UNIVERSIDADE FEDERAL DE MINAS GERAIS

Faculdade de Medicina

Programa de Pós-Graduação em Cirurgia e Oftalmologia

Virginia de Souza Leolino Mares

Inteligência artificial aplicada ao monitoramento de fluido na degeneração macular relacionada à idade forma neovascular

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Tese apresentada à Universidade Federal de Minas Gerais, como requisito parcial para obtenção do título de Doutor em Ciências aplicadas à Oftalmologia e Cirurgia.

Orientador: Professor Doutor Marcio B. Nehemy.

Co-orientadora: Professora Ursula Schmidt- Erfurth.

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CENTRO DE PÓS-GRADUAÇÃO
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ATA DE DEFESA DE TESE

Às nove horas do dia dezenove de dezembro de dois mil e vinte e quatro, na Faculdade de Medicina, na sala 526, realizou-se a sessão pública para a defesa da Tese de **VIRGINIA DE SOUZA LEOLINO MARES**. A presidência da sessão coube ao Prof. Márcio Bittar Nehemy (Orientador) – UFMG. Inicialmente, o presidente fez a apresentação da Comissão Examinadora assim constituída: Márcio Bittar Nehemy (Orientador) – UFMG, Ursula Margarethe Schmidt-erfurth (Coorientadora) – Universidade de Medicina de Viena, Laurentino Biccas Neto – EMESCAM, Maurício Maia – UNIFESP, Carlos Eduardo dos Reis Veloso – UFMG e Maria da Conceição Frasson Corrêa da Silva – UFMG. Em seguida, a candidata fez a apresentação do trabalho que constitui sua Tese de Doutorado, intitulada: INTELIGÊNCIA ARTIFICIAL APLICADA AO MONITORAMENTO DE FLUIDO NA DEGENERAÇÃO MACULAR RELACIONADA À IDADE FORMA NEOVASCULAR. Seguiu-se a arguição pelos examinadores e logo após, a Comissão reuniu-se, sem a presença da candidata e do público e decidiu considerar aprovada a Tese de Doutorado. O resultado final foi comunicado publicamente a candidata pelo presidente da Comissão. Nada mais havendo a tratar, o presidente encerrou a sessão e lavrou a presente ata que, depois de lida, se aprovada, será assinada pela Comissão Examinadora.

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Resumo

Introdução: A degeneração macular relacionada à idade (DMRI) é uma das principais causas de cegueira em todo o mundo. A Tomografia de Coerência Óptica (OCT) emergiu como uma ferramenta central no manejo da DMRI, permitindo a visualização de biomarcadores fundamentais, como fluidos retinianos, integridade da zona elipsoide e do epitélio pigmentar da retina. Recentemente, a inteligência artificial (IA) trouxe avanços significativos na precisão do diagnóstico, previsão da progressão da doença e na personalização de tratamentos.

Objetivos: O objetivo deste trabalho foi avaliar o uso de algoritmos de IA para quantificar biomarcadores retinianos em pacientes com DMRI neovascular e analisar a correlação entre os volumes de fluido em cada compartimento e os desfechos visuais e anatômicos em uma coorte europeia e em uma coorte brasileira.

Métodos: No primeiro trabalho foi realizada a análise automatizada de imagens de OCT utilizando o algoritmo de IA (*Fluid monitor,* RetInsight, Vienna) para quantificação dos fluidos intrarretinianos (FIR), sub-retinianos (FSR) e descolamento do epitélio pigmentar da retina (DEP), e desenvolvido um modelo baseado em *machine learning* para predizer a necessidade de tratamento, acuidade visual (AV) e desfechos anatômicos. No segundo trabalho, foi realizada a quantificação automatizada baseada em IA dos fluidos retinianos e foi realizada a segmentação automatizada da zona elipsoide (ZE) utilizando um conjunto de redes neurais na arquitetura U-net, com o propósito de correlacionar o impacto do volume basal dos fluidos retinianos e do DEP com a perda da integridade dos fotorreceptores. No terceiro trabalho, foi utilizado o mesmo algoritmo de quantificação dos fluidos retinianos em uma coorte brasileira, tendo sido correlacionado os volumes basais com desfechos visuais e anatômicos ao final de 2 anos. As análises estatísticas utilizaram modelos preditivos, modelos de regressão linear e regressão longitudinal para avaliar a correlação entre os fluidos em cada compartimento com a AV, a integridade da ZE e progressão de atrofia macular (AM) e fibrose sub-retiniana (FS).

Resultados: Os resultados dos três estudos mostraram que as ferramentas de monitoramento de biomarcadores da OCT baseada em IA foram eficazes para o acompanhamento de pacientes com DMRI tanto na coorte europeia quanto na brasileira. Com os algoritmos empregados, foi possível observar a correlação entre volumes elevados de FIR e DEP com afinamento e perda da integridade da ZE e

desfechos visuais piores, além de maior progressão para AM e FS. Observou-se também correlação entre FSR com melhores desfechos visuais, e menor progressão de atrofia. FSR, entretanto, apresentou correlação com maior necessidade de injeções intravítreas de anti-angiogênicos.

Conclusões: Algoritmos baseados em IA mostraram-se promissores na monitorização da DMRI neovascular, com potencial de predizer desfechos, refinar o diagnóstico e auxiliar abordagens personalizadas destes pacientes.

Palavras-chave: Degeneração macular relacionada à idade; anti-VEGF; inteligência artificial; neovascularização coroideana; *deep learning*; drusas; atrofia geográfica; fibrose subretiniana; tomografia de coerência óptica.

Abstract

Introduction: Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. Optical Coherence Tomography (OCT) has emerged as a central tool in AMD management, allowing visualization of key biomarkers such as retinal fluids, ellipsoid zone integrity, and retinal pigment epithelium. Recently, artificial intelligence (AI) has brought significant advancements in diagnostic accuracy, disease progression prediction, and personalized treatment approaches.

Objectives: This study aimed to evaluate the use of AI algorithms to quantify retinal biomarkers in patients with neovascular AMD and analyze the correlation between fluid volumes in each compartment and visual and anatomical outcomes in a European cohort and a Brazilian cohort.

