EPMA Journal (2021) 12:41–55
https://doi.org/10.1007/s13167-021-00235-4

RESEARCH

Health screening program revealed risk factors associated with development and progression of papillomacular bundle defect

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Received: 30 November 2020 / Accepted: 27 January 2021 / Published online: 4 March 2021

Abstract

Background/aims The papillomacular bundle (PMB) area is an important anatomical site associated with central vision. As preventive medicine and health screening examinations are now becoming commonplace, the incidental detection of papillomacular bundle defect (PMBD) on fundus photography has been increasing. However, clinical significance of incidental PMBD has not been well documented to date. Thus, through long-term and longitudinal observation, we aimed to investigate the risk factors for the development and progression of PMBD and its predictive role associated with systemic diseases and glaucoma.

Methods This longitudinal study included subjects who had undergone standardized health screening. We retrospectively reviewed patients for whom PMBD had been detected in fundus photography and followed up for more than 5 years. For a comparative analysis, non-PMBD groups of age- and gender-matched healthy controls were selected.

Results A total of about 67,000 fundus photographs were analyzed for 8.0 years, and 587 PMBD eyes were found. Among them, 234 eyes of 234 patients who had had fundus photographs taken for more than 5 years were finally included. A total of 216 eyes (92.3%) did not progress during the 8.1 ± 2.7 years, whereas 18 eyes (7.7%) showed progression at 7.6 ± 2.9 years after initial detection. A multivariate logistic regression analysis using 224 non-PMBD healthy controls revealed low body mass index (BMI < 20 kg/m^2), systemic hypertension, and sclerotic changes of retinal artery as the significant risk factors for the development of PMBD. Regarding PMBD progression, low BMI, concomitant retinal nerve fiber layer defect (RNFLD) at non-PMB sites, optic disc hemorrhage, and higher vertical cup/disc ratio were individual significant risk factors.

Conclusion PMBD is associated with ischemic effects. Although the majority of PMBD do not progress, some of cases are associated with glaucomatous damage in a long-term way. PMBD might be a personalized indicator representing ischemia-associated diseases and a predictive factor for diagnosis and preventive management of glaucoma.

Keywords Papillomacular bundle defect · Ophthalmology · Health screening examination · Program · Low body mass index · Ischemia-associated diseases · Risk assessment · Risk factors · Screening · Cardiovascular disease · Longitudinal study · Disease development and progression · Systemic effects and characteristics · Glaucoma · Predictive factors · Personalized indicator · Preventive management · Predictive preventive personalized medicine (PPPM/3PM)

Meeting presentation None

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Introduction

In recent years, the prevalence of the cardiovascular disease, metabolic disease, and cancer has rapidly increased in Korea [1, 2]. To address this problem, preventive medicine as for early diagnosis of disease and prediction of development has received increasing attention and a comprehensive approach, for example, health screening examinations are being recommended [3, 4]. In line with this issue, Korea is actively operating a health screening system or healthcare center, and is suggesting predictive, preventive, and personalized strategies according to individual characteristics [5, 6]. In the future, this supply and demand in medicine are expected to continue to increase worldwide.

Fundus photography is one of representative ophthalmic examinations in health screening programs and is becoming more popular. In parallel, early detection of vision-threatening diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma has been increasing [7–9]. Moreover, the retina is the only human tissue allowing direct visualization of vessels and nerve fibers. Retinal microvascular changes have been known as independent predictors for systemic diseases including diabetes, hypertension, coronary artery disease, and stroke, while significant associations between alterations of retinal nerve fiber layers and neurodegenerative diseases have been reported [10].

The papillomacular bundle (PMB) is a collection of retinal nerve fibers that carry the information from the macula, and papillomacular bundle defect (PMBD) is not infrequently discovered by chance in screening fundus photography. Although it has been reported that PMBD is likely to be caused by ischemic events [11] and the PMB area is usually spared until the end stage of glaucoma [12], clinical significance of incidental PMBD has not been well documented so far. In fact, focal and solitary PMBD may develop even in non-glaucomatous eyes [11, 13–15]. Therefore, knowledge of the development and progression of PMBD is essential for establishing its predictive, preventive, and personalized value.

Accordingly, through long-term and longitudinal observation, we investigated the individual risk factors related to the development and progression of incidentally detected PMBD in fundus photography and suggested customized guidelines to individuals.

Methods

This investigation was approved by the Institutional Review Board of Seoul National University Hospital (No. 1906-141-1043) and was conducted in accordance with all Declaration of Helsinki requirements.

Study population

This study enrolled individuals who had been attending a healthcare screening program for general check-ups at Seoul National University Hospital Healthcare System Gangnam Center during the period from 2010 to 2018 and were aged >18 years at the time of the initial examination. A total of about 67,000 fundus photographs were initially checked for the purposes of the present study's analysis (H.J.C.).

Inclusion and exclusion criteria

In this study, patients for whom PMBD had been incidentally detected on fundus photography and who met the following inclusion criteria were consecutively enrolled: (1) follow-up longer than 5 years; (2) at least five consecutive fundus photographs measured. The exclusion criteria were (1) history of intraocular surgery other than uncomplicated cataract surgery or of diseases that could affect the retinal nerve fiber layer (RNFL) (e.g., diabetic retinopathy, retinal vein occlusion, ischemic optic neuropathy, pituitary lesions, or demyelinating diseases), (2) optic disc pallor, and (3) media opacity rendering fundus reading difficult for diagnosis (significant cataract, asteroid hyalosis, or vitreous opacity). In cases where both eyes of a patient were eligible for inclusion, one eye with a larger PMBD size was selected as study eye.

Health screening examination

The health screening examination consists of two parts: a health interview survey and a health screening program including an ophthalmologic examination. The health interview survey, administered by trained research technicians, included standardized questionnaires on demographic variables as well as current and past medical conditions (e.g., diabetes mellitus, systemic hypertension, coronary heart disease, asthma, and hyperlipidemia) and health-influencing behaviors (e.g., smoking and alcohol consumption). The health screening program included measurement of body height, weight, waist circumference, and average systolic and diastolic blood pressures, as well as blood tests (e.g., complete blood cell counts, glucose, lipid profile, kidney function, liver enzyme, and thyroid function), routine urinalysis, and an ophthalmologic examination.

Height and body weight were measured on anthropometry. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest during exhalation. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. The BMI was categorized into 3 groups: BMI of less than 20 kg/m^2, BMI of 20~25 kg/m^2, and BMI of 25 kg/m^2 or more. The World Health Organization defines obesity as a BMI of 30 kg/m^2 or more and overweight status as a BMI of

25 kg/m^2 or less than 30 kg/m^2. However, because of the lower prevalence rates for overweight status and obesity in Asian countries compared with Western ones [16], we set the standard as a BMI of 25 kg/m^2 instead of 30 kg/m^2. Systolic blood pressure and diastolic blood pressure were measured in the right arm after a 5-min stabilization period using a standard mercury sphygmomanometer (Baumanometer; Baum, NY, USA). Further, the level of smoking was categorized as "have never smoked," "previously smoked but no longer smoking," or "currently smoking," and the level of alcohol consumption was categorized as "do not drink at all," "less than once a month," "2–3 times a month," "1–2 times a week," "3–4 times a week," or "almost every day." Of these, two or more drinks per week, considered to correspond to consumption of more than 140 g, were classified as "excessive consumption."

