Review

Imaging in Pachychoroid Disease

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Abstract

The term pachychoroid was proposed as a term indicating an abnormal increase in choroidal thickness. Eyes presenting with pachychoroid changes often exhibit dilation of the large choroidal vessels, compressing the overlying choriocapillaris and Sattler's layer. Pachychoroid spectrum diseases may present pathological findings such as pigment epitheliopathy, choroidal neovascularization (CNV), submacular serous detachment, and distinct choroidal and scleral alterations. Recent advancements in imaging modalities such as widefield indocyanine green angiography (WF-ICGA), optical coherence tomography angiography (OCTA), and enhanced depth imaging optical coherence tomography (OCT) have significantly improved our understanding of these conditions. WF-ICGA revealed venous outflow congestion in the peripheral retina as one of the characteristics of pachychoroid diseases. Scleral thickness measurements using ultrasound biomicroscopy and anterior segment OCT indicate that a thicker anterior sclera may contribute to choroidal congestion and disease pathogenesis. OCTA has emerged as a superior tool for identifying CNV and understanding the disease etiology, offering better sensitivity and specificity compared to traditional methods. These imaging advancements provide valuable insights into the structural and functional changes associated with pachychoroid diseases, potentially guiding future diagnostic and therapeutic strategies. The aim of the present review is to define the morphological characteristics of the pachychoroid spectrum of diseases, which share similar choroidal findings.

Keywords: Pachychoroid disease, indocyanine green angiography, imaging, optic coherence tomography angiography, optic coherence tomography, scleral thickness

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Introduction

Pachychoroid diseases are a group of clinical entities defined by a thickened choroid and sharing common underlying pathological mechanisms. These include central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), and focal choroidal excavation (FCE). Peripapillary pachychoroid syndrome (PPS) and peripheral exudative hemorrhagic chorioretinopathy (PEHCR) are two additional pathologies recently included in the spectrum. These pathologies can overlap somewhat, and even evolve from one entity to another.

Pachychoroid disease can be visualized through enhanced depth imaging optical coherence tomography (EDI-OCT) or swept source (SS)-OCT. It is characterized by a thickened Haller choroidal layer (exceeding 300 µm), thinning of the Sattler and choriocapillaris layers, and dilated and hyperpermeable vessels.[1] These vascular changes can disturb Bruch's membrane and cause retinal pigment epithelium (RPE) alteration, resulting in serous retinal detachment with or without subsequent choroidal neovascularization (CNV).[1] Furthermore, indocyanine green angiography (ICGA) and optical coherence tomography angiography (OCTA) enable detailed visualization of blood flow within the retinal and choroidal vasculature.

Nearly a decade since the term was introduced, a universal agreement on the definition of pachychoroid remains unclear, with some authors consolidating disease entities while others prefer separate analyses.[2] Current diagnostic criteria for pachychoroid include: (1) reduced fundus tessellation, (2) pachyvessels (dilated outer choroidal vessels causing attenuation/thinning of other choroidal layers) observed on OCT and ICGA, (3) absence of soft drusen (total area of >125-µm circle) except for pachydrusen, defined as irregular yellow-white deposits

distributed across the posterior pole, and (4) presence of CSC characteristics including choroidal vascular hyperpermeability, RPE abnormalities independent of macular neovascularization, or a history of CSC.[2]

The pathogenesis of pachychoroid remains unclear, but different theories include steroid metabolism and vortex vein congestion. Mineralocorticoid receptors are expressed in the choroid, and their activation can lead to increased choroidal thickness (CT) and congestion, which may explain why stress is a major risk factor for CSC.[3] Congestion or blockage in the vortex veins has also been theorized to underlie pachychoroid spectrum disorders.[1,4,5] Venous drainage from the choroid mainly occurs through large vortex veins that drain blood from the choroid into the sclera. Congestion in vortex venous blood flow is believed to cause these veins to dilate due to heightened venous pressure, resulting in the retrograde flow of blood into neighboring quadrants through existing anastomoses.[6] Increasing pressure can ultimately damage the choriocapillaris layer, giving rise to these conditions.

Pachychoroid disease is still not fully understood and remains an active area of research. However, with recent technological advancements, our understanding of these conditions continues to improve.

Optical Coherence Tomography

Recent technological advancements such as EDI-OCT and SS-OCT have significantly enhanced our ability to visualize choroidal structures and elucidate the change in CT associated with pachychoroid disease.

Choroidal Thickness

It is not merely the thickness of the choroid itself, but more so the increased diameter of larger choroidal vessels that contributes to the overall increase in CT.[3] Healthy eyes with unusually thick choroids may be described as having "pachychoroid" or "uncomplicated pachychoroid".[3] To diagnose pachychoroid disease, it is necessary to identify pathological signs resulting from the dilation of choroidal vessels.

Utilizing EDI-OCT or SS-OCT, the choroid-scleral interface is traceable in the majority of eyes, enabling quantitative analysis of CT.[3] CT varies widely, with a subfoveal CT >300 µm generally considered pathological.[3] In conditions such as PCV, thicknesses ranging from 223 to 590 µm have been seen.[7] Increased CT is primarily due to vessel dilation in Haller's layer, visible as larger hyporeflective lumens on cross-sectional OCT, specifically in patients with CSC, PCV, FCE, and PPS.[8,9] En-face OCT and ICGA reveal that pachyvessels do not taper off towards the posterior pole but end abruptly, making them distinguishable from normal choroidal vessels.

Additionally, regional variations in CT show that the area beneath the fovea is thickest, while the nasal regions are thinnest.[10] In severe cases, Haller's layer vessels can occupy the entire thickness of the choroid. Even with normal or decreased CT, pachychoroid disease may be present if there is a decrease in inner choroidal volume due to atrophy. Therefore, assessing morphology with the help of automated software that analyzes the proportion of choroidal vascular luminal area to the total choroidal area, known as the choroidal vascularity index (CVI), is essential for diagnosis.