Methods: In the first study, automated OCT image analysis was performed using an AI algorithm (Fluid monitor, RetInsight, Vienna) to quantify intraretinal (IRF), subretinal (SRF) fluids, and retinal pigment epithelium detachment (PED), and a machine learning-based model was developed to predict the need for treatment, visual acuity (VA), and anatomical outcomes. In the second study, automated AI-based quantification of retinal fluids was conducted, and automated segmentation of the ellipsoid zone (EZ) was performed using an ensemble U-net convolutional network, with the purpose of correlating the impact of baseline volumes of retinal fluids and PED with the loss of photoreceptor integrity. In the third study, the same algorithm for retinal fluid quantification was used in a Brazilian cohort, and baseline volumes were correlated with visual and anatomical outcomes after 2 years. Statistical analyses used predictive models, linear regression models, and longitudinal regression to evaluate the correlation between fluids in each compartment with VA, EZ integrity, and progression to macular atrophy (MA) and subretinal fibrosis (SF).

Results: The results of the three studies showed that AI-based OCT biomarker monitoring tools were effective in monitoring AMD patients in both the European and Brazilian cohorts. With the used algorithms, it was possible to observe a correlation between elevated IRF and PED volumes with thinning and loss of EZ and poorer visual outcomes, as well as greater progression to MA and SF. A correlation was also observed between SRF and better visual outcomes, and lower MA progression. However, SRF showed a correlation with an increased need for intravitreal anti-angiogenic injections.

Conclusions: AI-based algorithms proved promising in the monitoring of neovascular AMD, with potential to predict outcomes, refine diagnosis, and support personalized approaches for these patients.

Keywords: Age-related macular degeneration; artificial intelligence; anti-VEGF; choroidal neovascularization; deep learning; drusen; geographic atrophy; optical coherence tomography; subretinal fibrosis.

LISTA DE ABREVIATURAS E SIGLAS

AG atrofia geográfica

AM atrofia macular

BCVA *best correct visual acuity*

CNN *convolutional neural network*

DEP descolamento do epitélio pigmentar da retina

DL *deep learning*

DMRI degeneração macular relacionada à idade

EPR epitélio pigmentar da retina

FDA *Food and Drug Administration*

FIR fluido intrarretiniano

FRB! Fight Retinal Blindness!

FS fibrose sub-retiniana

FSR fluido sub-retiniano

GANs *generative adversarial network*

IA inteligência artificial

IRIS *Intelligent Research in Sight*

ML *machine learning*

MNV neovascularização macular

OCT tomografia de coerência óptica

OCT-A angio-tomografia de coerência óptica

OPTIMA Laboratório de Análise de Imagens Oftálmológicas

SRHM material hiper-refletivo subretiniano

TREND *Treat and Extend clinical trial*

VEGF fator de crescimento vascular endotelial

ZE zona elipsoide

SUMÁRIO

1 INTRODUÇÃO

A inteligência artificial (IA) abrange uma ampla gama de técnicas dentro da ciência da computação, executando tarefas que tradicionalmente são realizadas por humanos.[1] O termo *machine learning* (ML) é usado para descrever uma ramificação da IA, que foi descrita pela primeira vez por Arthur Samuel em 1959 como a combinação de ciência computacional e conceitos matemáticos usados para realizar tarefas específicas.[2] Algoritmos de ML passam por pelo menos duas etapas de desenvolvimento: uma primeira etapa de treinamento, em que o algoritmo aprende a extrair informações a partir de conceitos introduzidos por humanos, (por exemplo: o modelo aprende a reconhecer e caracterizar drusas, para então ser capaz de diagnosticar DMRI) e uma segunda etapa em que o algoritmo é testado em um conjunto de dados desconhecido para avaliar o desempenho.[3,4] Entre essas técnicas de ML, o *deep learning* (DL) se destaca por desenvolver redes neurais artificiais profundas, com múltiplos níveis de abstração, onde as características específicas da tarefa não são pré-definidas por engenheiros humanos, mas podem ser aprendidas diretamente a partir dos dados. O algoritmo é treinado a partir de um banco de dados grande e pode ser diretamente testado em outro banco de dados desconhecido, gastando menos tempo nesse processo de aprendizagem.[4,5] A performance do algoritmo de DL melhora quanto maior a quantidade de dados apresentadas, enquanto nos algoritmos de ML a performance melhora a partir da qualidade das informações manualmente inseridas no treinamento.

A integração da IA no campo da medicina também não é um fenômeno recente. O MYCIN, desenvolvido na década de 1970 na Universidade de Stanford, foi o primeiro algoritmo criado para auxiliar no diagnóstico e tratamento de infecções bacterianas.[6] Desde então, a quantidade de algoritmos automatizados se multiplicou e sistemas mais avançados baseados em IA foram desenvolvidos, incluindo as escalas de predição de risco que atualmente são utilizadas na prática clínica.[7–9] A aplicação de algoritmos automatizados em Oftalmologia ganhou significativa atenção, principalmente nos últimos 5 anos, devido à utilização de grandes conjuntos de dados digitais provenientes de imagens na prática clínica. A retina se destacou como o campo mais promissor para a aplicação da IA devido ao grande potencial das imagens multimodais utilizadas para diagnóstico e monitoramento de doenças que podem afetar a visão de forma permanente.

A degeneração macular relacionada à idade (DMRI) é uma das principais causas de perda visual em todo o mundo e é descrita como uma interação de elementos metabólicos, funcionais, genéticos e ambientais.[10,11] A DMRI avançada é caracterizada por lesões que comprometem a mácula, como a atrofia geográfica (AG) na DMRI não exsudativa ou a neovascularização macular (MNV) na DMRI neovascular.[12] Nas últimas duas décadas, houve avanços significativos nas ferramentas de diagnóstico por imagem. A tomografia de coerência óptica (OCT) de domínio espectral tornou-se a modalidade de imagem padrão-ouro na DMRI. A OCT possibilitou a captação de milhões de pixels por imagem e o uso da IA pode auxiliar na extração máxima de informações de forma imediata.[13] Os algoritmos baseados em IA têm o potencial de quantificar biomarcadores com precisão, auxiliar no diagnóstico, prever a progressão da doença e auxiliar nas decisões de tratamento tanto para fins de estudos acadêmicos quanto na prática clínica. Deve-se enfatizar que o objetivo dessas novas tecnologias é uma otimização no suporte médico ao tratamento ao invés de substituição de profissionais oftalmologistas.

