Hindawi
Journal of Ophthalmology
Volume 2020, Article ID 8865743, 6 pages
https://doi.org/10.1155/2020/8865743

Research Article

Comparative Analysis of the Clinical Features and Long-Term Outcomes of Pachychoroid Neovasculopathy and Type 1 Neovascular Age-Related Macular Degeneration

Jong In You and Kiyoung Kim

Department of Ophthalmology, Kyung Hee University Hospital, Kyung Hee University, Seoul, Republic of Korea

Correspondence should be addressed to Kiyoung Kim; pourma@khu.ac.kr

Received 27 August 2020; Revised 7 November 2020; Accepted 24 November 2020; Published 3 December 2020

Academic Editor: Dirk Sandner

Purpose. To evaluate the clinical characteristics and long-term prognosis of pachychoroid neovasculopathy (PCN) when compared with type 1 neovascular age-related macular degeneration (nAMD). *Methods*. We retrospectively analyzed 30 and 60 patients whose eyes were diagnosed as treatment-naïve PCN or type 1 nAMD, respectively. All subjects were followed up for 5 years. Baseline angiographic characteristics and long-term clinical outcomes were compared between the two groups. *Results*. PCN group consisted of patients of younger age and represented more choroidal vascular hyperpermeability, polypoidal lesion, and history of central serous chorioretinopathy (CSC) at the time of diagnosis (all $p < 0.01$). During the 5-year follow-up period, individuals in the PCN group received significantly fewer injections and reported better visual acuity compared to individuals in the type 1 nAMD group. A progressive decrease in the subfoveal choroidal thickness was observed in the type 1 nAMD group, while the thick choroid was maintained in the PCN group during the 5-year follow-up period. *Conclusions*. PCN developed in younger patients with a higher propensity of forming polypoidal lesions and a history of CSC. Long-term outcomes revealed that PCN had a thicker choroid and better visual prognosis with fewer number of intravitreal injection than that of type 1 nAMD.

1. Introduction

Type 1 choroidal neovascularization (CNV) is the most common subtype of neovascular age-related macular degeneration (nAMD) that is characterized by localization of abnormal vessels beneath the retinal pigment epithelium (RPE). Type 1 nAMD is typically defined by occult leakage observed on fluorescein angiography, late staining plaque on indocyanine green angiography (ICGA), and shallow irregular RPE elevation on optical coherence tomography (OCT). It has been suggested that the type 1 CNV may be a compensatory form of neovascular growth occurring in response to an ischemic outer retina [1].

Recently, new clinical entities have been suggested as pachychoroid spectrum disease that shares common features of choroidal thickening, comprising central serous chorioretinopathy (CSC), pachychoroid neovasculopathy (PCN), and polypoidal choroidal vasculopathy (PCV) [2–4]. The CNV induced by pachychoroid disease is characterized by the formation of a thick choroid with type 1 CNV, and its etiologies are likely to be different from type 1 nAMD [2–4]. It is known that these choroidal changes have an important role in the common pathogenesis of pachychoroid spectrum diseases. It occurs due to a pachychoroid-driven process, involving choroidal congestion and choroidal hyperpermeability that is manifested by choroidal thickening and dilated choroidal vessels in the absence of other causes of neovascularization [3–5]. Although the choroid is generally thicker in pachychoroid diseases than in AMD, pachychoroid spectrum diseases share many clinical manifestations with AMD. Intravitreal injection of antivascular endothelial growth factor (anti-VEGF) or photodynamic therapy (PDT) is considered as an effective treatment option against PCN [3, 6, 7]; the treatment regimen is similar to that of type 1

nAMD. Moreover, no definitive differences have been reported between these two diseases in terms of treatment responses to anti-VEGF treatment [8].

However, the definition of PCN is still under debate, and only few studies have compared long-term outcomes of PCN with that of type 1 nAMD. In this study, we evaluated the baseline angiographic features of PCN cases and their 5-year clinical outcomes and compared them with type 1 nAMD cases.

2. Materials and Methods

This retrospective study followed the guidelines of the Declaration of Helsinki. Approval was obtained from the institutional review board of the University Hospital Institutional Review Board. Informed consent was not required due to the retrospective nature of the study. The patients who visited our clinic and were initially diagnosed with type 1 CNV associated with nAMD or PCN were recruited between February 2006 and February 2014.

