review, we used only available information to estimate the prevalence, risk factors, and treatment of RVT.

Conclusion

This review allowed us to expand the understanding of the retinal vascular pathology problem in older patients. The prevalence of retinal vein occlusion increases significantly with age. It is associated with an increase in stroke, cardiovascular events, and mortality. The unfavorable prognosis in terms of visual function preservation, risk of neovascularization, difficulty in determining tactical treatment steps, development of side effects, and progression of the existing ocular vascular diseases requires further in-depth attention to the prevention of vascular risk factors, as well as the development of effective and safe treatment and rehabilitation measures for retinal vein occlusion in older adults.

Recommendations

Population of older adults represents a large demographic group in health care that requires long-term and complex medical rehabilitation. While the healthcare model for the working population has prioritized acute care and disease management, the older adults require more long-term care. Taking into account the population ageing and the increasing burden of chronic non-communicable diseases, an integrated approach to the assessment and interdisciplinary monitoring and correction of common risk factors for cardiovascular diseases, diabetes mellitus, other socially significant vascular conditions and ophthalmologic diseases, associated with high blood pressure is necessary. Due to the high risk of RVT development in older adults, it is necessary to develop an effective integrated approach to AH monitoring and correction, including telerehabilitation.

This will improve medical and social care, reduce the number of patients and disability of older adults, who have lost their visual functions. For this purpose, cooperation of different specialists is important and ophthalmologists need to cooperate with cardiologists, neurologists, endocrinologists, immunologists to create effective personalized protocols for ophthalmic pathology prevention, treatment and rehabilitation in older adults.

Abbreviations

RVT, Retinal vein thrombosis; CRV, Central retinal vein; RVO, retinal vein occlusion; AH, Arterial hypertension; CRVO, Central Retinal Vein Occlusion; BRVO, Branch Retinal Vein Occlusion; OF, ocular fundus; OCT, optical coherence tomography; anti-VEGF, vascular endothelial growth factor inhibitors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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