2 REVISÃO BIBLIOGRÁFICA

Estima-se que 288 milhões de pessoas sejam afetadas pela DMRI até 2040.[14] Cerca de 10-15% de todos os casos de DMRI avançam para DMRI neovascular e muitas vezes sofrem uma perda visual rápida e devastadora. Sendo assim, o advento do tratamento da DMRI neovascular por meio do uso intravítreo de inibidores do fator de crescimento endotelial vascular (VEGF) em 2006 foi um evento marcante no monitoramento da doença.[15,16] No entanto, a meia-vida desses medicamentos biológicos é curta e, no contexto do tratamento contínuo da DMRI, pode onerar de forma importante o paciente e o sistema de saúde.[17] Estudos clínicos como PULSAR, TENAYA e LUCERNE analisaram a eficácia do tratamento com anti-VEGF em regimes com intervalos mais prolongados para tentar minimizar este problema.[18,19] Além disso, os primeiros inibidores do sistema de complemento intravítreo foram aprovados pelo órgão regulatório americano “Food and Drug Administration” (FDA) em 2023 para tratar pacientes com atrofia macular (AM). Essa nova terapia representa uma evolução importante no tratamento desses pacientes, entretanto, pode trazer uma sobrecarga adicional significativa para os sistemas de saúde já saturados.[20]

O acompanhamento das patologias retinianas atualmente depende, principalmente, de parâmetros dicotômicos significando a avaliação subjetiva da presença ou ausência de biomarcadores específicos. Uma abordagem binária muitas vezes subestima a dinâmica dos biomarcadores e a natureza complexa de todas as condições retinianas, incluindo a DMRI. As abordagens multimodais, cada vez mais utilizadas na prática clínica, levam a uma enorme quantidade de informações para cada paciente em cada visita. No entanto, variações sutis como o crescimento da área de atrofia na AM ou o volume e a flutuação do fluido na DMRI neovascular são parâmetros difíceis de quantificar e comparar com os métodos tradicionais. Além disso, novos biomarcadores sub-clínicos estão se tornando cada vez mais relevantes, como a perda da camada de fotorreceptores consistente com a atenuação da zona elipsoide (ZE). Portanto, ferramentas avançadas de detecção e quantificação por IA podem auxiliar de maneira rápida e confiável o estadiamento clínico da doença na DMRI atrófica, assim como na neovascular.

A detecção precoce é fundamental no manejo das doenças retinianas, pois permite uma intervenção oportuna em caso de conversão para estágios da doença que ameacem a visão. A avaliação multimodal por imagens ainda é o padrão-ouro para identificar biomarcadores retinianos. Historicamente, a retinografia colorida desempenhou um papel importante no rastreamento das doenças da retina por ser uma técnica não invasiva e pela maior disponibilidade de dispositivos nos consultórios, incluindo o surgimento de dispositivos portáteis ou uso de *smartphones* para adquirir essas fotografias.[21] Devido à menor complexidade desta modalidade de imagem, algoritmos menos complexos são capazes de analisar e detectar biomarcadores como drusas, hemorragias e mobilização de pigmento e classificar o olho seguindo uma escala multi-classe (sem DMRI, precoce, intermediária ou avançada).[22,23] Um estudo prévio mostrou que a sensibilidade e especificidade da triagem de DMRI intermediária e avançada baseada em IA usando retinografia foi de 93,2% e 88,7%, respectivamente.[24] A autofluorescência surgiu como uma modalidade de imagem não invasiva capaz de detectar a emissão de luz de fluoróforos como a lipofuscina, e melhor identificar lesões como pseudo-drusas e atrofia.[25] Foram desenvolvidos algoritmos baseados em IA aplicados às imagens de autofluorescência, com o potencial de segmentar automaticamente as lesões maculares na AG.[26] No entanto, os equipamentos de autofluorescência não estão sempre presentes nas clínicas

oftalmológicas. Além disso, as interpretações de padrões de depósitos peri-lesionais podem ser subjetivas e nem sempre se correlacionarem de forma direta com a progressão da lesão atrófica, uma vez que as estruturas neurosensoriais, tais como os fotorreceptores, não são representadas pelo exame de autofluorescência.

A OCT é uma ferramenta de imagem também não invasiva capaz de visualizar microestruturas oculares em alta resolução por meio de interferometria de baixa coerência.[27] Ela fornece cortes transversais da retina, usando ondas de luz para criar imagens tridimensionais dos tecidos internos do olho.[28] A quantidade de informações obtidas de uma imagem de OCT aumenta de forma exponencial ao usar IA, devido à análise pixel a pixel.[29] A utilização de algoritmos robustos em imagens de OCT tem o potencial de diagnosticar e prever estágios avançados de doenças retinianas, bem como avaliar resposta ao tratamento e resultados visuais na DMRI. De Faw et al., do grupo Google, apresentaram o uso de algoritmos automatizados baseados em imagem de OCT na triagem de doenças retinianas e determinando a necessidade de encaminhamento terapêutico no hospital *Moorfields Eye*, em Londres. Um dos algoritmos apresentou recomendações de encaminhamento que atingiu ou excedeu o desempenho dos profissionais em saúde ocular para uma série de doenças retinianas.[30] Esses resultados devem ser avaliados dentro do contexto testado, mas levantam uma possibilidade que pode aumentar a acessibilidade em saúde ocular em áreas de desequilíbrio entre profissionais de saúde e pacientes. A utilização de algoritmos baseados em IA para a detecção de fluido retiniano em pacientes com DMRI também foi comparado com profissionais em saúde ocular e mostrou maior precisão, reforçando o poder dessas ferramentas de medição automatizadas.[31]

A angiotomografia de coerência óptica (OCT-A) é uma tecnologia que possibilitou visualizar a microvasculatura da retina de forma não invasiva e detalhada, tendo sido cada vez mais utilizada no diagnóstico e acompanhamento de doenças retinianas. A utilização de algoritmos de IA em imagens de OCT-A permite a segmentação automatizada de vasos sanguíneos, quantificação de áreas de não perfusão, bem como mensuração da área de neovascularização com alta precisão e rapidez.[32] Essas informações podem auxiliar na melhor caracterização das diferentes MNV na DMRI e sua aplicação em doenças vasculares como a retinopatia diabética têm ganhado cada vez mais importância.