The ophthalmic screening examination included visual acuity (Snellen chart), measurements of intraocular pressure (IOP) using a non-contact tonometer (CT-80 or CT-1P; Topcon Inc., Tokyo, Japan), and fundus photographs using a 45° digital non-mydriatic fundus camera (CR6-45NW; Canon Inc., Utsunomiya, Japan, or TRC-NW8, Topcon Inc., Tokyo, Japan). The cup to disc ratio was evaluated both horizontally and vertically. The optic disc ovality was calculated by dividing the vertical disc diameter by the horizontal disc diameter. The peripapillary atrophy was defined as a peripapillary area that consisted of a zone with chorioretinal atrophy and visible large choroidal vessels and an outlining zone with irregular retinal pigment epithelium [17]. The severity of arterial sclerosis was graded by adopting Scheie's classification system [18] to assess each subject's ischemic status of the retina indirectly.

Definition of papillomacular bundle defect

Two independent glaucoma specialists (S.U.B. and H.J.C.) evaluated the presence and progression of PMBD on photographs. All of the fundus photography images were exported to ImageJ software (ImageJ version 1.50i; National Institutes of Health, Bethesda, MD, USA; available at https://imagej.nih.gov/ij/index.html) for analysis and rescaled to a unified scale for measurement of degree of PMBD as defined by its angular width and pattern of involvement.

The specific criteria for PMBD, as based on the previous literature [19–21], were as follows. The temporal region of the disc was divided evenly into six sectors of 30° and the PMB area was defined in this study as the angular location within −30.0~+30.0° (sector "c" or "d") of the reference line connecting the optic nerve disc and the macula (Fig. 1). Then, the location of the retinal nerve fiber layer defect (RNFLD) was described by sectors. A RNFLD was considered to be PMBD when the proximal border of the nearest defect was located in the PMB area (sector "c" or "d") [11, 19]. Additionally, the focality of the defects was assessed according to the detectability of their boundary.

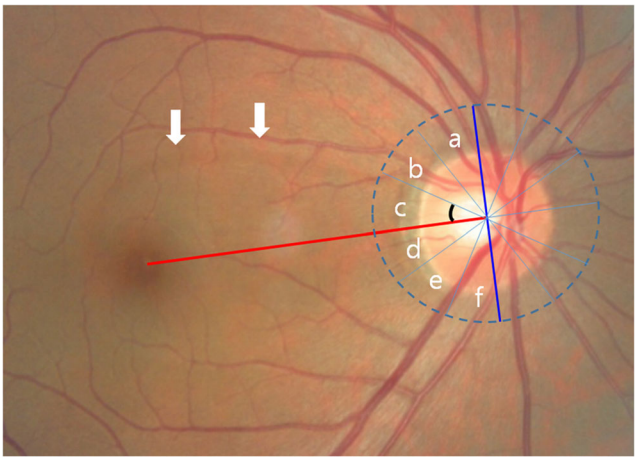

Fig. 1 Definition of papillomacular bundle defect (PMBD). The red line is a straight line from the center of the optic disc to the foveal center and is termed the "reference line." Draw a line (solid blue line) that runs perpendicular to the reference line and passes through the center of the optic disc. The dotted blue line is a 3.46-mm-diameter circle centered on the optic nerve head and including the reference line and vertical line. As a result, the hemisphere can be divided into six equal sectors (a~f sections). Among the six sectors, the central upper and lower sectors surrounding the reference line (c + d section) from −30 to +30° were defined as the PMB area. A retinal nerve fiber layer defect was considered to be PMBD (2 white arrows) when the proximal border of the nearest defect was located within "sector c or d"

Concomitant other RNFLDs found outside the PMB area were also checked and analyzed in both eyes. Localized RNFLD was defined as a well-outlined, dark wedge-shaped area in the bright striated pattern of the surrounding healthy RNFL with its tip touching the optic disc border [22].

Grouping according to papillomacular bundle defect

The *PMBD group* included cases where PMBD existed from the first baseline or did not exist initially but newly developed during the follow-up. In all cases, each *PMBD group* included only those observed continuously for at least 5 years after the first detection of PMBD.

For comparative analysis with the *PMBD group*, healthy individuals who had visited the same health screening center were enrolled for a *non-PMBD group*. In detail, the healthy subjects were age (performed to within 1 year of age)- and gender-matched with the *PMBD group* and had had a minimum of 5 years of follow-up. These *non-PMBD group* members were randomly registered using a randomization program without knowledge of any clinical information.

Definition of papillomacular bundle defect progression and grouping

Two observers (S.U.B. and H.J.C.) masked to the clinical information independently classified the pattern of progressive PMBD into one of the following categories [23]: (1) deepening or (2) widening of the pre-existing PMBD defect. First, deepening of the PMBD was defined as the presence of significant change overlapping with the pre-existing defect (Fig. 2a). Second, widening of the PMBD was defined as the presence of significant change to the edge of the pre-existing defect **(**Fig. 2b**).** Progressive PMBDs were confirmed by the same two experienced glaucoma specialists (S.U.B. and H.J.C.), each of whom was masked to the subject's identity and to all other test results. Any disagreements were resolved through discussion, and, if necessary, a third grader (K.H.P.) was consulted.

For the subsequent analysis, the *PMBD group* was subdivided into *progressors* and *non-progressors* according to progression of PMBD**.**

Statistical analysis

The baseline demographics and clinical variables were summarized by means and standard deviations or frequencies and percentages, as appropriate. The clinical characteristics of the *PMBD group* versus *non-PMBD group* and *progressors* versus *non-progressors* were compared using unpaired *t*-tests or Mann-Whitney's *U* tests for continuous values and the chi-square test for categorical variables.

The inter-observer reliability of the presence and progression of PMBD was assessed with fundus photography of 50 randomly selected eyes by 2 observers (S.U.B. and H.J.C.), and was calculated using the kappa statistic (poor agreement, <0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good 0.61–0.80, excellent; 0.81–100) [24]. The agreement for presence of PMBD was 0.89 (95% CI, 0.82–0.93), and that for PMBD progression was 0.77 (95% CI, 0.68–0.87).

Univariate and multivariate logistic regression analyses employing a forward conditional method were performed to determine the prediction of individual factors with presence and progression of PMBD; hazard ratios (HRs) and 95% confidence intervals (CI) were reported. To avoid multi-collinearity, variables correlated significantly with each other were not analyzed simultaneously. Instead, the variable with the highest significance among correlated variables was chosen. If significances were similar between correlated variables, multiple analyses were conducted separately using each variable. Kaplan-Meier survival analysis was used to compare the inter-group cumulative probability of sparing of the PMBD without progression, as stratified by the significant variables derived from multivariate logistic regression. All of the statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL, USA). All of the *P* values were two-sided and were considered significant when <0.05.