The initial diagnosis of type 1 CNV was based on the spectral-domain OCT (SD-OCT) and indocyanine green angiography (ICGA, Spectralis® HRA-OCT, Heidelberg, Germany). The inclusion criteria were as follows: (1) age more than 50, (2) patients who had not been treated with intravitreal or laser treatment, and (3) patients who had been regularly followed up for more than 5 years. Patients who were lost during the follow-up period or those who had a possibility of developing myopic choroidal neovascularization with myopia of -6 diopters or more, history of uveitis, severe cataracts, and other retinopathies including severe diabetic retinopathy and retinal vascular abnormalities were excluded from the study. Finally, all recruited subjects were divided into nAMD or PCN group.

PCN was diagnosed if all of the following criteria were met: (1) minimum cutoff value of subfoveal choroidal thickness (SFCT) was 300 μm for CNV in either eye; (2) no drusen greater than category 1 criteria is used in the age-related eye disease study; (3) presence of RPE abnormality; and (4) the presence of choroidal pachyvessels or thickening choriocapillaris directly below type 1 CNV. Representative cases are shown in Figure 1.

We investigated structural characteristics at baseline and during the period of prognosis over 5 years. At the time of diagnosis, best-corrected visual acuity (BCVA), SFCT, history of CSC, presence of choroidal hyperpermeability, polypoidal lesion, and drusen were investigated. For the longitudinal analysis, the number of intravitreal anti-VEGF injections, the history of PDT, change in BCVA, and SFCT were investigated at 1, 3, and 5 years. All the patients were treated with a loading phase of 3 monthly anti-VEGF injections and were then retreated as needed (PRN regimen). If patients were treated with combination therapy, PDT was performed at the same day of the first anti-VEGF injection.

Subfoveal choroidal thickness was measured by vertical distance from the outer edge of the hyperreflective line of RPE to the hyporeflective line of sclerochoroidal interface. If the quality of the HRA-OCT was poor to measure the thickness of the choroid, it was measured considering Cirrus® OCT (Carl Zeiss Meditec, Dublin, CA, USA) together. Choroidal hyperpermeability was defined as demarcated and large hyperfluorescent borders that appeared in the late stage of ICGA. Geographic atrophy was defined as the clear boundary of atrophic regions with a diameter of more than 175 μm in the region with hypopigmentation, depigmentation, or RPE loss.

Statistical analyses were performed using IBM SPSS Statistic ver. 23.0 (IBM Corp, Armonk, NY, USA). The baseline characteristics of PCN group and nAMD group were analyzed by paired t-test, Fisher's exact test, and Mann–Whitney test. The number of injections and changes in BCVA and SFCT during the follow-up period were analyzed using paired t-test. For all statistical tests, p value less than 0.05 was considered statistically significant.

3. Result

A total of 90 eligible subjects were included in the study. Thirty eyes were grouped as PCN, and 60 eyes were grouped as nAMD. The demographic and clinical characteristics of the patients before treatment are presented in Table 1.

There was significant difference between the two groups with respect to the SFCT and age. The SFCT of the PCN group was 335 ± 43 μm, and the nAMD group was 250 ± 41 μm. The mean age of the PCN group was 66.7 ± 11, making its members younger than the subjects in the nAMD group (75.3 ± 6.9). The baseline BCVA of PCN group was 0.39 ± 0.13, and nAMD group was 0.51 ± 0.14, with no statistically significant difference between them ($p = 0.137$). The history of CSC was more common in the PCN group (80%) than the nAMD group (15%) ($p < 0.001$). In terms of angiographic evaluation, the presence of choroidal hyperpermeability, polypoidal lesion, and any drusen was significantly different in the two groups. Choroidal hyperpermeability on ICGA was observed on 73.3% cases in the PCN group and 16.4% cases in the nAMD group ($p < 0.001$). The polypoidal lesion was more commonly observed in the PCN group (40%) than that in the nAMD group (23.3%) ($p < 0.001$). Any drusen was observed in 13.3% of PCN and 58.3% of nAMD cases ($p = 0.020$).

