

# Exfoliation Syndrome in a Large Vietnamese American Clinic Population: Clinical Characteristics Including Prevalence of Glaucoma and Narrow Angles

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**Purpose:** To determine the proportion with pseudoexfoliation, or exfoliation syndrome (EXF), among a clinic population of Vietnamese patients, and to assess their clinical and demographic characteristics.

**Patients and Methods:** We conducted a retrospective survey of all adult Vietnamese-identifying patients examined between August 2019 and December 2021 in a single glaucoma-trained physician clinic in San, Jose, CA, home to a large Vietnamese population. All patients received at least one dilated eye examination by a glaucoma-fellowship trained specialist to detect exfoliation. Patients with a billing diagnosis of EXF were further selected for detailed review of their electronic health records.

**Results:** Among the 4860 Vietnamese patients reviewed within the study period, 89 (1.8%) were found to have EXF. The average age of the EXF patients was 81±8 (range 66–99) years. There was equal gender distribution (44 female, 45 male). Among the 119 eyes with exfoliation, 66 (55.46%) had narrow angles, 71 (59.66%) had glaucoma and 54 (45.38%) had undergone cataract surgery.

**Conclusion:** This study is the first to investigate the prevalence and clinical characteristics of EXF in a Vietnamese American clinic population. In this cohort of Vietnamese patients from a single ophthalmic clinic, 1.8% were found to have exfoliation syndrome. Among the EXF cases, there were substantial numbers with narrow angles, glaucoma, and history of cataract surgery.

**Keywords:** exfoliation syndrome, glaucoma, Vietnamese patients, narrow angles, intraocular pressure

## Introduction

In exfoliation syndrome (EXF), extracellular fibrillar material is deposited throughout the body. Although EXF can be viewed as a systemic condition, its primary clinical effects are on ocular structures. In the eye, EXF material accumulates and deposits onto structures of the anterior segment, which can lead to structural instability of the lens and the development of secondary ocular pathologies.<sup>1</sup> EXF impacts up to 70 million people worldwide and is the most common identifiable cause of secondary open-angle glaucoma, a condition characterized by elevated intraocular pressure (IOP) leading to optic nerve damage and irreversible vision loss.<sup>2,3</sup> EXF is also associated with an increased risk for closed-angle glaucoma, premature cataracts, and retinal vein occlusions. The increased risk for angle closure appears to be related in part to zonular damage and subsequent anterior movement of the lens-iris diaphragm.<sup>4</sup>

Since its discovery in 1917, numerous studies have improved our understanding of EXF, including its genetics, epidemiology, and pathophysiology. EXF has shown significant age-related causality and a strong link to the LOXLI

gene, which encodes an enzyme involved in the metabolism of elastin, fibrillin, and other extracellular proteins that play a role in EXF pathophysiology.<sup>5</sup> Studies of clinical and demographic correlations with EXF have revealed helpful risk factors, however our current understanding of the risk profile remains incomplete. For instance, it is widely accepted in the literature that EXF has a strong positive correlation with age.<sup>6</sup> However, previous data on gender predilection is variable.<sup>7</sup> More recent findings have also linked patterns of sunlight exposure to the development of EXF.<sup>8</sup>

Regarding racial and geographic predisposition, it has been shown that individuals from Northern European countries have a higher risk for developing EXF. Several studies conducted in Scandinavian countries, including Finland, Sweden, Iceland, and Norway, report high prevalence ranging from 8.1% to 23% in individuals between 50 and 70 years of age, with one study reporting a prevalence as high as 61% at age 87.<sup>7,9–11</sup> Various other racial and ethnic groups have also been shown to have relatively high prevalence of EXF. In 1971, it was estimated that the prevalence of EXF among Navajo Nation residents was 38%. However, a recent retrospective study and the largest study to date in the Navajo population showed considerably lower prevalence of EXF at only 0.7%.<sup>12</sup> Additional prevalence reports have been seen in the following populations: black South Africans (6–7.7%),<sup>13</sup> southeastern US residents (1.6%),<sup>14</sup> Iranians (0.46%),<sup>15</sup> Estonians (26%),<sup>16</sup> Sri Lankans (1.1%),<sup>17</sup> US Louisianans (1.4%),<sup>18</sup> French (5.5%),<sup>19</sup> Pakistanis (6.45%),<sup>20</sup> south Indians (3.8%),<sup>21</sup> and residents of northwestern Spain (18.9%).<sup>22</sup>