Results

From 2010 to 2018, about 67,000 fundus photographs were checked and 587 eyes with PMBD were detected during the health screening examination. Among them, 234 eyes of 234 patients who had been identified as having PMBD for more than 5 years through fundus photography and who met the inclusion and exclusion criteria were finally enrolled in this study (Fig. 3). In particular, 224 age- and gender-matched

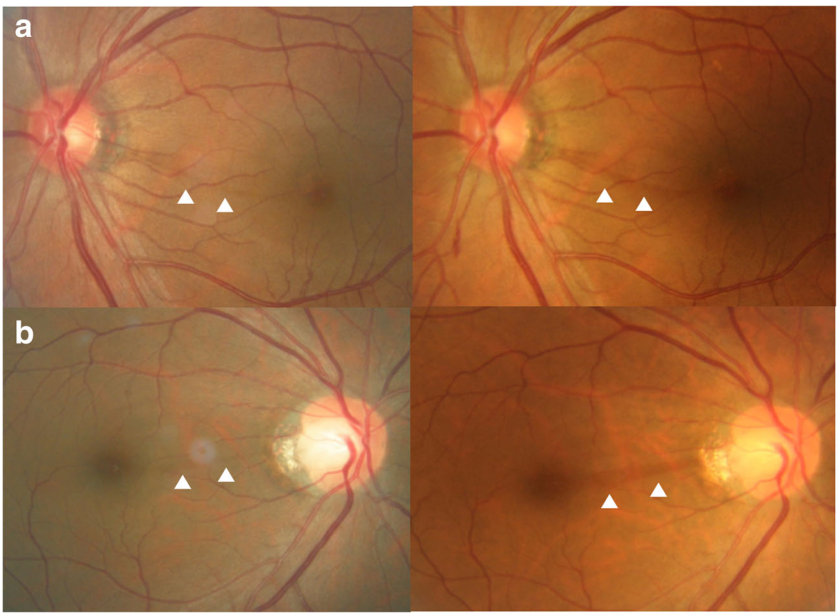

Fig. 2 Determination of progression of papillomacular bundle defect (PMBD). Patients with PMBD were classified into "*progressors*" and "*non-progressors*" based on the following criteria. (A) deepening or (B) widening of PMBD. **a** Deepening of PMBD was defined as the presence of significant change overlapping with a pre-existing defect. **b** Widening of PMBD was defined as a significant change to the edge of a pre-existing defect

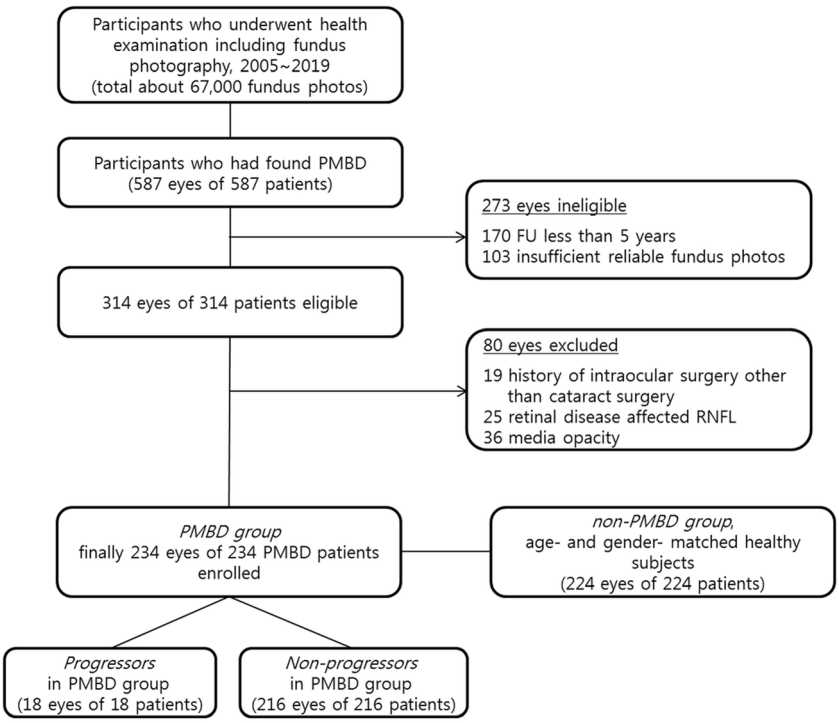

Fig. 3 Flow chart for enrollment and subgroup analysis

subjects who had visited the same health screening center were enrolled in the *non-PMBD group*.

Clinical patterns of papillomacular bundle defect

Initially, PBMDs were observed bilaterally in 11 patients (4.7%). In each eye, a solitary PMBD was observed in 171 eyes (69.4%), whereas 63 eyes (30.6%) showed multiple PMBDs. During the follow-up, 8 eyes (3.4%) showed a new PMBD at different sites. The cotton wool spot (CWS) was identified in 32 eyes (13.7%) at the same site before or at the same time when PMBD occurred. Ipsilateral and contralateral concomitant RNFLDs at non-PMB area were observed in 57 eyes (24.4%) and 27 eyes (11.5%), respectively, and optic disc hemorrhages (DHs) were shown in 14 eyes (5.9%).

Clinical characteristics and risk factors associated with development of papillomacular bundle defect

The demographics and baseline characteristics of the PMBD and non-PMBD groups are summarized in Table 1. The PMBD group showed significantly higher proportions of low BMI (<20 kg/m^2), systemic hypertension, and sclerotic changes of retinal vessels in fundus photographs ($P \leq 0.001$, 0022, and 0.003, respectively) and higher level of aspartate aminotransferase (AST) ($P = 0.041$).

With regard to the risk factors for the presence of PMBD, low BMI (<20 kg/m^2), systemic hypertension, AST, peripapillary atrophy, and sclerotic change on fundus photography were significantly different variables between the two groups by the univariate logistic regression model (Table 2). The subsequent multivariate logistic regression analysis revealed low BMI (HR = 2.602, 95% CI, 1.044–6.488; P = 0.040), systemic hypertension (HR = 1.574, 95% CI, 1.071–2.025; $P = 0.027$), and sclerotic change of retinal vessels (HR = 3.240, 1.600–6.560; $P = 0.001$) as the personalized risk factors for the presence of PMBD.

Clinical characteristics and risk factors associated with progression of papillomacular bundle defect

During the average 8.0 years of follow-up, 18 (7.7%) of 234 eyes showed progression of PMBD (*progressors*), while the majority of PBMDs in 216 eyes (92.3%) remained stationary until the last follow-up (*non-progressors*). In detail, the *progressors* showed widening (14 eyes) and deepening (4 eyes) of PMBD. Figure 4 shows representative cases of *progressors* and *non-progressors*.