Choroid Vascularity Index/Choroidal Vascularity Index Map

While CT is a valuable measure, it only measures the total choroidal vasculature without differentiating between the stromal and luminal vascular component.[11,12] Therefore, Agrawal et al.[13] proposed the CVI as a novel OCT parameter. CVI provides a quantitative assessment of choroidal vascularity by determining the proportion of the choroidal vascular luminal area relative to the total choroidal area. This measurement enables comparisons between healthy eyes and those in different stages of pachychoroid disease.[12] The CVI map divides the choroid into vascular luminal and stromal areas, visually representing the choroidal vascularity across the posterior pole of the eye. Areas of higher vascularity appear brighter or denser, while areas with lower vascularity appear darker or less dense.[14,15] Studies have proposed using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid-based method to measure CVI in the OCT scans of healthy subjects.[15] Shadow compensation and contrast enhancement techniques were included to improve OCT scan quality. The CVI was mapped across different regions of the macula according to the ETDRS grid, indicating that central macular CVI was lower compared to other quadrants in healthy subjects.[15] Although this analysis was restricted to the macular area, this new approach for CVI mapping with shadow compensation could contribute to a better understanding of various chorioretinal diseases, including pachychoroid diseases.

Agrawal et al.[13] examined CVI in the subfoveal choroidal area of eyes with CSC and fellow eyes and reported a higher CVI in the affected eyes. Increased CVI indicates greater choroidal vascularity in patients with acute CSC. In a more recent study, Sahoo et al.[14] found no significant difference in CVI values when comparing eyes with CSC, fellow eyes, and healthy controls using OCT. However, they did observe a rising CVI towards the macular center in CSC eyes. The most significant effect was observed in the subfoveal choroid, which showed a significant increase in choroidal luminal area. The higher CVI in this region suggests that subfoveal choroidal vessels are more reactive to stimuli than those in the rest of the choroid. Additionally, CT and CVI showed a positive correlation in CSC eyes, meaning that areas with a thicker choroid exhibited increased choroidal vascularity. This implies that stromal expansion and vascular dilation in CSC eyes are distributed unevenly, which may be a reflection of different responses to stimuli.[14]

Further studies comparing steroid-associated CSC and idiopathic CSC revealed that eyes with steroid-induced CSC had significantly higher CVI than those with idiopathic CSC.[16] The theory is that glucocorticoids may induce vascular dilation by binding to mineralocorticoid receptors in the choroidal vascular endothelium, thereby increasing CVI. Lower CVI eyes may have choroidal alterations, such as choroidal ischemia, which may be a helpful indicator of CNV risk in CSC.[14]

A large study comparing eyes with PCV to those with age-related macular degeneration (AMD) found that PCV was associated with a thicker baseline CT and a larger luminal choroidal area than AMD.[17] Therefore, CVI could be a practical measure for differentiating patients with AMD and PCV. Furthermore, CVI has been shown to be useful in distinguishing between two subtypes of PCV: those with choroidal vascular hyperpermeability (higher CVI) and those without (lower CVI).[17]

In order to distinguish between various pachychoroid conditions such as uncomplicated pachychoroid, PPE, PNV, CSC, and PCV, Demirel et al.[18] established cut-off levels for CVI. The CVI cut-off points were 72.7 for PPE versus PCV, 74.7 for PNV versus CSC, 72.6 for PNV versus PCV, and 73.6 for CSC versus PCV. These cut-offs help better understand the distinctions among these diseases. However, optimizing algorithms for CVI remains challenging, as research has indicated that factors such as blood, subretinal fluid, and pigment epithelial detachment (PED) can impact signal strength within the choroid, especially in eyes with PCV, CSC, and PNV.[17]

Imaging Use in Specific Conditions

Central Serous Chorioretinopathy

OCT has accurately depicted the dimensions and extent of serous neurosensory and pigment epithelium detachments associated with CSC. Although CSC was first identified using fluorescein angiography, RPE leakage in eyes with acute CSC has also been observed using OCT (Figures 1 and 2). Maltsev et al.[19] utilized en-face OCT images from OCTA to pinpoint