Overall, EXF is thought to be rare in Asian populations, especially when compared against European populations. However, some sources indicate that there may have been a historic underestimation of EXF in Asians.<sup>23</sup> Recent studies show marked elevations in EXF prevalence relative to reports from decades prior. For instance, The Beijing Eye Study found that 5.82% of their study cohort of 4403 subjects had EXF,<sup>24</sup> which is far higher than previous reports in Chinese populations.<sup>25</sup> Careful examination after dilation and appropriate vigilance are necessary to detect EXF. Because of this, large variations over time could indicate that EXF has been undetected, rather than rare, in Asian populations.

No prior studies have investigated the clinical characteristics of EXF in the Vietnamese population. According to the 2023 United States Census Bureau, there are an estimated 2.3 million people identifying as Vietnamese in the country, making Vietnamese Americans the fourth-largest Asian American population in the United States. Approximately 40% of Vietnamese Americans live in California, primarily residing in Los Angeles and San Jose.<sup>26</sup>

We have assessed data from a single physician clinic in San Jose, California, that serves a large Vietnamese patient population. The physician is a fellowship-trained glaucoma specialist who specifically examines all her patients for any glaucoma risk factors including the presence of EXF material. This study aims to determine the proportion of patients with EXF within this clinic population.

## Materials and Methods

A retrospective survey was conducted of all adult Vietnamese-identifying patients examined between August 1, 2019 and December 31, 2021 at the clinic of a single fellowship-trained glaucoma specialist (NN) located in San Jose, California, which is home to one of the largest Vietnamese populations in the world outside of Vietnam. Most of the patients presented to the clinic independently, while the rest were referred by general practitioners. This study was reviewed and determined to be exempt (Exemption Number: Pro00087212), in accordance with the Department of Health and Human Services regulations found at 45 CFR 46.104(d)(4), by a national Institutional Review Board (Advarra CIRBI, Advarra Inc, Columbia, MD). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Patients were included for detailed chart review if they had a diagnosis of EXF documented in their billing record. Patients were excluded if they were unable to comply with routine testing, including IOP measurements, optic nerve scans, and visual field testing, to ensure adequate documentation of key clinical parameters for analysis. Detailed chart review involved verifying that the documented clinical diagnosis matched the billing diagnosis. The data collected from electronic health records, eClinicalWorks (eClinical, Westborough, MA), included age (at last visit), gender, ethnicity (by self-description on initial visit questionnaire), laterality, glaucoma diagnosis, maximum IOP by Goldman applanation tonometry, gonioscopic examination (at initial visit), mean deviation of visual field (VF) using the Humphrey Field Analyzer 3 (HFA3; Carl Zeiss Meditec, Inc., Dublin, CA), axial length by optical biometry (IOLMaster 500; Carl Zeiss Meditec, Inc., Dublin, CA), cup-to-disc ratio (CDR; assessed by indirect slit lamp biomicroscopy with a 78-diopter handheld lens), central corneal thickness (CCT) and average retinal nerve fiber layer (RNFL) thickness by optical coherence tomography

(OCT; Cirrus HD-OCT 5000; Carl Zeiss Meditec, Dublin, CA), cataract and glaucoma surgery history, and number of glaucoma medications used. Gonioscopic data were collected from the first-visit encounter note, whereas all other data were collected from the last visit.