The changes in SFCT during the 5-year period area are shown in Figure 2. The SFCT of the PCN group after 1, 3, and 5 years was 331.61 ± 63.74, 335.06 ± 68.47, and 334.94 ± 88.84 μm. In the AMD group, the SFCT was 206.16 ± 45.40, 201.66 ± 50.45, and 192.51 ± 51.39 μm, respectively. The decrease in SFCT did not differ significantly between the two groups during the first year of this study. PCN group showed no significant change in SFCT from 3- to 5-year period when compared to the baseline, while the nAMD group showed significant decrease from baseline to 1- to 5-year follow-up.

The BCVA changes during the 5-year follow-up period are shown in Figure 3(a). The BCVA of the PCN group after 1, 3, and 5 years was 0.32 ± 0.13, 0.29 ± 0.12, and 0.35 ± 0.15 logMAR, respectively. In the AMD group, the BCVA was 0.40 ± 0.14, 0.42 ± 0.13, and 0.48 ± 0.19 logMAR after 1, 3, and 5 years, respectively. BCVA was significantly improved after 1 year in both the groups, and these

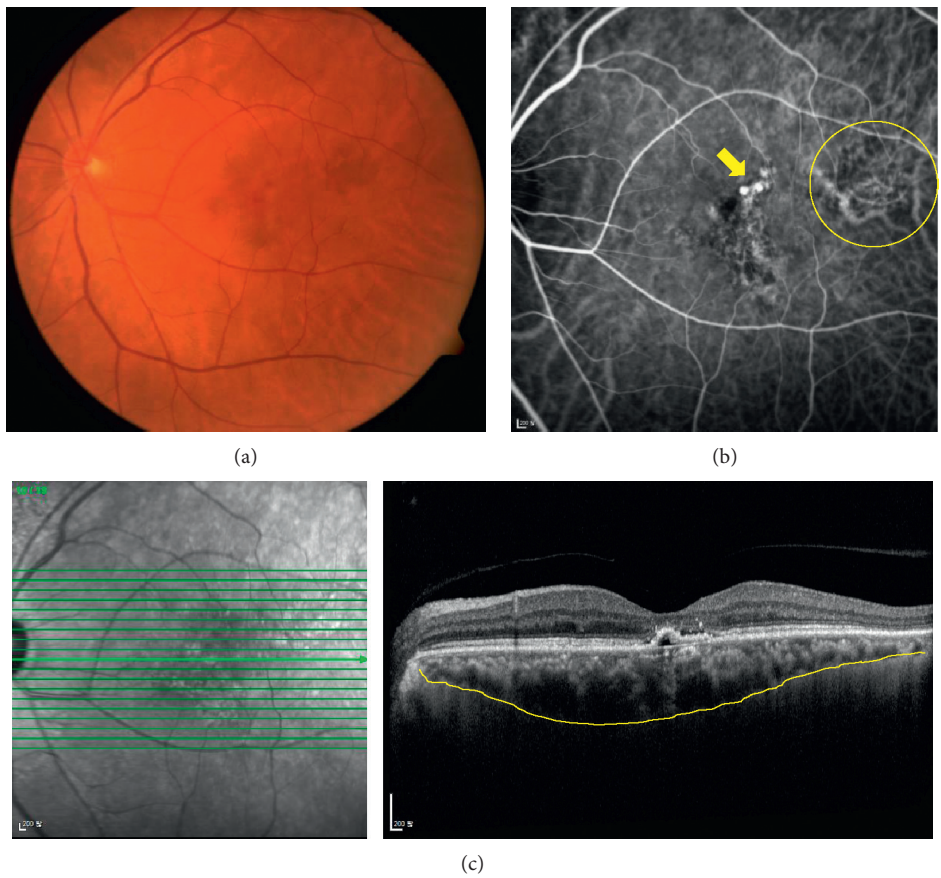

Figure 1: Multimodal image of a 54-year-old male with pachychoroid neovasculopathy in the left eye. (a) Color fundus photography displaying no evidence of drusen. (b) Choroidal vascular hyperpermeability (yellow circle) and hyperreflective polypoidal lesions are (yellow arrow) observed on early-phase indocyanine green angiography image. (c) Optical coherence tomography image showing that subfoveal choroidal thickness is over 300 μm (yellow line), and focal retinal pigment epithelium detachment is observed corresponding to the polypoidal lesions.

Table 1: Initial observations of distinct characteristics between individuals of the pachychoroid group and the AMD group.