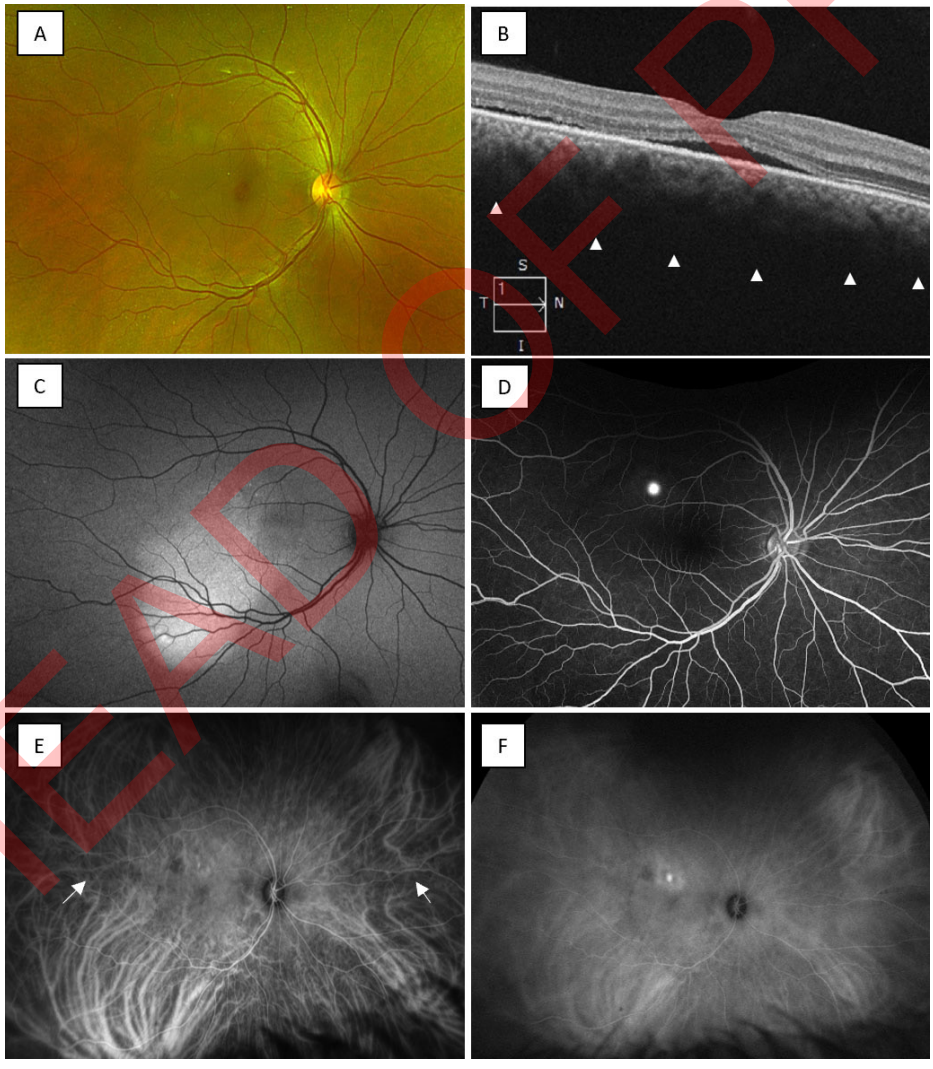

Figure 1. Multimodal imaging in central serous chorioretinopathy (CSC). A) Color fundus photograph of a 24-year-old female with CSC in the right eye. B) Optical coherence tomography scan through the fovea shows the presence of subretinal fluid, retinal pigment epithelium alterations, and pachychoroid (white arrow heads). C) Fundus autofluorescence shows the presence of hyperautofluorescent changes. D) Fluorescein angiography reveals a hyperfluorescent spot in the superotemporal parafoveal region. E) Early indocyanine green angiography (ICGA) shows the presence of choroidal vascular dilation and inter-vortex vein anastomoses (white arrows). F) Late ICGA shows a hypercyanescent spot in the superotemporal parafoveal region and multiple areas of hyperpermeability

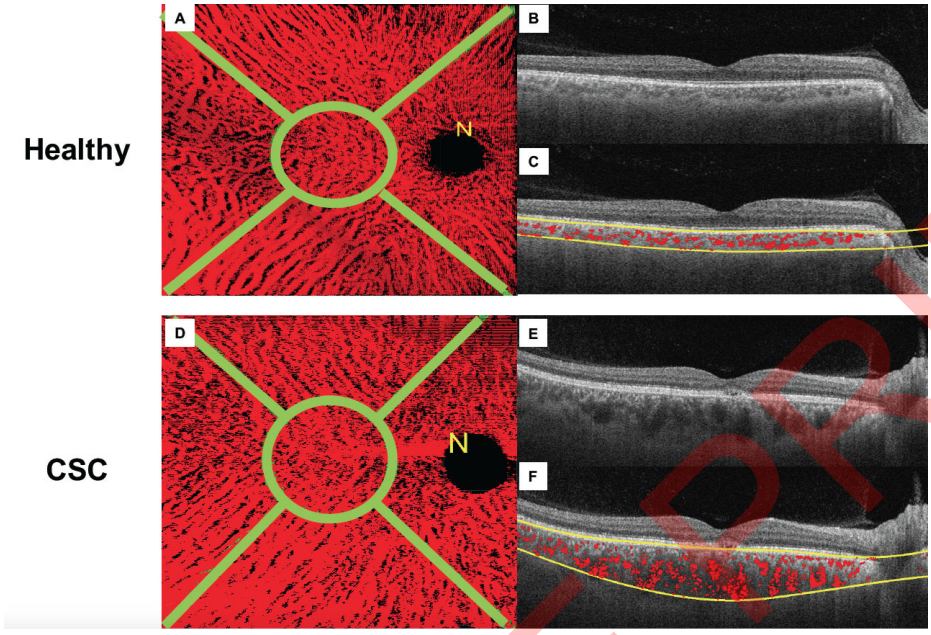

Figure 2. Three-dimensional (3D) reconstruction of the choroidal vessels in a healthy eye and an eye with central serous chorioretinopathy (CSC). A) 3D choroidal vessel map in a healthy 45-year-old man. B, C) Optical coherence tomography (OCT) B-scan and choroidal binarization, respectively. D) 3D choroidal vessel map in a 53-year-old man with CSC in the right eye. E) OCT B-scan showing subretinal fluid under the fovea. F) Choroidal binarization

the confirmed leakage point in 54.2% of CSC patients, eliminating the need for fluorescein angiography.

Individuals with CSC have a thicker choroid in all subfields compared to healthy eyes, as evidenced by EDI and SS-OCT (Figure 1). This increased thickness spans from the subfoveal region to peripheral areas, along with notable dilation of the veins within Haller's layer.[20] While cross-sectional OCT imaging shows increased CT in CSC patients, no corresponding changes are seen on ICGA. This disparity suggests a potential limitation of ICGA in capturing specific choroidal morphology alterations associated with CSC.[11,21] In contrast, the three-dimensional visualization provided by SS-OCT allows for more effective characterization of distinct retinal and choroidal layers. Additionally, the focal and diffuse choroidal dilations seen in en-face SS-OCT images align with hyperfluorescent areas on ICGA. These particular morphological changes in the choroidal vasculature that are visualized through en-face SS-OCT remain undetectable in conventional cross-sectional OCT images. Thus, en-face imaging emerges as an optimal modality for visualizing these features.[11]

OCT has been able to identify clinical characteristics that differentiate acute from chronic CSC. While both present with serous retinal neuroepithelial detachment, acute CSC shows serous retinal detachment that is primarily localized to the macular area and significantly elevated. In contrast, chronic CSC displays shallower detachment depths and more extensive detachment, often extending beyond the macular area or being multifocal.[22] Ruiz-Medrano et al.[23] also compared acute and chronic CSC findings using EDI-OCT and discovered hyperreflective spots and hyperreflective choroidal vessels but with varying prevalence: 83.3% and 75% in chronic CSC, compared to 33% and 6.7% in acute CSC, respectively. Ferrara et al.[11] investigated the effectiveness of en-face SS-OCT in identifying retinal and choroidal vasculature in patients with CSC, without the use of ICGA. At the level of the RPE, all eyes showed no signal corresponding to RPE detachment or loss, suggesting that the layer of cells nourishing the retina was intact. Enlarged vessels at the choriocapillaris level were present in more than 50% of the eyes. Furthermore, focal and diffuse choroidal dilation in Sattler's and Haller's layers were observed just beneath the area of RPE abnormalities, suggesting a potential relationship between choroidal changes and RPE abnormalities.[11] Overall, these findings suggest that en-face SS-OCT can identify choroidal and retinal neovascularization without the need for ICGA.