## EXF Diagnosis Criteria

In this study, “EXF” refers to exfoliation syndrome, defined by the presence of exfoliative material on the lens capsule and/or at the pupillary margin in at least one eye. “Exfoliation” refers to the presence of exfoliative material at the individual eye level. Defining evidence also included a “target” pattern of EXF material deposition on the anterior lens surface, with material deposited centrally and in the far periphery, sparing the mid-periphery. Loss of pupillary ruff and peri-pupillary iris transillumination defects were also used in the clinical assessment. Gonioscopy was performed for all patients before pupil dilation to assess angle width and trabecular meshwork pigmentation. All patients had at least one dilated examination. In pseudophakic subjects, EXF diagnosis was based primarily on the presence of exfoliative material at the pupillary margin. Iris and angle findings were also used as evidence in establishing EXF. Diagnostic criteria are aligned with prior population-based studies on EXF prevalence.<sup>10,12</sup>

## Assessment of Narrow Angles

Compression gonioscopy was conducted prior to pupil dilation for angle evaluation using a Zeiss four-mirror gonioscopy lens (Carl Zeiss, Oberkochen, Germany). The Shaffer classification system was implemented in all four quadrants (superior, inferior, nasal, and temporal), while noting presence of peripheral anterior synechiae (PAS), angle pigmentation or angle irregularities if applicable. Patients with an average Shaffer grade of 2 or lower have a higher risk of angle closure and are classified as narrow angles in this study, consistent with prior retrospective glaucoma studies from this clinic.<sup>27</sup>

## Glaucoma Diagnosis

The International Society of Geographical & Epidemiological Ophthalmology (ISGEO) classification system was used to define glaucoma, consistent with prior studies on glaucoma prevalence in the Vietnamese population from this clinic.<sup>27,28</sup> Diagnosis of glaucomatous optic neuropathy required the presence of the following: a CDR  $\geq 0.70$  and/or CDR asymmetry of approximately 0.20 or greater between both eyes, and reproducible visual field defects associated with glaucoma for at least two sessions. Patients that fulfilled only one of the criteria above, or had maximum IOP  $> 21$  mmHg without glaucomatous damage were diagnosed as glaucoma suspect. In the case of unsatisfactory VF results, evidence of severe damage to the optic disc and CDR  $\geq 0.90$  was sufficient for glaucoma diagnosis. If the optic disc was unable to be examined, glaucoma was diagnosed if the visual acuity was  $< 3/60$  and IOP  $> 21$  mmHg, or a previous history of glaucoma filtering surgery existed.

## Maximum IOP

Intraocular pressure used for glaucoma diagnosis in this study was the maximum IOP, which refers to the highest recorded IOP in a patient’s history at the clinic.

## Statistical Analysis

Clinical characteristics were assessed for normality using the Shapiro–Wilk test and visual inspection of distribution plots (histograms/Q-Q plots). Continuous variables with a normal distribution were summarized as mean  $\pm$  standard deviation, whereas non-normally distributed variables were summarized as median (interquartile range). Categorical variables were presented as counts (percentages). The required sample size was calculated using an expected prevalence of 0.12%,<sup>29</sup> a 95% confidence interval, and a margin of error of 0.1%, yielding a minimum sample size of approximately 4604 participants. Comparisons between eyes with exfoliation and those without exfoliation were performed using univariable linear regression with patient-clustered standard errors to account for correlation between fellow eyes from the same subject. Mean differences and risk differences between eyes with and without exfoliation were estimated from the regression models. All tests were two-sided, and  $p < 0.05$  was considered statistically significant. Analyses were conducted in Stata16.0 (Stata Corp, College Station, TX, USA).