Category	PCN group	AMD group	p value
Number of eyes (eyes)	30	60	
Subfoveal choroidal thickness† (μm)	335 ± 43	250 ± 41	<0.001 *
Age§ (years)	66.7 ± 11	75.3 ± 6.9	0.001 *
Sex‡ (male: female)	16 : 14	36 : 24	0.579
History of CSC‡ (eyes, (%))	24 (80%)	9 (15%)	<0.001 *
BCVA† (logMAR), F	0.39 ± 0.13	0.51 ± 0.14	0.137
Choroidal hyperpermeability‡ (eyes, (%))	22 (73.3%)	10 (16.4%)	<0.001 *
Polypoidal lesion‡ (eyes, (%))	12 (40%)	14 (23.3%)	<0.001 *
Presence of drusen‡ (eyes, (%))	4 (13.3%)	35 (58.3%)	0.020 *

Values are presented as mean ± SD, otherwise indicated. *, statistically significant value; †, analyzed by paired t-test; ‡, analyzed by Fisher's exact test; §, analyzed by Mann–Whitney test.

improvements were maintained for 3 years after the initial treatment in PCN groups. BCVA improvements during the 5-year period did not significantly differ between the two groups. Change in BCVA from baseline to 1, 3, and 5 years between PCN and nAMD groups is demonstrated in Figure 3(b).

The number of anti-VEGF injections during the treatment period of 5 years is shown in Table 2. The number of injections during the 1-, 3-, and 5-year period was 4.1 ± 0.9, 6.0 ± 1.1, and 7.2 ± 1.2 in the PCN group, respectively. In the nAMD group, the number of injections was 4.7 ± 1.1, 7.1 ± 1.3, and 9.5 ± 1.3 during the 1-, 3-, and 5-year period, respectively. The number of injections for nAMD was greater than that in the PCN group for the 1- and 3-year period; however, the difference was not significant. On the contrary, the total number of injections for the 5-year

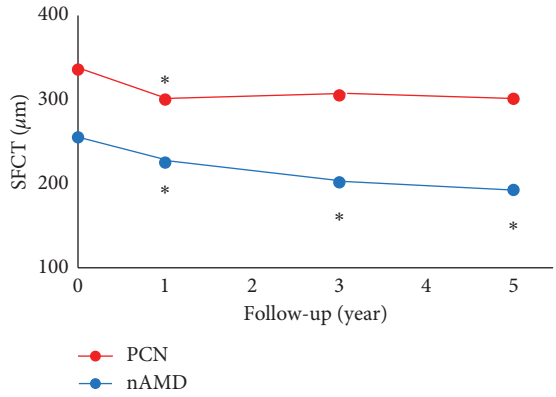

Figure 2: Serial changes in the subfoveal choroidal thickness (SFCT) of individuals from the pachychoroid and age-related macular degeneration groups during the 5-year follow-up period. The decrease in SFCT did not differ significantly between the two groups during the first year of this study. PCN group showed no significant change in SFCT from 3- to 5-year period when compared to the baseline, while the nAMD group showed significant decrease from baseline to 1- to 5-year follow-up.