In their abovementioned study, Sahoo et al.[14] mapped CVI in patients with unilateral CSC using the ETDRS grid. The authors indicated that the outer nasal CT was significantly lower than both the central and inner nasal CT. Additionally, a positive correlation between CVI and CT was identified in CSC eyes, while this relationship was slightly weaker in fellow eyes and absent in healthy eyes. Generally, CSC eyes demonstrated an upward trend of CVI towards the macular center and superiorly, while fellow and healthy eyes exhibited a downward trend towards the macular center.[14]

Polypoidal Choroidal Vasculopathy

PCV, or pachychoroid aneurysmal type 1 CNV (PAT1), was first described by Yannuzzi et al.[24] in 1982. It is characterized by multiple serosanguineous detachments of the RPE and neurosensory retina, accompanied by secondary leakage from a branching vascular network.[25,26] The term PCV describes the appearance of branching choroidal vessels with terminal, polyp-like aneurysmal dilations.[24] While ICGA has traditionally been considered essential for diagnosing PCV, OCT findings are more accessible and have shown a strong correlation with ICGA findings in various studies (Figure 3).[27,28,29,30,31]

OCT has shown remarkable sensitivity and specificity in distinguishing between PCV and neovascular AMD.[32,33] Furthermore, the evaluation of color fundus photographs and OCT images together has proven to be quite accurate in differentiating PCV from CSC, as well as between PCV and AMD.[34]

A 2019 study assessed the diagnostic potential of certain features identified through fundus photography, OCT, and fluorescein angiography individually and combined for diagnosing PCV without ICGA.[35] The results showed that the presence of at least two out of four highly indicative features detected using fundus photography and OCT had 95% sensitivity and specificity for diagnosing PCV. These highly suggestive features include a notched or hemorrhagic PED on fundus photography, a sharply peaked PED at an angle of 70° to 90° on OCT, a notched or multilobulated PED on OCT, and a PED with underlying hyperreflective ring on OCT.[35] However, the study focused on untreated eyes, which poses a limitation and casts doubt on the applicability of the findings to treated eyes.

Pachychoroid Neovasculopathy

PNV, a term introduced by Pang and Freund[36], describes a distinct maculopathy where CNV emerges amidst areas of choroidal thickening and dilation of choroidal vessels. There is continuing debate about whether PNV and AMD are distinct entities or part of a progression, and they can be mistaken for each other due to similarities in the blood vessel patterns observed.[37] Diagnosis has been challenging, particularly with techniques like fluorescein angiography, but OCT and OCTA offer clear imaging for accurate diagnosis. Key OCT biomarkers for PNV include a flat, irregular PED and the double-layer sign, which refers to visibility of the RPE and Bruch's membrane (Figure 4).[38,39,40] However, distinguishing between non-aneurysmatic PNV and aneurysmatic PAT1/PCV has become

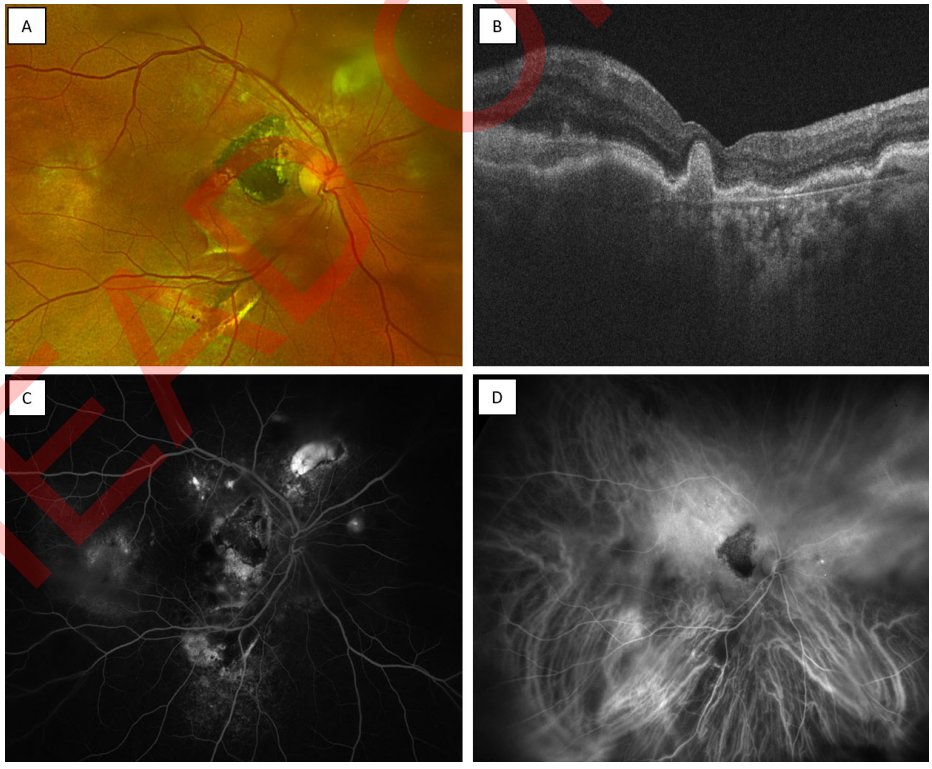

Figure 3. Multimodal imaging in polypoidal choroidal vasculopathy. A) Color fundus photograph of the right eye of a 64-year-old man. Note the retinal scars with the surrounding suprachoroidal hemorrhage in the peripapillary region. B) Optical coherence tomography scan through the fovea shows a complete alteration of the foveal profile. C) Fluorescein angiography shows the presence of hyper- and hypofluorescent areas in the macula and peripapillary region. D) Indocyanine green angiography shows the presence of dilated choroidal vessels, hyperpermeability, and hypercyanescent spots corresponding to the polypoidal lesions