The systemic and ophthalmic characteristics of the two groups are listed in Table 3. Among the *progressors*, subjects showed higher proportions of low BMI (<20 kg/m^2) and systemic hypertension as well as higher levels of white blood cell (WBC) counts, alanine aminotransferase (ALT), and triglycerides. Among the ophthalmic parameters, the proportions of co-occurrence of ipsilateral RNFLD at non-PMB area, newly developed PMBD at different sites, and DH on fundus

Table 1 Comparison of clinical characteristics between *papillomacular bundle defect* (*PMBD*) and *non-PMBD* (healthy subjects) *groups*

Total participants	PMBD group $N = 234$	Healthy subjects $N = 224$	*P* value
Age (years)	52.6 ± 8.7	53.3 ± 9.9	0.956*
Gender (male:female)	144:90 (1.60:1)	139:85 (1.63:1)	0.751†
Follow-up duration (years)	8.0 ± 2.7	7.5 ± 2.6	0.105*
Body mass index (kg/m^2)	23.6 ± 3.6	23.9 ± 3.4	0.685*
< 20 kg/m^2 (*n* (%))	52 (22.2)	24 (10.7)	**<0.001**†
> 25 kg/m^2 (*n* (%))	76 (32.5)	76 (33.9)	0.148†
Personal history			
Diabetes mellitus (*n* (%))	27 (11.5)	21 (9.4)	0.724†
Systemic hypertension (*n* (%))	101 (43.2)	72 (32.1)	**0.022**†
Coronary heart disease (*n* (%))	19 (8.1)	18 (8.0)	0.822†
Hyperlipidemia (*n* (%))	81 (34.6)	74 (33.1)	0.650†
Asthma (*n* (%))	5 (2.1)	4 (1.8)	0.752†
Aspirin use (*n* (%))	52 (22.2)	38 (17.0)	0.831†
Anti-coagulant use (*n* (%))	18 (7.7)	9 (4.5)	0.472†
Social history			
Cigarette smoking status (*n*) (non-smokers/ex-smokers/current smokers)	181/18/35	162/19/43	0.498†
Excess alcohol drinking (>140 g/week, *n* (%))	74 (31.6)	58 (25.9)	0.229†
Systolic blood pressure (mmHg)	123.16 ± 17.31	125.55 ± 15.14	0.304*
Diastolic blood pressure (mmHg)	79.31 ± 10.43	79.21 ± 10.44	0.952*
Blood concentration of			
WBC (×10^3/μL)	5.43 ± 2.94	5.76 ± 2.15	0.511*
Hemoglobin (g/dL)	14.24 ± 1.44	14.74 ± 1.41	0.122*
Hematocrit (%)	42.89 ± 4.60	43.31 ± 4.31	0.521*
HbA1c (%)	5.80 ± 0.73	5.56 ± 0.60	0.166*
Hepatic functions			
ALT (mg/dL)	25.20 ± 14.15	27.43 ± 16.84	0.318*
AST (mg/dL)	26.64 ± 11.21	29.66 ± 11.28	**0.041***
Urinary concentration of			
BUN (mg/dL)	16.03 ± 10.66	15.43 ± 3.64	0.482*
Creatinine (mg/dL)	0.97 ± 1.20	0.86 ± 0.20	0.182*
Lipid profile			
Total cholesterol (mg/dL)	185.49 ± 34.81	191.03 ± 33.02	0.213*
Triglycerides (mg/dL)	116.84 ± 68.24	101.20 ± 64.20	0.683*
LDL cholesterol (mg/dL)	115.25 ± 31.31	119.00 ± 32.94	0.417*
HDL cholesterol (mg/dL)	54.74 ± 13.88	55.52 ± 12.98	0.696*
Thyroid functions			
TSH (mg/dL)	2.76 ± 1.32	2.65 ± 1.49	0.432*
Intraocular pressure (mmHg)	14.71 ± 3.75	14.24 ± 2.82	0.290*
Optic nerve head parameters			
Vertical cup/disc ratio	0.40 ± 0.16	0.36 ± 0.13	0.079*
Horizontal cup/disc ratio	0.39 ± 0.15	0.35 ± 0.15	0.166*
Disc ovality (long axis/short axis)	1.15 ± 0.13	1.10 ± 0.11	0.168*
Peripapillary atrophy (present, *n* (%))	76 (32.5)	60 (26.8)	0.060*
Ischemic change on fundus photography			
Sclerotic change (Scheie classification, grades I–IV)	Gr 0 (144), Gr I (71), Gr II (19)	Gr 0 (188), Gr I (36), Gr II (0)	**0.003**†

*Mann-Whitney *U* tests. † Chi-square test. Bolded values represent significance, $P < 0.05$

PMBD, papillomacular bundle defect; *RNFL*, retinal nerve fiber layer defect; *WBC*, white blood cell; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *TSH*, thyroid-stimulating hormone; *Gr*, grade

photography were more frequent ($P = 0.034$, 0.039, and <0.001, respectively), and mean IOP and vertical cup to disc ratio (VCDR) on fundus photography were significantly higher ($P = 0.032$ in both) in the *progressors*.

Regarding the risk factors for the progression of PMBD, the multivariate analysis indicated that PMBD progression was significantly associated with low BMI (HR = 3.895, 1.618–8.376; $P = 0.003$), ipsilateral RNFLD at non-PMB area (HR = 2.990, 1.618–8.376; $P = 0.003$), DH (HR = 12.205, 2.879–45.114; $P = 0.001$), and VCDR (HR = 20.526, 1.356–103.359; $P = 0.025$), while the result of the univariate analysis revealed higher mean IOP as significant variable in addition to aforementioned parameters (Table 4). Figure 5 reflects the estimation and comparison of the cumulative probability of PMBD progression according to each variable. Higher proportion of low BMI (<20 kg/m^2), ipsilateral RNFLD at non-

Table 2 Univariate and multivariate logistic regression analyses of systemic and ocular parameters for the presence of papillomacular bundle defect (using healthy subjects as a reference)

	Univariate			Multivariate		
	Hazard ratio	95% Confidence interval	*P* value	Hazard ratio	95% Confidence interval	*P* value
Age (years)	0.968	0.938–1.007	0.794			
Gender (male)	1.053	0.916–2.020	0.866			
Body mass index (kg/m^2)	0.983	0.904–1.069	0.684			
< 20 kg/m^2 (*n*)	0.041	0.005–0.339	**0.005**	2.602	1.044–6.488	**0.040**
> 25 kg/m^2 (*n*)	0.032	0.004–1.047	0.101			
Personal history						
Diabetes mellitus	1.041	0.873–1.242	0.654			
Systemic hypertension	1.631	1.080–2.125	**0.020**	1.574	1.071–2.025	**0.027**
Coronary heart disease	1.011	0.977–1.184	0.411			
Hyperlipidemia	1.201	0.243–5.942	0.822			
Aspirin use	0.919	0.559–2.604	0.633			
Anti-coagulant use	1.718	0.379–7.787	0.483			
Social history						
Current smokers	0.170	0.548–4.376	1.379			
Excess alcohol drinking (>140 g/week)	1.659	0.892–3.085	0.110			
Systolic blood pressure (mmHg)	0.991	0.973–1.010	0.340			
Diastolic blood pressure (mmHg)	1.001	0.973–1.029	0.951			
Blood concentration of						
WBC (×10^3/μL)	0.967	0.885–1.056	0.452			
Hemoglobin (g/dL)	0.763	0.606–1.069	0.082			
Hematocrit (%)	0.981	0.924–1.041	0.528			
HbA1c (%)	1.475	0.859–2.533	0.159			
Hepatic functions						
ALT (mg/dL)	0.991	0.973–1.009	0.321			
AST (mg/dL)	0.979	0.956–1.002	**0.045**	0.965	0.947–1.017	0.075
Urinary concentration of						
BUN (mg/dL)	1.009	0.966–1.054	0.686			
Creatinine (mg/dL)	1.509	0.438–5.204	0.514			
Lipid profile						
Total cholesterol (mg/dL)	0.995	0.987–1.003	0.213			
Triglycerides (mg/dL)	0.998	0.994–1.002	0.380			
LDL cholesterol (mg/dL)	0.996	0.987–1.005	0.415			
HDL cholesterol (mg/dL)	0.996	0.975–1.017	0.694			
Thyroid functions						
TSH (mg/dL)	1.001	0.973–1.029	0.956			
Intraocular pressure (mmHg)	1.368	0.983–1.553	0.102			
Optic nerve head parameters						
Vertical cup/disc ratio	12.636	1.798–88.815	0.091	4.722	0.579–38.498	0.147
Horizontal cup/disc ratio	6.039	0.807–45.176	0.080			
Disc ovality	7.377	0.127–228.736	0.335			
Peripapillary atrophy	1.968	0.964–4.018	0.063	1.896	0.862–4.714	0.112
Ischemic change on fundus photography						
Sclerotic change (Scheie classification, grades I–IV)	3.105	1.544–6.241	**0.001**	3.240	1.600–6.560	**0.001**