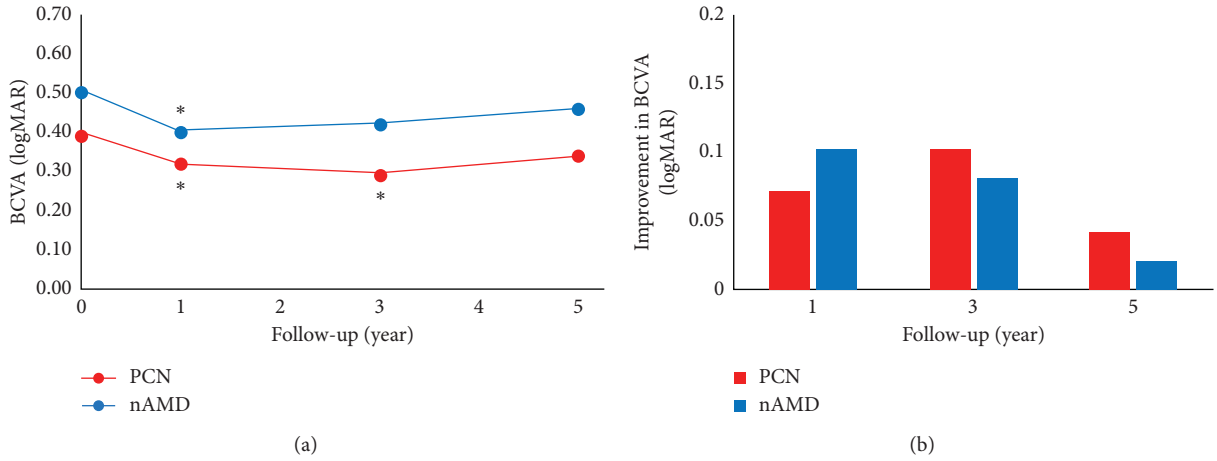

Figure 3: (a) Serial changes in the best-corrected visual acuity (BCVA) in the logMAR scale of individuals in the PCN and nAMD groups during the 5-year follow-up period. BCVA was significantly improved after 1 year in both the groups, and these improvements were maintained for 3 years after the initial treatment in PCN groups. However, BCVA improvements during the 5-year period did not significantly differ between the two groups. (b) Change in BCVA from baseline to 1, 3, and 5 years in terms of PCN and nAMD groups.

Table 2: Long-term disease progression and treatment history of pachychoroid group and AMD group.

Category	PCN group	nAMD group	p value
Number of intravitreal injection for 1 year†	4.1 ± 0.9	4.7 ± 1.1	0.545
Number of intravitreal injection for 3 years†	6.0 ± 1.1	7.1 ± 1.3	0.081
Number of intravitreal injection for 5 years†	7.2 ± 1.2	9.5 ± 1.3	0.028 ∗
Treatment of PDT‡ (eyes, (%))	15 (50%)	20 (33.3%)	0.114

Values are presented as mean ± SD, otherwise indicated. ∗, statistically significant value; †, analyzed by paired t-test; ‡, analyzed by Fisher's exact test.

follow-up was significantly fewer in the PCN group than that in the nAMD group. Lastly, there was no significant difference between the two groups with respect to the proportion of eye that was treated with PDT at the first time of anti-VEGF injection.

During the 5-year treatment period, geographic atrophy (GA) developed in 10 eyes (10%) in the nAMD group; however, only one (3.3%) developed GA in the PCN group that showed a significant difference ($p = 0.004$).

4. Discussion

Since the PCN was published as a criterion of CNV, many studies have been published about PCN displaying a shared morphology with type 1 CNV without evidence of nAMD [2, 3]. Recent studies have reported clinical phenotypic difference between PCN and nAMD [9]. In the current study, it could be observed from the results of baseline analysis that individuals in the PCN group were significantly

younger and had better BCVA, greater SFCT, more polypoidal lesion, more history of CSC, more choroidal hyperpermeability, and less drusen than those with nAMD. This was consistent with previous studies. To the best of our knowledge, this study is the first to report a 5-year comparison between PCN and type 1 nAMD with respect to the clinical outcomes.

Although PCN groups had better baseline BCVA than the nAMD group, the BCVA improvements during the 5-year follow-up period were not significantly different between the two groups. The number of anti-VEGF injections was not significantly different between the two groups at 1- and 3-year follow-up. This result may be due to the initial three monthly injection treatment subjected to individuals in both the groups. However, significantly fewer injections were used for PCN than that for nAMD for the 5-year period (7.2 ± 1.2 vs 9.5 ± 1.3). An earlier study evaluated the efficacy of a treat and extend anti-VEGF injection while treating-naïve PCN and type 1 nAMD cases. They found that PCN required significantly fewer injections than nAMD during a 2-year follow-up [10]. Furthermore, Cho et al. [11] compared a 12-month clinical outcome between PCN and nAMD cases who were initially treated with three monthly injection followed by the PRN regimen. Although there was no significant intergroup difference in terms of visual acuity achievement, they suggested that the response to anti-VEGF treatment could be different between PCN and nAMD groups. The PCN group showed a significantly lower need for retreatment and exhibited a longer mean retreatment-free period after loading injections. The reason for the difference in the response to anti-VEGF treatment between PCN and type 1 nAMD is still unclear. This result could be associated with baseline characteristics such as younger age or better baseline visual acuity in the case of the PCN group, which could effectuate a relatively good visual outcome. Management of PCN with significantly fewer injections might be related to the lower intraocular VEGF concentration in PCN [12]. In addition, aqueous VEGF levels showed a negative correlation with subfoveal choroidal thickness [13].