## Results

### Descriptive Analysis

There were 4860 Vietnamese patients reviewed in the study period. Of these, 89 patients were found to have EXF, yielding an overall prevalence of 1.83% (95% CI 1.47–2.25%). There were 119 eyes with visible exfoliation out of the 177. One patient had a left eye prosthesis. The mean age of patients with EXF was 80.75 (SD 7.94) years. There were equivalent numbers of male and female patients (45 males and 44 females) with EXF. In terms of laterality, 30 patients had bilateral EXF while 59 had unilateral EXF. Glaucoma was diagnosed in 71 (59.66%) eyes with exfoliation and 31 (53.45%) eyes without exfoliation; the difference between groups was not statistically significant ( $p = 0.319$ ). Of the 71 exfoliation eyes with glaucoma, 2 were associated with secondary glaucoma due to a non-exfoliative etiology (steroid-induced glaucoma). In addition, 2 exfoliation eyes had Posner-Schlossman syndrome without glaucomatous disc findings. Exfoliation eyes were associated with higher maximum IOP (mean difference = 2.33 mmHg; 95% CI: 0.21 to 4.46;  $p = 0.032$ ) and larger cup-to-disc ratio (mean difference = 0.11; 95% CI: 0.05 to 0.17;  $p < 0.001$ ) compared to eyes without exfoliation. Exfoliation eyes were also associated with thinner RNFL (mean difference = - 5.25 microns; 95% CI: -9.46 to -1.04;  $p = 0.015$ ) and larger disc area (mean difference = 0.20 mm<sup>2</sup>; 95% CI: 0.08 to 0.32;  $p = 0.001$ ) compared to eyes without exfoliation (Table 1). Exfoliation eyes had a stronger association with history of cataract surgery (risk difference = 0.28; 95% CI: 0.16 to 0.40;  $p < 0.001$ ). Narrow angles were observed in 66 (55.46%) exfoliation eyes and 26 (44.83%) eyes without exfoliation; the difference was not statistically significant (mean difference = 0.13; 95% CI: 0.00 to 0.26;  $p = 0.114$ ; pseudophakia-adjusted  $p = 0.060$ ). Additional descriptive statistics are shown in Table 1.

### Comparison of Unilateral Eyes with Exfoliation and Contralateral Eyes without Exfoliation

Table 2 compares characteristics between eyes with exfoliation and contralateral eyes without exfoliation among patients with unilateral EXF. Of the 59 patients who had unilateral EXF, one patient was excluded from this comparison due to

**Table 1** Descriptive Statistics of Vietnamese Patients with Exfoliation Syndrome

	Total	No Exfoliation Eyes	Exfoliation Eyes	p-value
No. of patients, n	89			
No. of eyes, n	177	58	119	
Age (year) [mean (SD)]	80.75 (7.94)	82.04 (7.88)	80.16 (7.97)	0.378
Female gender [no. of patients (%)]	44 (49.44%)	15 (53.57%)	29 (47.54%)	0.600
Narrow angle [no. of eyes (%)]	92 (51.98%)	26 (44.83%)	66 (55.46%)	0.114 0.060 <sup>a</sup>
Glaucoma [no. of eyes (%)]	102 (57.63%)	31 (53.45%)	71 (59.66%)	0.319
Maximum IOP (mmHg) [mean (SD)]	22.41 (7.78)	20.84 (5.66)	23.17 (8.53)	0.032*
Axial length (mm) [mean (SD)]	23.49 (1.02)	23.57 (1.05)	23.46 (1.01)	0.598
Central corneal thickness (μm) [mean (SD)]	533.82 (38.35)	537.47 (45.85)	532.18 (34.59)	0.360
Cup-to-disc ratio [median (IQR)]	0.60 (0.30, 0.80)	0.40 (0.20, 0.65)	0.60 (0.40, 0.80)	<0.001*
Average RNFL thickness (μm) [mean (SD)]	82.73 (15.70)	86.31 (10.46)	81.06 (17.41)	0.015*
Disc area (mm <sup>2</sup> ) [median (IQR)]	1.99 (1.70, 2.23)	1.84 (1.56, 2.10)	2.00 (1.79, 2.28)	0.001*
Cataract surgery [no. of eyes (%)]	64 (36.16%)	10 (17.24%)	54 (45.38%)	<0.001*