A utilização de análises *post-hoc* constituem uma opção comum para validar e refinar os algoritmos de IA, utilizando dados previamente coletados em um estudo já encerrado. Entretanto, a utilização de banco de dados de vida real de larga escala, como o do projeto *Intelligent Research in Sight* (IRIS),[33] uma iniciativa da Academia Americana de Oftalmologia criada para promover pesquisas colaborativas e baseadas em grandes volumes de dados oftalmológicos, se tornam ferramentas ainda mais atraentes na avaliação prospectiva de sistemas de IA devido a diversidade populacional e, portanto, maior possibilidade de generalização. No entanto, uma limitação para utilizar esses bancos de dados internacionais está no fato de que no IRIS e em outros bancos de dados de vida real, a coleta de imagens ainda não foi integralizada a sistemas automatizados de IA, e além disso, a variabilidade de equipamentos e padrões de varredura utilizados representará um obstáculo importante na realização de uma análise de imagem uniforme.[34]

2.1 Modelos de inteligência artificial na OCT

As análises de imagens de OCT baseadas em IA geralmente dependem de diferentes métodos de DL, incluindo redes neurais convolucionais (CNNs). As CNNs exploram o fato de que os valores dos pixels adjacentes na imagem são correlacionados e se destacam na extração de características hierárquicas das imagens, tornando-as particularmente eficazes para a vasta quantidade de dados de imagem de alta resolução presentes na OCT.[35] No contexto da DMRI, os algoritmos de DL podem detectar automaticamente estruturas retinianas relevantes e realizar diversas tarefas, como segmentação das camadas da retina, identificação de focos hiper-refletivos e quantificação de fluidos.[36] A segmentação de camadas retinianas é um passo crítico na extração de informações das imagens de OCT. Os algoritmos de segmentação alimentados por IA empregam técnicas como U-Net, uma arquitetura de CNN adaptada para tarefas como a segmentação de camadas retinianas. De fato, uma segmentação precisa ajuda a identificar alterações típicas da doença como a perda da integridade da ZE, definida como segmentação descontínua da área entre o topo da ZE e a borda externa da zona de interdigitação, e a ruptura da camada do EPR, permitindo o diagnóstico e avaliação da progressão da doença.[37,38]

As redes adversárias generativas (*generative adversarial network*-GANs) são um método de aprendizado profundo que consiste em duas redes neurais, um gerador e

um discriminador, trabalhando automaticamente em conjunto para produzir dados sintéticos de alta qualidade. Na análise das imagens de OCT na DMRI, as GANs podem auxiliar na ampliação de dados, diminuindo o desafio de conjuntos de dados desbalanceados, e para treinar modelos que identificam anormalidades na OCT sem a necessidade de segmentação manual, que demanda um longo período de tempo.[39] As imagens geradas por GANs também podem ser aplicadas para a redução de ruídos nas imagens de OCT.[40]

A capacidade do modelo de fundação de analisar vastos conjuntos de dados para o reconhecimento de variações sutis pode desempenhar um papel importante na detecção precoce de doenças retinianas. Um modelo de fundação baseado em aprendizado não supervisionado por humanos (auto-supervisionado) foi recentemente descrito como capaz de treinar em imagens retinianas não padronizadas e mostrar um desempenho satisfatório na detecção de doenças oculares e previsão de doenças sistêmicas com base em imagens retinianas. Além disso, esses modelos prometem democratizar o acesso a algoritmos de IA na área médica e acelerar sua implementação na prática clínica, fornecendo um recurso publicamente disponível.[41]

2.2 IA em OCT na DMRI neovascular

A espessura macular central é uma ferramenta de medição automatizada, há anos disponível nos aparelhos de OCT e amplamente utilizada como desfecho e/ou guia para decisões de tratamento em muitos ensaios clínicos.[42,43] No entanto, a mensuração da espessura macular não distingue entre camadas neurossensoriais, compartimentos de fluidos retinianos e descolamentos do epitélio pigmentar. Além disso, muitas vezes as alterações não estão perfeitamente alinhadas ao centro da mácula doente. Estudos anteriores mostraram uma correlação fraca entre espessura macular e acuidade visual, bem como entre espessura macular e volumes de fluidos retinianos.[44,45]

Os algoritmos baseados em IA desenvolvidos para OCT na DMRI envolvem a identificação de biomarcadores como drusas, pontos focais hiper-refletivos, material hiper-refletivo sub-retiniano (SRHM), quantificação de volume de fluido intrarretiniano (FIR), fluido subretiniano (FSR) e o descolamento do epitélio pigmentar da retina (DEP), e segmentação das camadas retinianas. Recentemente, a segmentação e

mensuração da espessura da ZE e da camada nuclear externa da retina (contemplando os segmentos internos dos fotorreceotores) têm ganhado destaque no monitoramento da DMRI.[3,4,12,46] Apesar da importância de todos os biomarcadores de alta ordem na classificação e progressão da doença, análises *post-hoc* do estudo TREND (Treat and Extend) e do conjunto de dados Fight Retinal Blindness! (FRB) usando DL e ML mostraram que o fluido retiniano ainda é o biomarcador anatômico mais importante para prever a atividade da doença, a demanda de tratamento e os resultados visuais na DMRI neovascular.[47,48] De fato, análises recentes mostraram que não apenas a localização do fluido é importante para a progressão da doença, mas a flutuação e dinâmica dos fluidos em cada compartimento tem um impacto significativo nos resultados.[48] Maior volume de FIR e maior DEP foram associados a piores resultados visuais, apesar de FIR ser o tipo de fluido com resposta mais rápida à terapia anti-VEGF. FSR mostrou uma resolução mais lenta, intuitivamente levando a um maior número de injeções durante o primeiro ano em um regime *pro-re-nata*, no entanto, nenhuma correlação significativa com piores resultados visuais foi encontrada.[47,49,50] A presença de FSR predominante fora do 1 mm central da fóvea pode ter relação com esse achado. Isso sinaliza a necessidade de reavaliação no acompanhamento dos pacientes em tratamento com anti-VEGF, incluindo uma correlação rigorosa entre estrutura/função. No longo prazo, os volumes de fluido retiniano e a acuidade visual são correlacionados, indicando um processo neurodegenerativo concomitante. Além disso, apesar do tratamento "regular", a maioria dos pacientes com DMRI neovascular está propensa a desenvolver fibrose sub-retiniana (FS) e atrofia macular (AM) ao longo do tempo.[51,52] Maiores quantidades e flutuações no volume de fluido, a presença de material hiperrefletivo sub-retiniano e o tipo de neovascularização foram correlacionados com o desenvolvimento de atrofia ou fibrose.[49,53,54] A interrupção da ZE e a perda do EPR também foram fortemente correlacionadas com o desenvolvimento de atrofia macular.[55] Esses achados sugerem que uma avaliação detalhada das mudanças na ZE associadas ao comportamento dos fluidos retinianos podem auxiliar na compreensão dos desfechos tardios. Algoritmos de IA desenvolvidos para avaliar qualitativamente, quantitativamente e espacialmente os fluidos nos tecidos retinianos e sub-retinianos tem o potencial de permitir uma análise refinada dos efeitos desses fluidos nos desfechos clínicos.