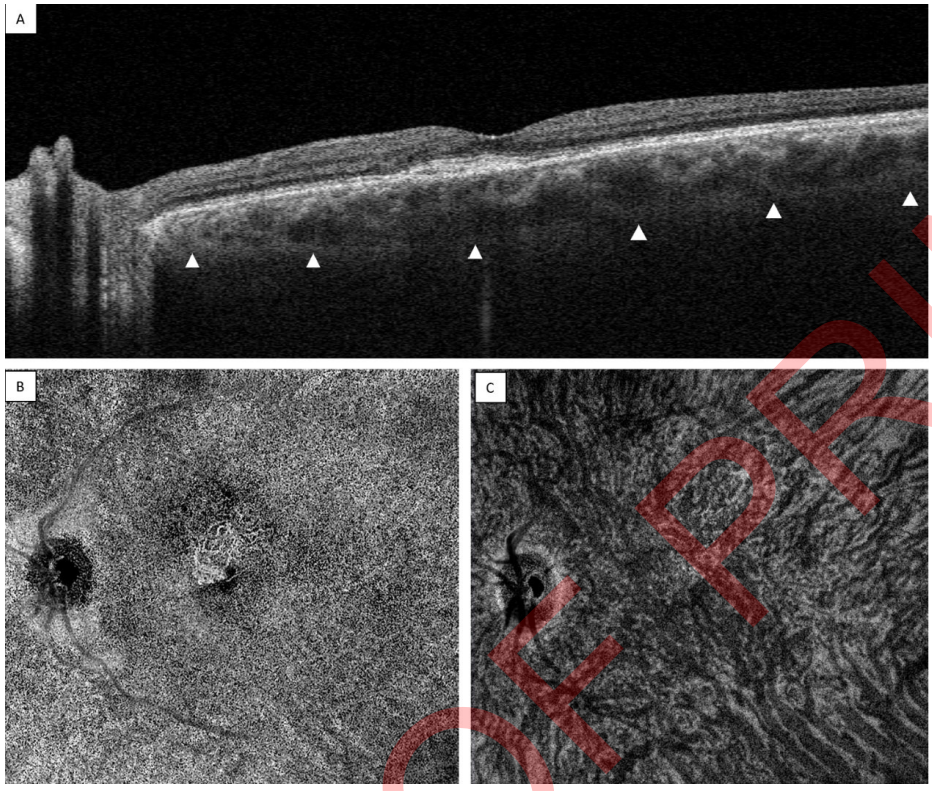

Figure 4. Optical coherence tomography (OCT) and OCT angiography (OCTA) in pachychoroid neovasculopathy. A) OCT scan through the fovea shows the presence of a flat, irregular pigment epithelium detachment (PED) in the subfoveal region. Note the pachychoroid (white arrow heads). B) En-face OCTA shows the presence of a choroidal neovascularization corresponding to the flat, irregular PED on OCT. C) En-face OCTA at the level of the choroid shows the presence of dilated choroidal vessels in the macula

increasingly complex and may be underappreciated due to the growing recognition of PNV as a new diagnostic entity.

Recent studies suggest that a significant portion of eyes diagnosed with PNV may have the aneurysmal form of pachychoroid neovascularization (PAT1/PCV).[41] Although ICGA is typically used for diagnosing PAT1/PCV, OCT is more widely available and can aid in diagnosis, especially in settings where ICGA is not accessible.[41] Given these circumstances, establishing a more precise set of diagnostic criteria for PAT1/PCV on OCT has become crucial to enhance clinical care. Specific OCT features, such as PED height, subretinal hyperreflective material above the PED peak, sub-RPE fluid, and hyperreflective material localized to the subretinal space are strong indicators of PAT1/PCV.[42] These findings underscore the importance of utilizing OCT alongside other imaging techniques, such as ICGA, for accurate diagnosis and differentiation between PNV and PAT1/PCV.

Pachychoroid Pigment Epitheliopathy

PPE is defined by RPE changes in pachychoroid eyes without the presence or history of subretinal fluid or soft drusen.[43] It is considered a form fruste of CSC, as the range of RPE abnormalities is similar to those found in CSC.[3] Karacorlu et al.[44] classified PPE into four types: RPE elevation with microbreak appearance, PED, RPE thickening, and hyperreflective RPE spikes.

Using SS-OCT and SS-OCTA, researchers have gained a deeper understanding of the relationship between choroidal vascular hyperpermeability observed with ICGA, choriocapillaris flow density, and CT in eyes with PPE. These advanced OCT technologies have revealed decreased choriocapillaris flow density, increased CT, and the co-localization of choroidal vascular hyperpermeability in PPE eyes.[45] Specifically, a 15% reduction in choriocapillaris flow density was observed in the quadrants affected by choroidal vascular hyperpermeability compared to the unaffected quadrants in the same eye. This finding suggests that despite choroidal thickening, vascular hyperpermeability, and venous dilation (indicating higher choroidal blood flow and vessel congestion), there is ischemia in the inner choroid, RPE, and outer retina due to decreased choriocapillaris vascularity.[45] The advent of SS-OCT angiography has significantly improved choriocapillaris imaging compared to fluorescein angiography and ICGA.

Focal Choroidal Excavation

FCE is a concavity in the choroid of unknown etiology, occurring without any adjacent scleral abnormality or ectasia. This condition progresses slowly, with good visual acuity

maintained over time with minimal changes. Jampol et al.[46] first described this in 2006 using time-domain OCT. In 2010, Wakabayashi et al.[47] reported unilateral choroidal excavation using spectral-domain (SD)-OCT, which provided more detailed visualization of retinal and choroidal structure than time-domain OCT. SS-OCT uses an even longer wavelength than SD-OCT, allowing for better visualization of the choroid.[48] Overall, OCT is particularly important for its ability to provide detailed images of the retinal structure.[49,50,51]

Peripapillary Pachychoroid Syndrome

PPS, described by Phasukkijwatana et al.[9] in 2017, is characterized by a thick and hyperpermeable choroid in the peripapillary area and nasal macula. This choroidal congestion causes fluid accumulation within the retina and beneath the retina around the optic nerve, leading to a crowded appearance of the optic disc, choroidal folds, and occasionally optic disc edema (Figure 5).[52] OCT scans can detect intraretinal fluid in both the nasal and temporal regions near the optic discs, along with choroidal hypertransmission and atrophy of the RPE,