**Note:** \* $p < 0.05$ . <sup>a</sup>Adjusted for pseudophakia.

**Abbreviations:** IOP, intraocular pressure; RNFL, retinal nerve fiber layer.

**Table 2** Characteristics of Eyes with Exfoliation Compared to Contralateral Eyes without Exfoliation in Vietnamese Patients with Unilateral Exfoliation

	Total	No Exfoliation Eyes	Exfoliation Eyes	p-value
No. of eyes, n	116	58	58	
Right eye [n (%)]	58 (50.00%)	28 (48.28%)	30 (51.72%)	0.795
Narrow angle [n (%)]	51 (43.97%)	26 (44.83%)	25 (43.10%)	0.741 0.996 <sup>a</sup>
Glaucoma [n (%)]	64 (55.17%)	31 (53.45%)	33 (56.90%)	0.416
Maximum IOP (mmHg) [mean (SD)]	22.15 (7.27)	20.84 (5.66)	23.44 (8.42)	0.017*
Axial length (mm) [mean (SD)]	23.64 (1.04)	23.57 (1.05)	23.71 (1.05)	0.604
Central corneal thickness (μm) [mean (SD)]	534.63 (42.29)	537.47 (45.85)	531.85 (38.76)	0.200
Cup-to-disc ratio [median (IQR)]	0.40 (0.20, 0.72)	0.40 (0.20, 0.65)	0.40 (0.23, 0.80)	0.027*
Number of glaucoma medications [median (IQR)]	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)	1.00 (0.00, 2.00)	<0.001*
Glaucoma surgery [n (%)]	5 (4.55%)	0 (0.00%)	5 (9.09%)	NA
Cataract surgery [n (%)]	30 (25.86%)	10 (17.24%)	20 (34.48%)	0.003*
Average RNFL thickness (μm) [mean (SD)]	82.95 (14.97)	86.31 (10.46)	79.59 (17.89)	0.007*
Disc area (mm <sup>2</sup> ) [median (IQR)]	1.84 (1.59, 2.11)	1.84 (1.56, 2.10)	1.84 (1.59, 2.19)	0.913
Mean deviation (dB) [median (IQR)]	-4.12 (-7.21, -1.95)	-4.29 (-6.91, -2.20)	-3.70 (-7.25, -1.47)	0.604

**Note:** \*p<0.05. <sup>a</sup>Adjusted for pseudophakia.

**Abbreviations:** IOP, intraocular pressure; RNFL, retinal nerve fiber layer.

having a left eye prosthesis. The prevalence of glaucoma did not differ significantly between exfoliation and non-exfoliation eyes ( $p = 0.416$ ). There was no statistically significant difference in the prevalence of narrow angles between groups (mean difference = 0.00; 95% CI: -0.11 to 0.11;  $p = 0.741$ ; pseudophakia-adjusted  $p = 0.996$ ) Eyes with exfoliation had a stronger association with history of cataract surgery (risk difference = 0.17; 95% CI: 0.06 to 0.28;  $p = 0.003$ ) compared to contralateral eyes without exfoliation. Glaucoma surgery was observed in 5 exfoliation eyes and in none of the non-exfoliation eyes. History of cataract surgery was not associated with either glaucoma or prior glaucoma surgery. The presence of exfoliation was correlated to a higher maximum IOP ( $p = 0.017$ ) and higher number of glaucoma medications used (mean difference = 0.76; 95% CI: 0.39 to 1.13;  $p < 0.001$ ) in the affected eye. Eyes with exfoliation also had a tendency towards thinner RNFL (mean difference = -6.72 microns; 95% CI: -11.50 to -1.95;  $p = 0.007$ ) and larger cup-to-disc ratio (mean difference = 0.04; 95% CI: 0.004 to 0.07;  $p = 0.027$ ).