Apesar da maior ênfase dada à quantificação dos fluidos retinianos, objetivo do estudo dessa tese, algoritmos baseados em IA capazes de detectar e quantificar outros biomarcadores na DMRI estão em constante desenvolvimento. Para o diagnóstico da DMRI e possível progressão da doença em estágios iniciais, as drusas continuam sendo o biomarcador de referência. Sendo assim, vários algoritmos capazes de segmentá-las e quantificá-las na OCT com alta acurácia foram desenvolvidos.[56,57] A evolução da DMRI inicial e intermediária para estágios avançados como a neovascularização e atrofia constituem material de constante estudo, afim de tentar evitar esse desfecho desfavorável. A presença de pontos hiper-refletivos na retina está relacionada com a progressão da DMRI intermediária para AG.[58] Apesar da fisiopatologia dessas lesões não serem completamente compreendida, na DMRI esses pontos estão relacionados com células da microglia, depósitos de lipídios, migração do EPR e fotorreceptores.[59] Bogunovic *et al* descreveu um algoritmo de DL para segmentar os pontos hiper-refletidos a fim de predizer a evolução da doença.[57] A presença de SHRM está associada à neovascularização na DMRI e a quantificação automatizada de SHRM nos dados do estudo OSPREY evidenciou uma associação entre o desfecho visual e a diminuição do volume de SHRM durante o acompanhamento.[60]

Como mencionado previamente esses algoritmos possibilitam a análise rápida de um volume de dados muito grande, provenientes da gigantesca quantidade de pixels oferecidas pela OCT. Para que estes avanços sejam definitivamente incorporados à prática clínica, entretanto, é fundamental que sejam criteriosamente validados em amostras representativas de pacientes com DMRI. Idealmente estas amostras devem incluir pacientes com características diversas, incluindo etnia, localização geográfica e achados presentes em amostras de vida real, achados estes que frequentemente são excludentes para pacientes de estudos multicêntricos. Diante desses fatos impõem-se estudos que utilizem IA para a avaliação de pacientes com estas características. O objetivo desta tese é, assim, contribuir para a avaliação e validação de algoritmos de IA que analisem os efeitos dos fluidos retinianos nos desfechos clínicos de pacientes com DMRI tratados com medicamentos anti-VEGF.

3 OBJETIVOS

O objetivo principal deste trabalho foi avaliar o uso da ferramenta de quantificação do fluido retiniano na OCT, baseada em IA, no acompanhamento de pacientes com DMRI neovascular.

Os objetivos de cada estudo foram:

- Prever a acuidade visual, os resultados morfológicos e as necessidades de tratamento com o anti-VEGF na DMRI, usando a quantificação de fluidos por IA em uma coorte de vida real.

- Quantificar a perda de ZE durante a terapia anti-VEGF e correlacionar esses achados com a atividade da doença usando algoritmos baseados em inteligência artificial.

- Avaliar a correlação entre quantidade de fluido e acuidade visual, bem como a progressão da doença para estágios mais avançados da doença como FS e AM testando o algoritmo em uma coorte brasileira**.**

4 MATERIAL E MÉTODOS

Foram avaliados retrospectivamente dados clínicos e imagens da OCT de pacientes do banco de dados do FRB! Registry de Zurique, (que é um banco de dados internacional dedicado ao monitoramento de resultados clínicos em pacientes portadores de doenças retinianas, como a DMRI e o edema macular diabético) e de uma coorte de pacientes atendidos em um hospital oftalmológico terciário,o Instituto da Visão de Belo Horizonte, Brasil de 2012 a 2022. Dados demográficos e do exame oftalmológico registrados em prontuário médico foram coletados. Os dados clínicos colhidos contemplaram acuidade visual, que quando adquirida com tabela de Snellen foi posteriormente convertida para ETDRS, biomicroscopia e fundoscopia. As imagens da OCT dos pacientes foram transferidas post-hoc para o Laboratório de Análise de Imagens Oftálmicas (OPTIMA) da Universidade de Medicina de Viena em um formato pseudonimizado (formato em que identificadores diretos, como nomes, data de nascimento e números de identificação, foram substituídos por pseudônimos,

protegendo a identidade dos indivíduos) para, então, serem realizadas as análises baseadas em IA.

As análises apresentadas nesse estudo foram realizadas em conformidade com a declaração de Helsinque e foi obtida aprovação pelos respectivos Comitês de Ética da Universidade de Medicina de Viena (EK Nr: 1246/2016) e da Universidade Federal de Minas Gerais (CAAE: 58850622.4.0000.5149). O parecer consubstanciado do comitê de ética está anexado a essa tese na seção de apêndice.

A detecção e a quantificação dos fluidos foram realizadas em cada *B-scan* de cada imagem de OCT com um método de segmentação baseado em DL. Foram incluídas nos três estudos dessa tese imagens de OCT do Heidelberg Spectralis, Heidelberg Engineering, Alemanha, com padrão de varredura de pelo menos 19 B-scans. Cada pixel foi classificado com uma CNN em várias escalas e recebeu uma probabilidade de pertencer a uma das quatro classes: pano de fundo, retina, FIR ou FSR. Além disso, o DEP foi identificado como uma região entre o EPR e a membrana de Bruch, que foi segmentada automaticamente usando os algoritmos de referência de Iowa.[61]

Os desfechos de AM e FS foram avaliados pelo médico responsável em cada visita e coletados dos prontuários. Essa avaliação foi baseada em fundoscopia, imagens de OCT, fotografia de fundo de olho e autofluorescência, quando disponíveis.[62]

A presença de AM e FS no *baseline* foi critério de exclusão para os 3 estudos. A perda do EPR associada à perda de fotorreceptores da retina com mais de 250 µm de diâmetro, detectada na área central de 3 mm, foi excluída como AM. Imagens de OCT mostrando material hiper-refletivo multilaminar compacto situado acima ou abaixo do EPR na área central de 3 mm foram excluídas como FS.[62]

A metodologia envolvida em cada estudo está descrita em detalhes nos respectivos artigos anexados a essa tese. As análises estatísticas foram realizadas de acordo com o objetivo de cada estudo. Modelos de regressão linear multivariável e modelo de regressão longitudinal em painel foram utilizados para correlacionar o volume de fluido com a melhor acuidade visual corrigida, afinamento e perda da ZE e desenvolvimento de AM e SF. A comparação entre o impacto do volume de fluidos na mácula por subgrupo (grupo de volume mais alto versus grupo de volume mais baixo) na perda da ZE foi realizada usando testes de Wilcoxon rank-sum com intervalos de confiança obtidos por *bootstrap.* Para todos os testes estatísticos, um valor de p abaixo de 0,05

foi considerado significativo. Os testes utilizados e a metodologia de cada estudo estão detalhadamente descritos nos respectivos artigos.