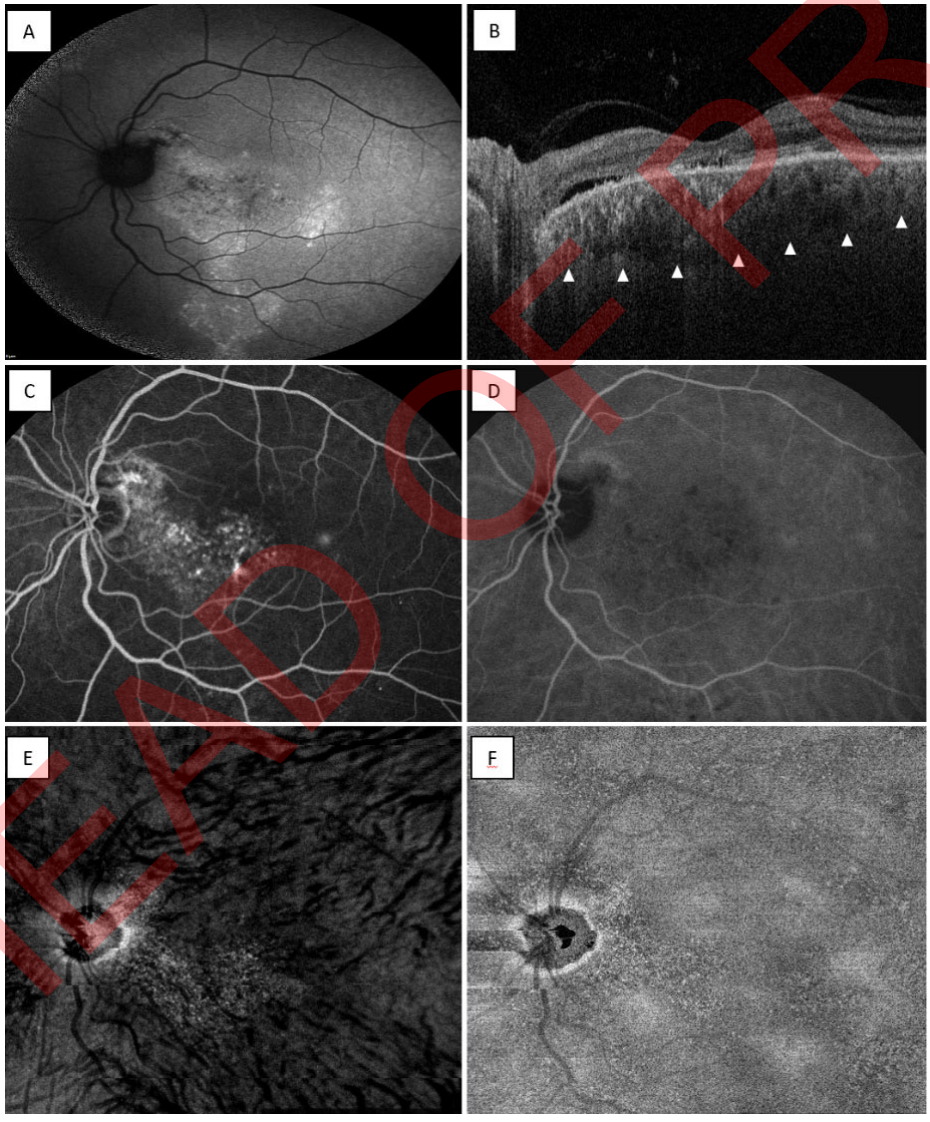

Figure 5. Multimodal imaging in peripapillary pachychoroid syndrome (PPS). A) Fundus autofluorescence in a 64-year-old man with PPS. Note the presence of hyper- and hypoautofluorescence in the peripapillary region and in the macula, in a typical pattern defined as "femur sign". B) Optical coherence tomography (OCT) scan through the fovea shows the presence of macular and peripapillary subretinal fluid. Note that the peripapillary choroid is thicker than the choroid in the temporal macula. C) Fluorescein angiography shows the presence of hyperfluorescent spots in the peripapillary region. D) Indocyanine green angiography demonstrates hyperpermeability in the peripapillary region and the macula. E) En-face OCT angiography shows the presence of dilated choroidal vessels in the peripapillary region. F) En-face OCT angiography at the level of the choriocapillaris shows the presence of flow alterations in the macula and in the peripapillary region

ellipsoid zone, and external limiting membrane.[53] Peripapillary pachyvessels are more noticeable in nasal than temporal regions. EDI-OCT detects intraretinal fluid with cysts in the nasal macula that extend to the temporal optic disc margin, accompanied by focal atrophy of the RPE, ellipsoid zone, and external limiting membrane in both eyes. This small cystoid space, otherwise known as a "peripapillary fluid pocket" has been thought to represent a possible entry of fluid from the choroid to the retina, and represents a biomarker of PPS.[53]

Peripheral Exudative Hemorrhagic Chorioretinopathy

PEHCR is a rare condition first described by Reese and Jones[54] in 1961, characterized by peripheral hematomas under the RPE. It has often been mistaken for choroidal melanoma, which requires different management approaches. At first, PEHCR was considered a peripheral variant of AMD due to shared clinical features such as hemorrhage and exudation, alongside macular drusen and RPE changes observed in some cases.[55] Recent research using EDI-OCT indicates that PEHCR may be a part of the spectrum of pachychoroid diseases.[56] Comparing choroidal vascular changes and thickness between PEHCR and healthy eyes, PEHCR eyes showed a gradual thickening of the choroid from the nasal to the temporal periphery. In contrast, healthy eyes exhibited maximum CT subfoveally. Moreover, choroidal vessel thickness tended to be greater in the PEHCR group compared to healthy eyes. These results indicate that the increased CT and pachyvessels in PEHCR support its classification as a pachychoroid disease.[56]

Subsequent findings on ICGA, such as abnormal choroidal vascular networks and polyp-like telangiectasis, suggested a potential link to PCV (Figure 3).[26,57] ICGA findings in PEHCR include polyps (0-59%), pathologic choroidal network (30-84%), and late hypercyanescence or leakage of uncertain etiology (60-62%).[57,58,59]

However, imaging PEHCR lesions with OCT can be challenging due to their peripheral location. Regardless, these lesions are often characterized by subretinal fluid or PEDs over Bruch's membrane without infiltration of the underlying choroid.[58–60] Additionally, OCT of the macula may show the spread of subretinal fluid, exudates, or the formation of macular fibrosis.