## Comparison of Glaucomatous Eyes with and without Exfoliation

**Table 3** compares characteristics between glaucomatous eyes with and without exfoliation in our cohort of Vietnamese patients with exfoliation syndrome. Among the 89 Vietnamese patients with exfoliation syndrome, 102 eyes (out of 177) had glaucoma. Eyes with exfoliation and glaucoma were associated with larger cup-to-disc ratio (mean difference = 0.10; 95% CI: 0.02 to 0.19;  $p = 0.017$ ) and history of cataract surgery (risk difference = 0.21; 95% CI: 0.05 to 0.37;  $p = 0.021$ ). Glaucoma surgery had been performed in 7 glaucomatous exfoliation eyes and in none of the glaucomatous eyes without exfoliation. Eyes with exfoliation and glaucoma were on higher number of glaucoma medications when compared to eyes with no exfoliation and glaucoma (mean difference = 1.13; 95% CI: 0.59 to 1.67;  $p < 0.001$ ). The prevalence of narrow angles did not differ significantly between exfoliation and non-exfoliation eyes (mean difference = 0.16; 95% CI: -0.03 to 0.34;  $p = 0.113$ ; pseudophakia-adjusted  $p = 0.097$ ).

**Table 3** Characteristics of Glaucomatous Eyes with and without Exfoliation in Vietnamese Patients with Exfoliation Syndrome

	Total	No Exfoliation Eyes	Exfoliation Eyes	p-value
No. of eyes, n	102	31	71	
Age (year) [mean (SD)]	80.41 (7.68)	80.71 (8.19)	80.28 (7.50)	0.735
Female gender [n (%)]	54 (52.94%)	14 (45.16%)	40 (56.34%)	0.175
Narrow angle [n (%)]	63 (61.76%)	16 (51.61%)	47 (66.20%)	0.113 0.097 <sup>a</sup>
Maximum IOP (mmHg) [mean (SD)]	22.89 (6.81)	22.35 (6.34)	23.13 (7.04)	0.558
Axial length (mm) [mean (SD)]	23.42 (1.13)	23.60 (1.42)	23.36 (1.05)	0.536
Central corneal thickness (μm) [mean (SD)]	532.53 (39.35)	535.55 (49.79)	531.18 (34.05)	0.566
Cup-to-disc ratio [median (IQR)]	0.70 (0.40, 0.80)	0.60 (0.25, 0.80)	0.70 (0.50, 0.85)	0.017*
Number of glaucoma medications [median (IQR)]	1.00 (0.00, 2.00)	0.00 (0.00, 1.00)	2.00 (1.00, 2.50)	<0.001*
Glaucoma surgery [n (%)]	7 (7.14%)	0 (0.00%)	7 (10.29%)	NA
Average RNFL thickness (μm) [mean (SD)]	80.62 (16.54)	82.70 (10.45)	79.77 (18.47)	0.346
Disc area (mm <sup>2</sup> ) [median (IQR)]	2.00 (1.78, 2.26)	1.86 (1.63, 2.12)	2.02 (1.87, 2.26)	0.055
Mean deviation (dB) [median (IQR)]	-4.54 (-8.15, -2.44)	-4.95 (-6.61, -2.43)	-4.44 (-8.19, -2.70)	0.509
Cataract surgery [n (%)]	38 (37.25%)	7 (22.58%)	31 (43.66%)	0.021*

**Note:** \*p<0.05. <sup>a</sup>Adjusted for pseudophakia.

**Abbreviations:** IOP, intraocular pressure; RNFL, retinal nerve fiber layer.

## Discussion

This is the first study investigating the prevalence and clinical characteristics of EXF among a clinic population of Vietnamese Americans. Within our large Vietnamese clinic population, the proportion who exhibited EXF was 1.8% (89 subjects out of 4860). It is well understood that EXF has a propensity towards certain geographic distributions and ethnic groups. Historically, EXF has been thought to be highly prevalent in European populations while rare in Asian populations, particularly East Asians. However, recent reports offer updated estimates on the proportions of EXF in East Asians, ranging from 0.12–5.82%.<sup>24,29–31</sup> Differences in study methodology, definition of exfoliation syndrome, geographic variation, and ethnic heterogeneity among Asians may account for the wide variance of prevalences.