5 RESULTADOS

Os resultados desta tese foram reportados no formato de 3 artigos principais. Os resultados de cada um dos estudos serão brevemente pontuados após o artigo anexado a esta tese. O artigo 1 intitulado **“Approved AI- based fluid monitoring to identify morphological and functional treatment outcomes in neovascular age-related macular degeneration in real- world routine (FRB!)”,** foi publicado no British Journal of Opthalmology doi: 10.1136/ bjo-2022-323014.

Artigo 1

Clinical science

Approved AI-based fluid monitoring to identify morphological and functional treatment outcomes in neovascular age-related macular degeneration in real-world routine (FRB!)

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ABSTRACT

Aim To predict antivascular endothelial growth factor (VEGF) treatment requirements, visual acuity and morphological outcomes in neovascular age-related macular degeneration (nAMD) using fluid quantification by artificial intelligence (AI) in a real-world cohort.

Methods Spectral-domain optical coherence tomography data of 158 treatment-naïve patients with nAMD from the Fight Retinal Blindness! registry in Zurich were processed at baseline, and after initial treatment using intravitreal anti-VEGF to predict subsequent 1-year and 4-year outcomes. Intraretinal and subretinal fluid and pigment epithelial detachment volumes were segmented using a deep learning algorithm (Vienna Fluid Monitor, RetInSight, Vienna, Austria). A predictive machine learning model for future treatment requirements and morphological outcomes was built using the computed set of quantitative features.

Results Two hundred and two eyes from 158 patients were evaluated. 107 eyes had a lower median (≤7) and 95 eyes had an upper median (≥8) number of injections in the first year, with a mean accuracy of prediction of 0.77 (95% CI 0.71 to 0.83) area under the curve (AUC). Best-corrected visual acuity at baseline was the most relevant predictive factor determining final visual outcomes after 1 year. Over 4 years, half of the eyes had progressed to macular atrophy (MA) with the model being able to distinguish MA from non-MA eyes with a mean AUC of 0.70 (95% CI 0.61 to 0.79). Prediction for subretinal fibrosis reached an AUC of 0.74 (95% CI 0.63 to 0.81).

Conclusions The regulatory approved AI-based fluid monitoring allows clinicians to use automated algorithms in prospectively guided patient treatment in AMD. Furthermore, retinal fluid localisation and quantification can predict long-term morphological outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Spectral-domain optical coherence tomography (OCT) is the imaging gold standard in the management of neovascular age-related macular degeneration (nAMD). Artificial intelligence (AI) provides a highly precise quantification of all retinal fluid compartments based on OCT scans.

WHAT THIS STUDY ADDS

⇒ This study provides robust evidence that a validated and regulatory-approved automated AI-based fluid monitoring tool is able to predict antivascular endothelial growth factor (VEGF) treatment requirements in a 1-year follow-up and forecast late-stage outcomes in nAMD patients in a real-world cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results from our study are a promising step towards OCT-guided prediction of optimal treatment intervals in anti-VEGF therapy of nAMD and identification of limitations of long-term treatment.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of legal blindness in developed countries with a profound impact on quality of life in affected individuals.[1] Despite substantial advances in diagnostic and therapeutic modalities in neovascular AMD (nAMD), worldwide vision loss increased by 23% for blindness and 24% for severe vision loss between 2005 and 2015, compromising 900 million individuals in total.[2] Retinal fluid is a critical biomarker in the assessment of nAMD disease activity and resolution of retinal fluid by intravitreal vascular endothelial growth factor (VEGF) inhibition represents the current standard of care.[3 4] However, no therapeutic regimen established in clinical practice fully satisfied therapeutic standards while avoiding over and undertreatment. Furthermore, real-world studies evaluating anti-VEGF therapy in nAMD have reported fewer anti-VEGF injections and worse visual outcomes compared with clinical trials.[5]

Artificial intelligence (AI) with deep-learning-based image segmentation methods provides a highly precise and reproducible quantification of all retinal fluid compartments on a pixel base level.[6 7] Fluid images are conventionally analysed using parameters such as central retinal thickness

(CRT) or binary qualitative manner (presence or absence of fluid). However, detailed quantitative measurements of retinal fluid and localisation in each compartment are being recognised as clinically relevant biomarkers in nAMD.[7] Recently developed AI algorithms precisely measure fluid volumes based on optical coherence tomography (OCT) B-scans, specifying the amount and dynamic course of intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED) separately and during long-term follow-up.[3 8]

However, while fluid responds to timely therapy with efficient resolution followed by stabilisation or even improvement in visual acuity (VA), other features seen during the disease progression are persistent and advancing in nature such as macular atrophy (MA) and subretinal fibrosis (SF). The triggers of MA pathophysiology remain unclear[9] and SF is also driven by multifactorial risk factors.[10] Moreover, a neovascular lesion can eventually become fibrotic despite optimal anti-VEGF treatment.[11] The prediction of late nAMD stages by fluid-based biomarker identification at earlier stages can predefine prognosis and improve treatment strategies in clinical routine.[12]

There are few studies using AI to predict anti-VEGF treatment burden, most of them using data from clinical trials.[13 14] The purpose of our study is to investigate the value of the first medical device regulation (MDR) (European Union) 2017/745 approved AI-based fluid monitoring tool to predict anti-VEGF treatment requirements, VA and late-stage morphological outcomes in nAMD patients in a real-world cohort.