Bolded values represent significance, $P< 0.05$

WBC, white blood cell; *ALT*, alanine aminotransferase; AST, aspartate aminotransferase; *BUN*, blood urea nitrogen; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *TSH*, thyroid-stimulating hormone; *Gr*, grade

PMB area, DH, and larger VCDR all showed greater cumulative probability of progression of PMBD (P = 0.003, <0.001, 0036, and 0.041 by log-rank test, respectively).

Discussion

Through long-term longitudinal observation, the present study reported the clinical course of PMBD incidentally detected in a health screening examination. We found that most of PMBDs remained stationary during the mean follow-up period of 8.1 years, whereas some PMBDs can progress. In particular, the risk factors for PMBD development as analyzed by systemic and ophthalmic factors were ischemic components such as low BMI, systemic hypertension, and sclerotic change on retinal vessels. Meanwhile, the risk factors for PMBD progression were glaucomatous components such as co-occurrence of RNFLD at non-PMB area, DH, and large

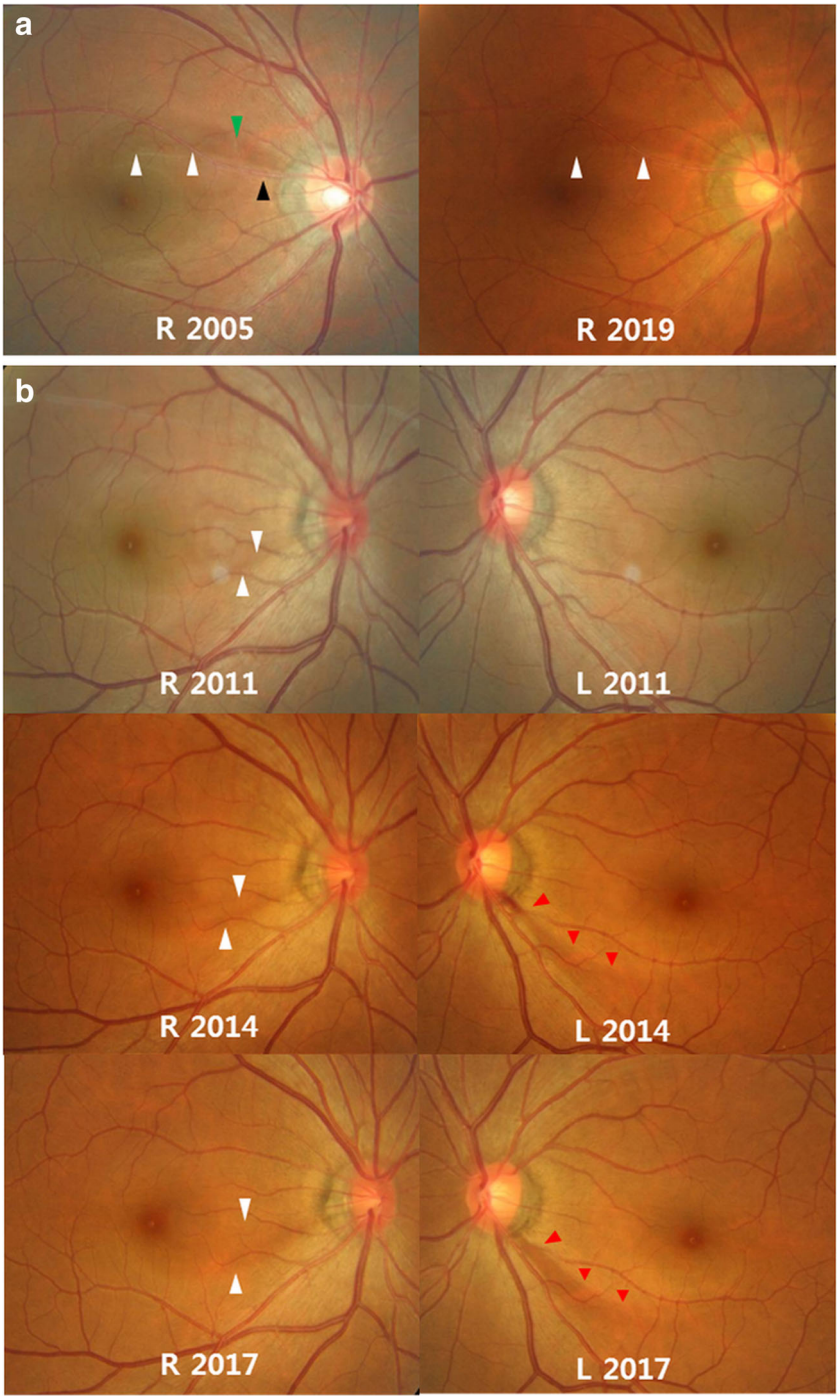

Fig. 4 Representative **a** *non-progressor* and **b** *progressor* cases in papillomacular bundle defect (PMBD) group. **a** A 49-year-old man with systemic hypertension and hyperlipidemia demonstrated cooper wire-like sclerosis on the retinal vessels in fundus photography (black arrow). A PMBD (white arrow) began to be observed with cotton wool spot (green arrow) in the right eye since 2005 and remained stationary for 14 years until 2019. **b** A 40-year-old female patient with no underlying disease initially had a suspicion of PMBD on her right eye (white arrow) in 2011, which continued to increase in size until 2017. During the follow-up, retinal nerve fiber layer defect developed with optic disc hemorrhage on the left eye (red arrow)

VCDR. To the best of our knowledge, the current study is the first to analyze natural course of incidental PMBD and suggest its clinical significance as a predictive, preventive, and personalized indicator based on large volumes of health examination data.

Since the PMB has been known to be an important structure for determining central vision and retinal sensitivity, PMBD can significantly affect a patient's quality of life [25, 26]. Therefore, the role of PMBD in alleged ocular diseases has been researchers' major concern so far. Glaucoma patients with PMBD have been shown to suffer central scotoma even at the early stage of the disease [27, 28], although the PMB area is usually impaired at the end stage of glaucoma [12]. Furthermore, ischemic injury to the PMB has been reported to be a predictive marker for poor vision in eyes with branch retinal artery occlusion [29] or non-arteritic anterior ischemic optic neuropathy [30]. However, there have been no reports on clinical significance of incidentally detected solitary PMBD.