Several factors may impact the documented prevalence of EXF among Asians. One factor could be related to discrepancies in ocular screening priorities in Asian patients. Diagnosis requires dilation of the eyes, and the examiner must be vigilant in the detection of the syndrome. Because there is a standing bias that EXF is not prevalent in Asian populations, there may be the presence of a reverse detection bias. Additionally, the high prevalence of narrow and closed angles among Asians may sway screening priorities away from EXF in those patients. Challenges in the clinical detection of exfoliation may be another contributing factor. The higher melanin pigmentation and thicker stroma within Asian irises may obscure visibility of exfoliative deposits at the pupillary margin on slit-lamp exams.<sup>32</sup> These challenges are further complicated by difficulty dilating patients with EXF, which is thought to be due to degenerative effects of exfoliative deposits on the pupillary sphincter and dilator muscles.<sup>33</sup>

There is a strong genetic component to the pathophysiology of EXF that remains understudied in the Vietnamese population. Numerous studies have discovered associations between LOXL1 polymorphisms and exfoliation syndrome in Europeans and East Asians, including Chinese and Korean populations.<sup>5,34,35</sup> However, no studies to date have examined exfoliation genetics in the Vietnamese population. Future studies involving genetic testing of LOXL1 gene variants within this cohort may also help shed light on discrepancies.

There is a strong link between EXF and glaucoma. Exfoliation glaucoma progresses more rapidly and presents with a more severe clinical manifestation than other forms of glaucoma. This is thought to be related to: (a) deposition of exfoliative material in the trabecular meshwork leading to aqueous outflow tract obstruction, (b) loss of proteins essential for maintaining structural integrity of the lamina cribrosa, making the retinal ganglion cell axons of the optic nerve more vulnerable to pressure-related injury, and (c) weakening of the lens zonules leading to displacement and angle closure.<sup>36</sup> In our study, eyes with glaucoma and exfoliation were more likely to be associated with higher maximum IOP, greater number of glaucoma medications, and history of glaucoma surgery compared to glaucomatous eyes without exfoliation (Table 3).

Interestingly, among patients with unilateral EXF, glaucoma prevalence did not differ significantly between eyes with exfoliation and contralateral eyes without exfoliation (Table 2). Of note, however, the degree of glaucoma in the eyes without exfoliation appeared milder in this comparison. Specifically, eyes without exfoliation were associated with lower maximum IOPs, no history of glaucoma surgery, and fewer prescribed medications compared to eyes with exfoliation (Table 2). It has been previously observed that both eyes in patients with unilateral EXF are at increased risk for glaucoma compared to eyes in individuals without EXF.<sup>37</sup> Puska et al reported that glaucomatous optic disc changes were present in both eyes of unilateral EXF patients, suggesting that exfoliative glaucoma may begin developing even before exfoliative material becomes readily detectable.<sup>38</sup> Given these findings and the added clinical challenges of screening for exfoliation in Asian eyes, we hypothesize that the eyes classified as “without exfoliation” in our cohort may exhibit early glaucomatous changes due to undetected exfoliative material and/or bilateral primary glaucoma mechanisms. These results reinforce the importance of monitoring both eyes in patients with apparently unilateral EXF.

This study has demonstrated that a large proportion of Vietnamese eyes with exfoliation also exhibit narrow angles (55.46%). Previous studies have documented a high prevalence of narrow angles in patients with EXF,<sup>39,40</sup> especially when compared to controls.<sup>41</sup> Angle narrowing and closure in the setting of EXF is considered to be due to zonular weakness and forward displacement of the lens leading to secondary pupillary block angle closure.<sup>4</sup> Identification of angle closure in patients with EXF is clinically important as it requires additional management and can be associated with significant visual morbidity if left untreated.