METHODS

Participants

This study represents a post hoc analysis of the Fight Retinal Blindness! Registry (FRB!) data from the Department of Ophthalmology at the University Hospital Zurich, Switzerland.

Four hundred and thirty eyes from 215 consecutive patients with nAMD were initially evaluated and automatically filtered using the following inclusion and exclusion criteria: only gradable scans of treatment-naïve nAMD patients with a minimum of a 1-year follow-up and treated with aflibercept or ranibizumab were included. Exclusion criteria were defined as ungradable scans and/or presence of MA or SF at baseline. Two hundred and thirty-five eyes were automatically included. Hereafter, a manual validation was performed by the authors (VM and PF) to exclude patients with other concomitant macular disease or presence of MA and SF at baseline unstated in the routinely collected data. Thirty-three eyes were excluded at this stage, 1 with angioid streaks, 1 with vitreo-macular traction, 1 with macular hole and 30 with perifoveal fibrosis and/or perifoveal atrophy. The final sample consisted of 202 eyes from 158 patients (figure 1). Spectral-domain OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) volumes were processed at baseline and after the first two initial anti-VEGF treatments (processed on the day of the third injection) to predict the subsequent 1-year treatment requirement. Initial treatment was defined as 2 monthly injections in this analysis, and not 3 monthly injections usually described as a loading dose due to inhomogeneous follow-up intervals beyond the third injection, as common in a real-world practice cohort. Patient's treatment frequency was clustered into two groups: one with higher retreatment frequencies, defined as more than seven injections in the 12 months period, and the other group with lower retreatment frequencies defined as equal or less than seven injections in the 12 months period. A 4-year follow-up analysis was done to predict SF or MA. The negative samples were eyes that did not present MA or SF in the OCT scans in the fourth-year follow-up.

Determination of VA, MA and SF

VA was recorded as the number of letters read on the logarithm of the minimum angle of resolution VA chart. VA score was considered the best reading whether uncorrected, corrected or pinhole.[15]

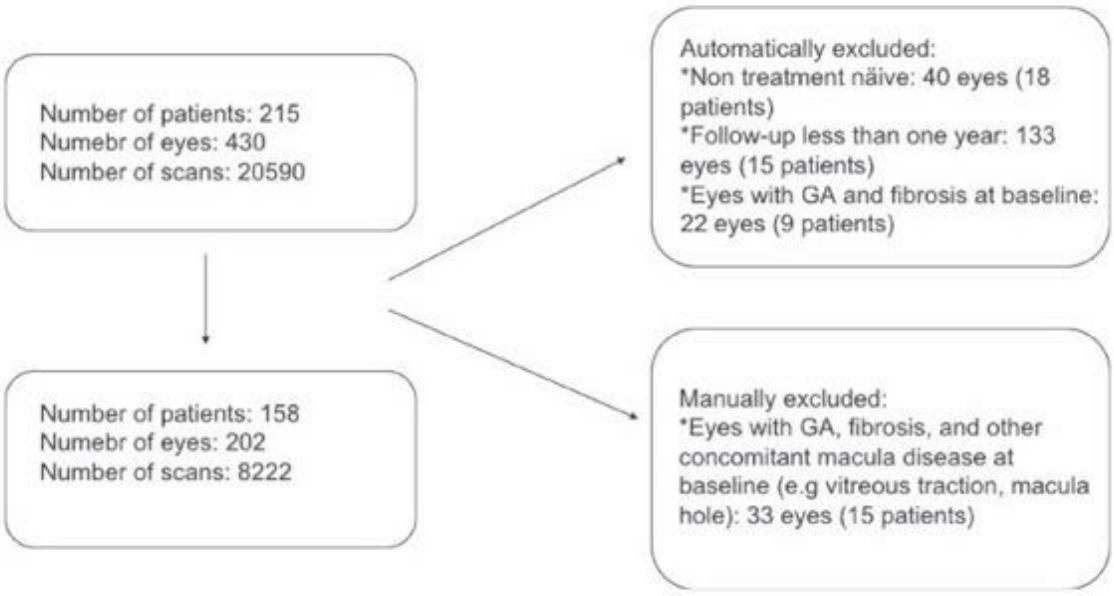

Figure 1 Automatically and manually patient's exclusion criteria. GA, geographical atrophy.

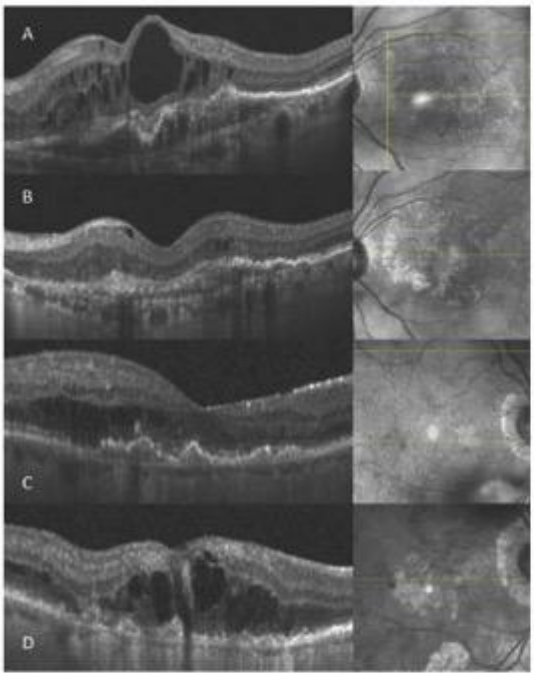

Figure 2 Examples of fibrosis and macula atrophy development over time, respectively. (A): Baseline. (B): After 4 years of follow up of the patient in (A). (C): Baseline. (D): After 3 years of follow-up of the patient in (C).

MA and SF were graded by the attending physician at each visit on a standardised chart into FRB! dataset. This assessment was based on either OCT images, funduscopy, fundus photography and on fundus autofluorescence images when available.[16] Retinal pigment epithelium (RPE) loss with associated retinal photoreceptor loss more than 250 µm in diameter detected at the central 3 mm area were excluded as MA. OCT images showing a compact multilaminar hyperreflective material situated above or below the RPE in the central 3 mm area was excluded as SF.[17] Figure 2 shows examples of SF and MA development over time.