Table 3 Comparison of clinical characteristics between *progressor* and *non-progressors* in papillomacular bundle defect

Variables	*Progressors* (*N* =18)	*Non-progressors* (*N* =216)	*P* value
Age (years)	50.5 ± 10.4	52.7 ± 8.5	0.289
Gender (male:female)	13:5	127:79	0.122†
Body mass index (kg/m^2)	22.40 ± 3.20	23.74 ± 3.58	0.110†
< 20 kg/m^2 (*n* (%))	9 (50.0)	43 (22.2)	**0.003**†
> 25 kg/m^2 (*n* (%))	5 (27.7)	71 (32.5)	0.659†
Personal history			
Diabetes mellitus (*n* (%))	2 (11.1)	25 (11.6)	0.887†
Systemic hypertension (*n* (%))	7 (38.9)	82 (37.9)	0.644†
Coronary heart disease (*n* (%))	1 (5.5)	32 (14.8)	0.120†
Hyperlipidemia (*n* (%))	5 (27.7)	76 (35.2)	0.204†
Asthma (*n* (%))	0 (0)	5 (2.3)	0.514†
Aspirin use (*n* (%))	1 (5.5)	41 (18.9)	0.267†
Anti-coagulant use (*n* (%))	1 (5.5)	14 (6.5)	0.896†
Social history			
Cigarette smoking status (non-smokers/ex-smokers/current smokers)	15/1/2	166/17/33	0.531†
Excess alcohol drinking (>140 g/week, *n* (%))	6 (33.3%)	68 (31.5%)	0.835†
Follow-up duration (months)	7.6 ± 2.9	8.1 ± 2.7	0.471*
Number of fundus photographs	7.4 ± 3.2	6.6 ± 3.0	0.270*
Patterns of PMBD			
Multiple PMBD (*n* (%))	6 (33.3)	57 (26.4)	0.939†
Newly developed PMBD at different sites during the follow-up (*n* (%))	6 (33.3)	31 (14.3)	**0.034**†
Associated with cotton wool spot (*n* (%))	3 (16.6)	29 (13.4)	0.702†
PMBD + RNFLD at non-PMB area (ipsilateral eye, *n* (%))	8 (44.4)	49 (22.7)	**0.039**†
PMBD + RNFLD at non-PMB area (contralateral eye, *n* (%))	2 (11.1)	25 (11.6)	0.953†
Associated with disc hemorrhage	4 (22.2)	9 (4.2)	**<0.001**†
Systolic blood pressure (mmHg)	124.06 ± 17.42	123.08 ± 17.33	0.820*
Diastolic blood pressure (mmHg)	78.22 ± 9.74	79.40 ± 10.51	0.646*
Blood concentration of			
WBC (×10^3/μL)	7.24 ± 9.75	5.28 ± 1.25	**0.006***
Hemoglobin (g/dL)	14.07 ± 1.15	14.25 ± 1.47	0.531*
Hematocrit (%)	42.26 ± 2.78	42.93 ± 4.71	0.359*
HbA1c (%)	5.72 ± 0.47	5.81 ± 0.74	0.477*
Hepatic functions			
ALT (mg/dL)	20.83 ± 8.90	25.61 ± 14.42	**0.050***
AST (mg/dL)	26.06 ± 10.06	26.68 ± 11.32	0.804*
Urinary concentration of			
BUN (mg/dL)	14.11 ± 3.25	16.19 ± 11.05	0.058*
Creatinine (mg/dL)	0.80 ± 0.12	0.98 ± 1.24	0.061*
Lipid profile			
Total cholesterol (mg/dL)	183.78 ± 36.46	185.63 ± 34.75	0.837*
Triglycerides (mg/dL)	93.61 ± 35.93	118.79 ± 69.99	**0.015***
LDL cholesterol (mg/dL)	114.50 ± 34.86	115.30 ± 31.11	0.921*
HDL cholesterol (mg/dL)	60.94 ± 13.54	54.21 ± 13.80	0.057*
Thyroid functions			
TSH (mg/dL)	1.99 ± 1.85	2.76 ± 13.25	0.422*
Intraocular pressure (mmHg)	16.00 ± 3.40	14.51 ± 2.34	**0.032***
Optic nerve head parameters			
Vertical cup/disc ratio	0.48 ± 0.20	0.39 ± 0.16	**0.032***
Horizontal cup/disc ratio	0.44 ± 0.19	0.38 ± 0.14	0.087*
Disc ovality (long axis/short axis)	1.19 ± 0.22	1.14 ± 0.10	0.149*
Peripapillary atrophy (present)	8 (44.4)	68 (31.5)	0.261*
Ischemic change on fundus photography			
Sclerotic change (Scheie classification, grades I–IV)	Gr 0 (12), Gr I (5), Gr II (1)	Gr 0 (132), Gr I (66), Gr II (18)	0.598†

*Mann-Whitney *U* tests. † Chi-square test. Bolded values represent significance, $P< 0.05$

PMBD, papillomacular bundle defect; *RNFLD*, retinal nerve fiber layer defect; *WBC*, white blood cell; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *TSH*, thyroid-stimulating hormone; *Gr*, grade

In this study, the comparative analysis with the *non-PMBD group* revealed that the risk factors for the development of PMBD were low BMI, systemic hypertension, and sclerotic change on retinal arteries. Interestingly, these factors already have been identified as the personalized profile associated with ophthalmic ischemic conditions [31, 32]. A poor vascular

Table 4 Univariate and multivariate logistic regression analyses for the progression of papillomacular bundle defect (using *non-progressors* as a reference)

	Univariate			Multivariate		
	Hazard ratio	95% Confidence interval	*P* value	Hazard ratio	95% Confidence interval	*P* value
Age (years)	0.735	0.907–1.027	0.391			
Gender (male)	0.125	0.178–1.241	0.091			
Body mass index (kg/m^2)	0.913	0.811–1.028	0.133			
< 20 kg/m^2 (*n*)	4.023	1.506–10.746	**0.005**	3.895	1.618–8.376	**0.003**
> 25 kg/m^2 (*n*)	0.785	0.269–2.289	0.658			
Personal history	0.598	0.386–0.927	0.322			
Diabetes mellitus	1.080	0.744–1.112	0.564			
Systemic hypertension	1.015	0.815–1.095	0.335			
Coronary heart disease	0.748	0.454–1.004	0.156			
Hyperlipidemia	0.902	0.689–1.012	0.228			
Asthma	0.637	0.512–1.328	0.492			
Aspirin use	0.919	0.261–3.241	0.895			
Anti-coagulant use	0.274	0.143–1.094	0.601			
Social history						
Current smokers	0.090	0.304–1.895	0.451			
Excess alcohol drinking (>140 g/week)	0.849	0.337–2.139	0.728			
Follow-up duration (months)	0.994	0.980–1.010	0.470			
Duration of stationary PMBD (years)	1.100	0.914–1.323	0.315			
Number of fundus photographs	1.093	0.933–1.279	0.271			
Patterns of PMBD						
Multiple PMBD	0.962	0.360–2.575	0.939			
Newly developed PMBD at different sites during the follow-up	2.984	1.043–8.537	0.062			
Associated with cotton wool spot	1.290	0.352–4.731	0.701			
PMBD + RNFLD at non-PMB area (ipsilateral eye)	2.727	1.021–7.284	**0.045**	2.990	1.041–8.609	**0.042**
PMBD + RNFLD at non-PMB area (contralateral eye)	0.955	0.207–4.401	0.953			
Associated with disc hemorrhage	12.057	2.909–49.967	**0.001**	12.205	2.879–45.114	**0.001**
Systolic blood pressure (mmHg)	1.003	0.975–1.033	0.818			
Diastolic blood pressure (mmHg)	0.990	0.947–1.034	0.644			
Blood concentration of						
WBC (×10^3/μL)	1.104	0.980–1.243	0.102			
Hemoglobin (g/dL)	0.922	0.678–1.253	0.604			
Hematocrit (%)	0.958	0.837–1.096	0.530			
HbA1c (%)	0.812	0.359–1.839	0.618			
Hepatic functions						
ALT (mg/dL)	0.964	0.915–1.015	0.161			
AST (mg/dL)	0.995	0.951–1.041	0.819			
Urinary concentration of						
BUN (mg/dL)	0.918	0.807–1.044	0.194			
Creatinine (mg/dL)	0.164	0.010–2.578	0.198			
Lipid profile						
Total cholesterol (mg/dL)	0.998	0.985–1.012	0.828			
Triglycerides (mg/dL)	0.992	0.981–1.002	0.132			
LDL cholesterol (mg/dL)	0.999	0.983–1.016	0.921			
HDL cholesterol (mg/dL)	1.032	1.000–1.064	0.052			
Thyroid functions						