The difference in narrow angle prevalence between exfoliation and non-exfoliation eyes remained nonsignificant across multiple comparisons, including in a multivariable model adjusting for pseudophakia (Tables 1–3). Because our analysis was patient-clustered and the mean age was older (81 years), age-related anterior segment changes, including increased lens vault, may have been the primary mechanism for angle narrowing in this population, consistent with prior studies from this same clinic.<sup>42</sup> While these factors may influence the relationship between exfoliation and angle narrowing in our cohort, the overall high proportion of narrow angles among adult Vietnamese patients with EXF still stands to highlight the importance of targeted gonioscopic screening of both eyes in this population.

We report that Vietnamese eyes with exfoliation had a very significant association with cataract surgery, with 36.16% of exfoliation eyes having undergone cataract surgery compared to 17.24% of eyes without exfoliation (Table 1). This association remained significant across multiple comparisons (Table 2 and Table 3). Given that the mean age between groups was similar, our finding likely reflects the known causal link between exfoliation and age-related cataract formation, a process that is accelerated by extracellular fibrillin accumulation on the lens.<sup>43</sup> However, it is important to note that more exfoliation eyes had prior glaucoma surgery than non-exfoliation eyes (Table 2), which may confound the relationship between exfoliation and cataract surgery in the event that cataract surgery was performed in combination with surgery for IOP control. The overall high co-prevalence of glaucoma, narrow angles, and cataracts among eyes with exfoliation raises the possibility that the deposition of fibrillin and subsequent zonular instability may contribute to multiple disease processes. However, whether these associations reflect overlapping mechanisms or arise independently remains unclear. Future studies are necessary to provide a better understanding of the link between EXF, cataracts, and other associated ocular complications in Vietnamese.

The main limitation of this study is its retrospective, clinic-based design. Given that our study was conducted in a glaucoma subspecialty clinic, selection bias is inherent, suggesting that the observed prevalence may not reflect the overall population prevalence. Large-scale population-based studies are required to measure the true prevalence of EXF among Vietnamese. Because the geographic distributions of EXF are not fully understood and our study population was comprised solely of Vietnamese patients at a single clinic site, caution should be exercised in generalizing these results to

the entire Vietnamese population. Additionally, missing data from patients may introduce selection bias. Selection of patients by billing record may have led to an underestimation of EXF if patients with EXF were misclassified as open angle glaucoma on their billing record. Challenges in the clinical detection of exfoliation may also introduce misclassification bias and underestimation of prevalence. For instance, in pseudophakic eyes, where the lens capsule cannot be examined, EXF was diagnosed based on the presence of exfoliative deposits along the pupillary margin and iris, which can be more subtle and difficult to detect. However, the single physician who examined all subjects is a board-certified ophthalmologist and fellowship-trained glaucoma specialist who was specifically attuned to evaluating patients for EXF, reducing the risk of missed cases.

## Conclusion

In summary, the proportion of Vietnamese patients with EXF from a single ophthalmic clinic was 1.8%. Among these cases, there was a large number with narrow angles, glaucoma, and a history of cataract surgery. Eyes with and without exfoliation had similar proportions of glaucoma and narrow angles, underscoring the importance of carefully monitoring both eyes of patients with apparently unilateral EXF. Studies incorporating technologies such as anterior segment OCT (AS-OCT) may allow for better characterization of the extent of angle closure and association of various AS-OCT parameters with EXF. Future prospective, population-based studies, incorporating more diverse geographical regions, are necessary to provide better understanding of the epidemiology, risk factors, and true prevalence of EXF in Vietnamese.

## Ethics Statement

This study was reviewed and determined to be exempt (Exemption Number: Pro00087212), in accordance with the Department of Health and Human Services regulations found at 45 CFR 46.104(d)(4), by a national Institutional Review Board (Advarra CIRBI, Advarra Inc, Columbia, MD). This study was conducted in accordance with the tenets of the Declaration of Helsinki.

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## Disclosure

Dr Sunita Radhakrishnan is a consultant for and reports stock options from Netra Systems Inc, outside the submitted work. The authors report no other conflicts of interest related to this work.

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