The maintenance of a thick choroid in PCN cases could be one of the reasons for better treatment outcomes. In this study, SFCT showed significant decrease at a 1-year treatment period from baseline in both PCN and nAMD groups. The SFCT reduction was significantly greater in the nAMD group than that in the PCN group after a 1-year period. Intravitreal injection of anti-VEGF agents is known to affect the choroidal circulation. Prior studies have shown that aflibercept reduces choroidal thickness to a greater extent than ranibizumab [14, 15]. Suppressing VEGF is thought to reduce choroidal vascular hyperpermeability or constrict choroidal vessels via a decrease in nitric oxide production, thereby reducing choroidal thickness [16]. Accordingly, more frequent anti-VEGF injection might be one reason why SFCT was significantly reduced in the nAMD group after 3-year follow-up. Initially, three monthly injection and PDT in the PCN group might cause similar decrease in SFCT in the nAMD group within the first year. This result is consistent with a previous study that showed that decrease in choroidal thickness of PCN after 1-year treatment of anti-VEGF injection was significantly related to the number of intravitreal injections [17]. Also, decrease in choroid thickness following anti-VEGF treatment had been known as a risk factor of GA progression [18]. Our results also revealed that GA incidence was significantly lower in the PCN than that in the nAMD group. Significantly higher choroidal thickness and lower number of anti-VEGF injections in the PCN group could be associated with the relatively lower incidence of GA development. More frequent injection has been associated with higher incidence GA development in nAMD [19].

Several studies from literature suggested that etiologies of the two conditions must be different [9]. Pang and Freund suggested that PCN should be considered in the differential diagnosis of eyes with characteristics of type 1 CNV and choroidal thickening in the absence of signs of AMD or degenerative changes [3]. They also proposed that PCV might be developed from the pachychoroid-driven process involving choroidal congestion and choroidal hyperpermeability manifested by thick choroid and dilated choroidal vessels. Consequently, pachyvessels, along with attenuation of the inner choroid and loss of choriocapillaris, produce an ischemic environment, leading to overexpression of angiogenic factors and choroidal neovascularization. In addition, a previous longitudinal study reported that pachychoroid pigment epitheliopathy (PPE) lesions can be the precursor lesion for PCN or PCV [20]. They hypothesized that increased choroidal pressure and choroidal hyperpermeability may lead to disruption in gap junctions between RPE cells, and a small amount of subretinal fluid which cannot be visualized by OCT may leak into the sub-RPE space from microbreaks and lead to focal RPE detachment, observed as elevation of RPE. Then, increasing sub-RPE fluid may cause conversion of RPE microleaks to PED lesions [20]. Furthermore, a recent large-scale genetic study on choroidal thickness clearly elucidated the crucial difference between pachychoroid and drusen-originated AMD [21]. In the respect of the CFH gene association, drusen-driven AMD and pachychoroid diseases should belong to different disease spectrums [22]. Previously proposed characteristics of PCN including thick choroid and choroidal vascular hyperpermeability are now confirmed by objective evidence of genetic associations. However, until recently, a clear definition differentiating PCN from nAMD has not been established, and sufficient pathophysiological or clinically rational grounds had not been provided to confirm the significance of differentiating PCN from nAMD.

The limitation of this study was the retrospective study design and relatively small number of cases. Second, the effect of treatment according to the type of anti-VEGF drug had not been considered due to the retrospective nature. Finally, PCN still remains a subjective term with no clear definition. The study included subjects who showed polypoidal lesions on ICGA in the PCN group. Some studies were excluded from PCN if polypoidal lesions were detected on ICGA [8], whereas in other studies, type 1 neovascularization with polypoidal lesions was included in the inclusion criteria of PCN [10, 12]. We expect further studies that would reduce the ambiguities associated with the

definition and prognosis of PCN involving a large cohort and prospective study design.

In conclusion, PCN is presented in younger age and has a higher likelihood to have CSC history, polypoidal lesion, and choroidal hyperpermeability compared to type 1 nAMD. A long-term follow-up analysis over 5 years revealed that a thicker choroid showed better visual prognosis with fewer number of anti-VEGF injections. Therefore, distinguishing PCN from nAMD may be advisable to estimate long-term prognosis and determine appropriate treatment plan.

Data Availability

The datasets used to support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding this paper.

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