Table 4 (continued)

	Univariate			Multivariate		
	Hazard ratio	95% Confidence interval	*P* value	Hazard ratio	95% Confidence interval	*P* value
TSH (mg/dL)	0.989	0.900–1.088	0.826			
Intraocular pressure (mmHg)	1.176	1.015–1.388	**0.045**	1.014	0.998–1.308	0.072
Optic nerve head parameters						
Vertical cup/disc ratio	22.260	1.226–404.199	**0.036**	20.526	1.356–103.359	**0.025**
Horizontal cup/disc ratio	15.724	0.650–380.180	0.090			
Disc ovality	7.966	0.459–138.283	0.154			
Peripapillary atrophy	1.741	0.658–4.607	0.264			
Ischemic change on fundus photos						
Sclerotic change (Scheie classification, grades I–IV)	0.806	0.361–1.796	0.597			

Bolded values represent significance, $P< 0.05$

PMBD, papillomacular bundle defect; *RNFL*, retinal nerve fiber layer defect; *WBC*, white blood cell; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *TSH*, thyroid-stimulating hormone; *Gr*, grade

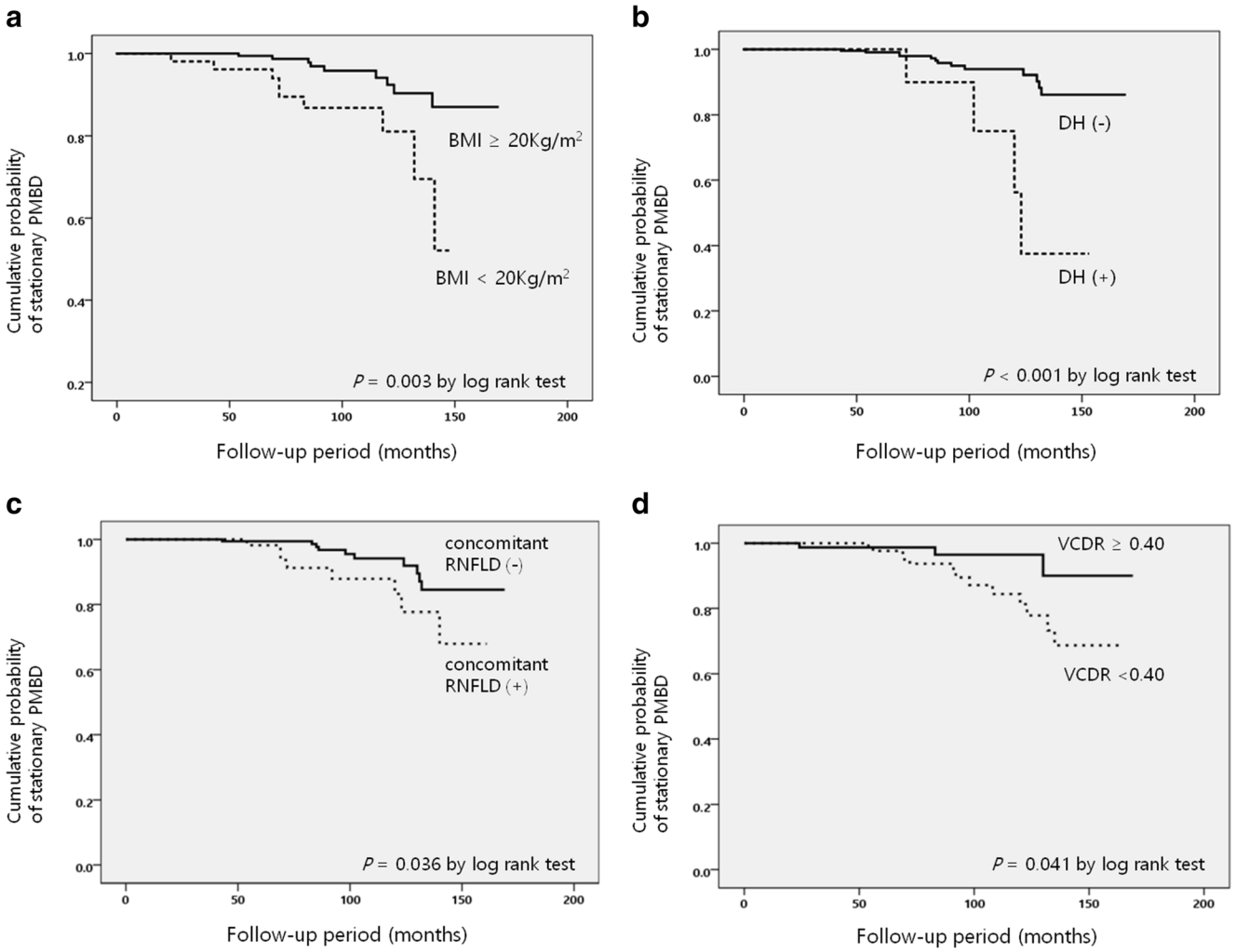

Fig. 5 Kaplan-Meier survival analysis of stationary papillomacular bundle defect (PMBD). The subgroups were stratified as **a** body mass index (BMI) < 20 or ≥ 20 kg/m^2, **b** presence or absence of optic disc hemorrhage, **c** concomitant retinal nerve fiber layer defect on ipsilateral eye, and **d** vertical cup to disc ratio ≥ 0.40 or < 0.40

supply in the temporal region of the optic disc can contribute to the development of PMBD [20]. Chihara et al. classified PMBD as the focal type of RNFLD, which resembles the presumed ischemic defects observed along with CWS [11]. CWS is the result of acute non-perfusion to the retina causing blockage of axoplasmic transport [33]. In this study, we also observed CWS in 13.7% of eyes with PMBD before or at the same time of the development of PMBD. These suggest that PMBD might be one of presentations of ocular ischemic events, and thus, a predictor for ocular ischemic diseases. Expanding the related meaning, it is well known that there is a link between eye and cardiovascular diseases [34]. Atherosclerosis in the retinal artery has been well documented to be related with atherosclerosis in the coronary and carotid arteries [35]. Therefore, incidentally detected PMBD also might be associated with systemic atherosclerosis, which causes systemic ischemic diseases such as coronary artery disease and stroke.