Indocyanine Green Angiography

ICGA enhances choroidal imaging due to the RPE's greater transparency to longer wavelengths. However, the main limitation remains its inability to localize features to specific tissue layers because of vertical summation.[61]

ICGA is a specialized imaging system that provides detailed visualization of the choroidal vasculature, contributing to our understanding of pachychoroid diseases. More recently, ultra-widefield ICGA has been introduced, significantly expanding our field of view, particularly in assessing peripheral choroidal features.[62,63] Ultra-widefield ICGA enables comprehensive *in vivo* visualization of the choroidal circulation, covering areas from the posterior pole to beyond the vortex vein ampullae.[64,65] This advanced imaging technique has been utilized to assess choroidal vascular changes in eyes affected by pachychoroid disease entities. The findings support the hypothesis that venous outflow congestion may contribute to the pathogenesis of these conditions.[66]

In CSC, ultra-widefield ICGA has identified several characteristic features, including dilation of choroidal veins,[67,68] choroidal venous anastomoses that do not adhere to the watershed zone between distinct vortex vein quadrants,[4,62] and asymmetric venous drainage causing enlarged or deflated vortex vein ampullae (Figure 1).[5,67,68] These changes are consistent with findings seen on EDI-OCT.[3]

A study using ultra-widefield ICGA imaging on 52 patients with various pachychoroid conditions determined that 88% of eyes exhibited choroidal venous anastomoses.[66,69] Furthermore, choroidal vascular hyperpermeability was noted in all eyes affected by pachychoroid-related conditions. Postoperative widefield ICGA identified vortex vein anastomoses in 10 out of 12 eyes within three months following vortex vein occlusions. These observations were accompanied by widespread ICGA hyperfluorescence in the quadrant where the occlusion had occurred.[66,69]

ICGA has always been the preferred method for diagnosing PCV. In the early phase of ICGA, one or more polyps may be visible. However, both flash digital fundus photography with ICGA and confocal scanning laser ophthalmoscopy systems have shown the ability to detect at least 80% of typical nodular lesions of PCV. Recent studies have proposed further classification of PCV subtypes based on appearances on ICGA and supported by choroidal vascular features observed on SD-OCT.[25]

On ICGA, pachyvessels are seen as clusters of relatively straight and dilated choroidal vessels. Other findings include dilation of choroidal veins, filling defects in the choroid, delayed arterial filling in the early phase, and focal or punctate hyperfluorescence in eyes with CSC, PCV, and FCE (Figures 1 and 3). These observations suggest the possibility of choroidal ischemia.[70,71,72] In the mid to late phase, ICGA reveals patchy areas of hyperfluorescence that correspond to the leakage and staining sites observed on fluorescein angiography. Previous studies have indicated that choroidal hyperpermeability is present in more than 90% of eyes with PPE and CSC[72] and 10-50% of those with PCV.[73,74]

Additionally, punctate hyperfluorescent spots were seen in the mid to late phases of ICGA in eyes affected by CSC and PCV.[74,75] Both diffuse and punctate hyperfluorescent spots appear in the contralateral eyes of CSC and PCV and persist even after the subretinal fluid has resolved. These observations suggest that choroidal alterations are likely the primary cause of these conditions.

Scleral Thickness Measurement

Alterations in scleral thickness may impact pachychoroid diseases such as CSC and can be examined through ultrasound biometry (UBM) and anterior segment (AS)-OCT. In CSC, compression of vortex veins can lead to choroidal venous congestion, causing delays in choriocapillaris filling and ischemic

areas, termed "venous overload choroidopathy".[76] However, the precise role of scleral changes, including thickness, in affecting vortex vein drainage and contributing to pachychoroid disorders remains uncertain.

Studies investigating anterior scleral thickness (AST) and subfoveal CT in CSC and PNV using SS-OCT and EDI-OCT found that patients with CSC/PNV had thicker AST compared to controls in addition to higher subfoveal CT. This suggests that a thicker anterior sclera may contribute to the speculated venous overload, triggering pachychoroid phenotypes.[76] Other studies also demonstrated thicker AST in hyperopic eyes and thinner AST in myopic eyes, consistent with previous findings. However, there was no notable difference in AST between sexes. Thickening of the anterior sclera might impede vortex vein outflow, potentially contributing to choroidal thickening and the onset of pachychoroid disorders.[76]

One study primarily focused on AST in patients with CSC versus healthy individuals and aimed to evaluate the reliability of scleral thickness measurements obtained using UBM compared to AS-OCT. It was found that mean AST measured by AS-OCT was significantly higher in CSC cases compared to controls.[77] There was also a significant difference in AST measurements between AS-OCT and UBM in CSC cases, with AS-OCT yielding higher measurements. Although a positive correlation between AST measured by AS-OCT and UBM was observed, differences in scleral border demarcation and inclusion of episcleral tissue in AS-OCT images may have affected the measurements. Another limitation was that manual measurements with a digital caliper were considered more accurate in AS-OCT than in UBM. Therefore, it was concluded that AST measurements obtained by UBM did not align with those obtained by AS-OCT.[77]

Optical Coherence Tomography Angiography

The primary applications of OCTA are in research to understand etiopathogenesis, and in clinical settings to improve the diagnosis of pachychoroid neovascularization.

En-face OCT and OCTA scans can show choriocapillaris ischemia and choroidal anastomotic vessels, thereby improving the understanding of the pathophysiological mechanisms.[78] SS-OCT provides the benefit of longer wavelengths for greater tissue penetration along with the rapid capture of numerous images, greatly improving image quality. Moreover, the choriocapillaris structure can be visualized better in vivo by averaging en-face OCTA images. These show choriocapillaris ischemia/flow void areas corresponding to the location of dilated Haller vessels. The co-localization of dilated vessels, choroidal thickening, and choriocapillaris attenuation has been demonstrated in cross-sectional OCT, with OCTA findings indicating reduced flow signal within the choriocapillaris.[79] It was suggested that the dilation of the large blood vessels in Haller's layer may compress the layers above it, including the medium-sized vessels in Sattler's layer and the choriocapillaris. This compression can disrupt blood flow in the choriocapillaris, leading to reduced oxygen supply in the overlying RPE and retina and promoting CNV.[45]