The present analysis of the predictive factors of PMBD progression showed clinical differences with those of PMBD development. With regard to PMBD progression, concomitant RNFLD at non-PMB area, DH, and increased optic disc cupping were associated with increased risk of progression. Indeed, DH is an important individual predisposition for the development and progression of glaucoma [36–38]. Glaucomatous optic disc, defined as increased VCDR and running counter to the ISNT rule, has been significantly associated with glaucoma progression [39]. Considering that the essential pathologic process of glaucoma is the loss of retinal ganglion cells and their axons, progressive PMBD is likely to be a positional variant that occurs in the PMB area instead of the superotemporal or inferotemporal sectors. In other words, progressive PMBD might be an important clinical clue for early diagnosis of glaucoma and reasonable evidence to start preventive medicine. Therefore, when PMBD is accidentally observed in screening fundus photography, meticulous evaluation of concomitant RNFLD at non-PMB area and optic disc morphology should be done and close follow-up examination is needed, because such risks may lead to a high probability of developing central scotoma through PMBD progression.

Especially in the present study, low BMI, a core component of the Flammer syndrome (FS) [40], was found to be the predictive factor involved in both PMBD development and progression. Low BMI is associated with the paracentral visual field loss POAG subtype [41] and this relationship could result from impaired endothelium-dependent vasodilation [42]. Additionally, low BMI is known to be an element of primary vascular dysregulation, which is associated with ischemic damage in glaucoma [31, 32]. Dysfunctional vascular autoregulation of the eye produces impaired ocular blood flow, and this phenomenon may cause RNFLD-associated diseases such as glaucoma, retinal CWS, and ischemic optic neuropathy in the PMB area [43, 44]. Therefore, progression of PMBD as observed in this study can be explained by the interaction between ischemic damage (microinfarction) and the glaucomatous susceptibility of the optic nerve head itself. Meanwhile, the microinfarctions in different organs have known to be typical for subjects with the FS [43]. This explains two extremes; cardiovascular disease and the FS can lead to similar disease patterns [45]. The choroidal infarcts and occlusion of the cilioretinal vessels are common in such people with low BMI [46]. In addition, depending on the location, such microinfarction can probably induce autoimmunity such as multiple sclerosis [47]. Further follow-up studies on the link between PMBD and other elements of FS such as migraine, cold extremities, personality, and stress [40, 43, 48] are thought to be meaningful.

Health screening facilitates early detection of diseases and allows for early access to proper treatment, which in turn leads to reduced incidence and overall morbidity. A paradigm shift from post-diagnosis disease care to early management of comorbidities and targeted prevention is warranted to deliver a cost-effective medical services and desirable healthcare economy [49]. In that sense, the current study also would be valuable as it showed clinical significance of incidental PMBDs in the aspect of a predictive, preventive, and personalized medicine (PPPM). Although most of these PMBDs do not progress, the presence of PMBD itself suggests ischemic changes that require ocular and systemic assessment. Such a diagnostic clue may be especially useful for identifying individual health profiles in subjects who have not been diagnosed with specific diseases such as diabetes mellitus, hypertension, ischemic heart disease, or stroke. Meanwhile, some PMBDs have additional meaning especially when they progress as time goes on. In these rare cases, each PMBD would be considered an atypical presentation of RNFLDs observed in glaucoma and might be one of predictive markers for early diagnosis and severity assessment of glaucoma like red blood cell distribution width and axial length [50, 51]. Therefore, anti-glaucoma medication might be started based on the individual benefit-risk assessment to prevent further glaucomatous damage.

Some points need to be considered when interpreting the results of the current study. First, this study was not population-based but healthcare center-based, and we recruited only patients who had been followed up for more than 5 years. These imply that there is a possibility that subjects who are willing to take care of their own health mostly participated in this study, which might have resulted in selection bias. Second, optical coherence tomography (OCT) and VF tests could not be used to evaluate structural and functional damages associated with PMBD. OCT and visual field tests might have provided more information in case it was difficult to decide whether PMBD had progressed or not. Third, we used a non-contact tonometer instead of the Goldmann applanation tonometer. Although a previous study reported that there was no statistically significant difference between two tonometers within the normal IOP range [52], the variation of IOP values

obtained with the non-contact tonometer is usually greater than that with the Goldmann applanation tonometer. Actually, IOP showed marginal significance (multivariate analysis $P = 0.072$) as a risk factor for PMBD progression in the current study. Further analysis using the Goldmann applanation tonometer may suggest more confident relationship between IOP and PMBD progression. Finally, we cannot predict individual diseases based on the presence or progression of PMBD. Further study will be needed to clarify the role of incidentally detected PMBD as an independent predictor for ocular or systemic ischemic diseases.

Conclusions and expert recommendations

We found that the presence of PMBD through fundus photography in a health screening examination was associated with ocular and systemic ischemic components. Thus, careful assessment of fundus photography and confirmation of PMBD might be a noninvasive and useful tool to identify the individual's cardiovascular profile which can be easily incorporated in health screening examinations. The present study also showed that most incidentally detected PMBDs do not progress. Therefore, personalized observation with regular screening fundus photography and preventive check-up of ocular and systemic diseases would be sufficient for the majority of the patients. Meanwhile, some PMBDs can progress especially when they are accompanied by RNFLD at non-PMB area and glaucomatous optic disc, which means they might be atypical presentations of glaucomatous damages. Therefore, monitoring of detected PMBD could be a personalized-preventive strategy for glaucomatous damage. In those cases, clinicians would be in a better position to consider detailed work-up for early diagnosis of glaucoma and establish a customized treatment plan to prevent further glaucomatous damage. In summary, the PMBD would be a useful biomarker in the context of PPPM.

Abbreviations *ALT*, Alanine aminotransferase; *AST*, Aspartate aminotransferase; *BMI*, Body mass index; *CI*, Confidence intervals; *CWS*, Cotton wool spot; *DH*, Optic disc hemorrhage; *FS*, Flammer syndrome; *HR*, Hazard ratios; *IOP*, Intraocular pressure; *PMB*, Papillomacular bundle; *PMBD*, Papillomacular bundle defect; *PPPM*, Predictive, preventive, and personalized medicine; *RNFL*, Retinal nerve fiber layer; *RNFLD*, Retinal nerve fiber layer defect; *VCDR*, Vertical cup to disc ratio; *WBC*, White blood cell

Funding This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2019R1F1A1058426).

Declarations

Ethical approval The project was approved by Institutional Review Board of Seoul National University Hospital (No. 1906-141-1043)

Statement of informed consent The requirement to obtain written informed consent was waived by the Institutional Review Board, because our study was retrospective research based on medical records, and also because this research presented no more than minimal risk of harm to subjects

Statement of human and animal rights The study was carried out according to the Declaration of Helsinki

Conflict of interest The authors declare no competing interests.

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