Chronic CSC is commonly associated with serous or flat, irregular PED. Before OCTA was used as a clinical tool to diagnose CNV, studies showed that 10% of eyes with CSC had CNV as a complication, and 33% of eyes with CSC had flat, irregular PED on macular OCT examination. PEDs were suggestive of type 1 CNV in 18% of the eyes with flat, irregular PEDs. The remaining 81% of these flat PEDs remained clinically quiescent under observation.[80] It was assumed that most flat PEDs were quiescent, undiagnosed CNV, or debris, pigment, or pachydrusen. The first studies using OCTA in CSC included only eyes with flat, irregular PED in order to assess the occurrence of CNV. In one study, in spite of the fact that dye angiography showed neovascularization in only 29% of the eyes, OCTA revealed type 1 neovascular tissue in 95% of the eyes.[81] In another study, ICGA revealed choroidal neovascular plaques in 42% of eyes (n=8), whereas OCTA showed CNV in 74% of eyes (n=14).[82] Overall, it was reported that OCTA was as good as fluorescein angiography as a gold standard technique for CNV, and even better than the combination of OCT, fluorescein angiography, and ICGA for the diagnosis of PNV (Figure 4). Demirel et al.[83] assessed the sensitivity and specificity of ICGA and OCTA and found that OCT was far more sensitive than ICGA (97.2% vs. 66.7%), while both techniques had 100% specificity. OCTA can non-invasively visualize neovascularization, shows vascular networks between the RPE and Bruch's membrane, is not affected by any kind of leakage, and may contribute to the diagnosis of CNV in suspicious cases. However, there are some shortcomings of dye angiography in chronic CSC. Diffuse RPE loss can cause widespread window defects and scattered points of RPE leakage in fluorescein angiography. Even ICGA, which is used to better visualize the problem, might show multiple patches of hyperfluorescence in the inner choroid that are also present with CNV. This can make things more complicated and hinder a correct diagnosis. In addition to those factors, the tendency of CNV to appear as a plaque in the late phase of angiography might not be the case in chronic CSC as is seen in AMD, which is characterized by a late-phase hypercyanescent plaque with a well-defined border.[84] Recently, Zola et al.[85] showed that leakage from type 1 CNV in central serous cases is less common in CSC than in AMD. Eyes with type 1 macular neovascularization in CSC are less likely to leak macromolecules from the macular neovascularization and accumulate them in the RPE and/or stroma, as evidenced by the late-phase hyperfluorescent plaque. In their series, Demirel et al.[83] reported that neovascularization showed hypercyanescence only in the early-mid ICGA phase in 10 of 24 eyes, but the border almost disappeared in the late phase of ICGA.

There might be some morphological distinctions between CNVs and pachychoroid, as there are many reports indicating differences in pathophysiology, genetic basis, and intraocular cytokine levels.[84] One study found that the indistinct pattern was more common in PNV eyes than in AMD eyes. However, the pruned vascular tree pattern, which is an OCTA sign of an inactive membrane, was less common in PNV eyes than in AMD

eyes with CNVs. Type 1 CNVs in PNV were characterized by a smaller CNV area and flow compared with type 1 CNVs in AMD.[86] Yanık et al.[86] used software that created a skeleton model from the Otsu binarization of en-face OCTA images and measured the total length and number of intersection points. Their study revealed differences not only in qualitative OCTA features but also in quantitative features. They reported that the macular neovascularization area was smaller, vessel density was lower, total vessel length was shorter, the number of intersection points was smaller, and fractal dimension showed less complexity in PNV compared to AMD. This form of CNV may represent an attempt at reforming the choriocapillaris, with a few anastomoses bringing sufficient oxygen and nutrients to the surrounding retina.[87]

Many studies found that SD-OCTA was not as good at diagnosing polypoidal vasculopathy as ICGA, but was better for visualizing the basal vascular network. A recent study suggested that SS-OCTA may be a better way to accurately detect both polypoidal lesions and branching vascular networks in PCV.[88] Bo et al.[89] found that polypoidal lesions are made up of dense or loosely mixed vascular structures at the edges of branching vascular networks or type 2 neovascularization. Polypoidal lesions are consistent with a neovascularization structure rather than an aneurysmal structure.

Discussion

The integration of advanced imaging techniques has considerably enhanced our understanding of pachychoroid spectrum diseases. Technologies like ICGA, OCTA, and EDI-OCT allow detailed visualization of the choroidal anatomy,[1,3,72,82,83] while UBM and AS-OCT visualize scleral anatomy, allowing the identification of key pathological features such as venous outflow congestion, choroidal vascular hyperpermeability, and anterior scleral thickening.[76,77] These findings suggest that scleral alterations play an important role in the development of pachychoroid diseases by impeding vortex vein outflow and contributing to choroidal thickening.

Although these imaging advancements have undeniably provided critical insights into the pachychoroid spectrum of diseases, it is important to acknowledge the limitations and ongoing controversies within the field. For example, despite the high resolution and deep tissue penetration offered by OCTA and EDI-OCT, there remains variability in the interpretation of these images.[3,11,12,21] Differences in the diagnostic criteria and classification of pachychoroid diseases across studies suggest that further standardization is needed to ensure consistency and comparability of findings.

Additionally, there are controversies regarding the pathogenesis of pachychoroid diseases, particularly regarding the role of scleral changes and venous congestion in disease progression. While some studies suggest a direct link between anterior scleral thickening and choroidal congestion, others have not found consistent correlations, indicating that more robust longitudinal studies are needed to clarify these associations.[76,77] Looking ahead, future research should focus on longitudinal studies to establish causal relationships between scleral and choroidal changes and disease progression. Developing standardized imaging protocols and quantitative analysis methods will enhance the reproducibility and accuracy of these measurements.

The pathogenesis of the disease will be further clarified through development of imaging technologies, longitudinal studies that accurately track the disease stages, and investigations into genetic and molecular mechanisms underlying these structural changes. These steps will also help identify new targets for therapeutic intervention, which will improve patient care. At present, treatment options consist of anti-vascular endothelial growth factor agents for eyes complicated with CNV and/or polypoidal enlargement,[90,91] photodynamic therapy for the treatment of CSC,[92] and laser treatment such as subthreshold laser systems to enhance RPE function.[19]

Conclusion

In summary, advanced non-invasive imaging technologies with higher resolution and deeper penetration can lead to earlier detection of pachychoroid pathologies, more personalized treatment, and greater global accessibility to innovative diagnostics, ultimately improving patient care and outcomes.

Declarations

Authorship Contributions

Surgical and Medical Practices: S.D., A.Y., Concept: S.D., A.Y., J.C., Design: S.D., A.Y., N.V., J.C., Data Collection or Processing: S.D., A.Y., N.V., Analysis or Interpretation: S.D., A.Y., N.V., J.C., Literature Search: S.D., A.Y., Writing: S.D., A.Y., N.V., J.C.

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