Automated quantification of retinal fluid

IRF, SRF and PED were segmented using a deep learning convolutional neural network (Vienna Fluid Monitor, RetInSight, Vienna, Austria), which has been validated extensively internally and externally and has been published previously.[18] The AI-based algorithm segments the retina in a pixel-wise manner and localises the fluid pixels between the subcategories IRF, SRF, PED and normal tissue. The number of assigned pixels to each fluid subcategory can be computed into an estimation of fluid volumes in nanoliters and their respective location.

To compute CRT, retinal layers were segmented with a graph-theoretic approach using the Iowa Reference Algorithms.[19] We defined the boundaries of the CRT to be the internal limiting membrane and the surface of the RPE. Subsequently, a set of quantitative features consisting of CRT and fluid compartments were computed across the three central subfields (1 mm, 3 mm and 6 mm) to describe retinal pathomorphology both quantitatively and spatially.

Finally, using the computed set of features, several predictive models were built using a machine learning classifier and were evaluated with a 10-fold patient-level cross-validation. For this purpose, random forest models were built for treatment requirements during follow-up, VA, consecutive SF and MA development. Random forest was grown with 2000 trees, minimum node size of 1 and 6 features randomly sampled as candidates at each split of a tree. Finally, class weighting was performed according to their prevalence.

Development of the prediction

For every OCT volumetric raster scan, with at least 19 B-scans, a total volume of IRF, SRF and PED in the central 1 mm, 3 mm and 6 mm were computed. Additionally, CRT was assessed resulting in a total of 10 structural features per OCT volume. The features extracted from the baseline OCT were concatenated with those of the OCT after initial treatment, and further concatenated the difference between the OCT features at those two time points. Finally, best-corrected VA (BCVA) at baseline and after initial treatment as well as the difference were included. Thus, 30 structural features and 3 functional features were used as the 33-dimensional vector input to the prediction models.

RESULTS

Prediction of treatment requirement

Two hundred and two eyes from 158 patients were evaluated for a 1-year period following the initial treatments (months 3–15 from baseline), correlating fluid biomarkers with resulting treatment patterns based on OCT images. The treatment intervals ranged from 4 to 13 weeks over 1 year after the initial treatments. A total of 107 eyes had a lower median frequency with 7 or less injections, and 95 eyes had an upper median of 8 or more injections over the 12 months period. The model identified the two groups (lower and upper median) based on number of injections with a mean accuracy of 0.77 (95% CI 0.71 to 0.83) area under the curve (AUC) (figure 3). The sensitivity and specificity were 0.61 and 0.84, respectively. Detailed analysis of biomarkers for predicting treatment requirement confirmed that the amount of SRF after initial treatments and at baseline and in the central 3 mm area were the two most important predictive factors, respectively (figure 4A). PED in the central 6 mm and 3 mm areas also played a role for an increased number of injections during the first year.

Development of MA and SF

For predicting MA and SF, the analysis was extended to 4 years of follow-up. One hundred and thirty eyes from 104 patients were graded for MA development over 4 years whereof 61 eyes (46,9%) developed MA. The model was able to accurately distinguish MA from non-MA eyes about 70% of the time, mean accuracy of 0.70 (95% CI 0.61 to 0.79) AUC. Atrophy development was more related to functional features: VA after the two loading doses and at baseline, respectively, followed by morphological features: IRF in the central 3 mm after loading injections and in the central 1 mm at baseline (figure 4B). SRF had less relevance as a biomarker predicting developing central atrophy, however, if present in the central 1 mm and at baseline SRF may increase the risk.

SF developed in 34 of 134 eyes from 109 patients (25%) within 4 years. The model was able to accurately predict SF about 74% of the time, mean accuracy of 0.74 (95% CI 0.63 to 0.81) in the AUC (figure 4C). The gradings for MA and SF were extracted from the FRB! records and graded by the treating physician. The

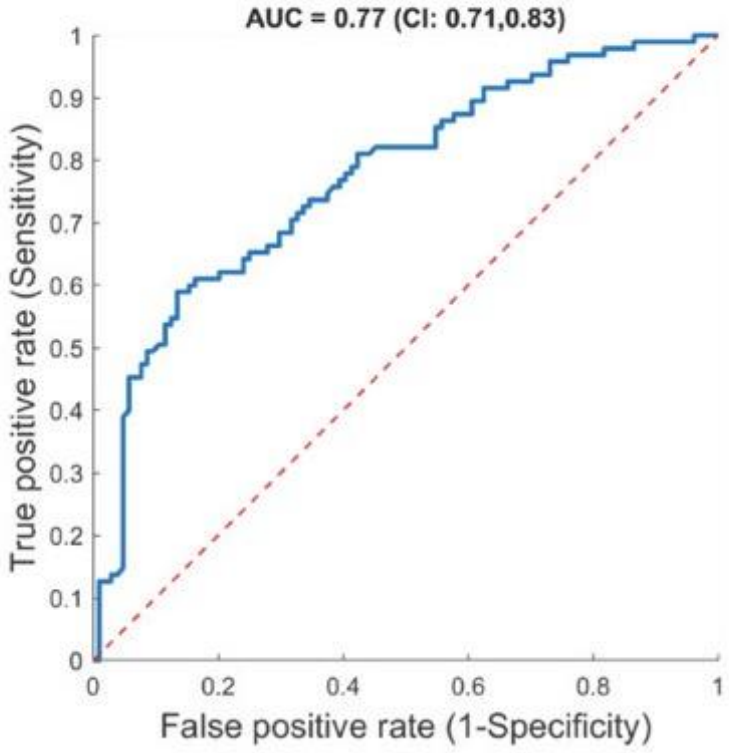

Figure 3 Receiver operating characteristic curve analysing area under the curve (AUC) for predicting treatment needs.

presence of each feature was graded independently from each other. Retinal fluid volumes in the entire central 6 mm area were found to be important in developing SF. IRF in the central 6 mm area at baseline was the most important predictor identified. VA after loading doses also proved to be relevant, followed by the change in IRF volumes at baseline and after the initial treatment. SRF showed to be less critical than IRF for the development of SF.

Prediction of VA development

For prediction of VA outcomes during 1 year of follow-up, we analysed the total sample size of 202 eyes from 158 patients. The mean and SD of BCVA for the difference between prediction and ground truth in this analysis were 0.1 and 9.2 letters, respectively. The change between BCVA at baseline and after initial treatment was the most important parameter to predict 1-year visual outcomes. VA at baseline was the most relevant individual feature with good prognostic accuracy in the automated analysis, since the prediction had a high correlation with the VA measurements obtained in practice (figure 5). Correlation coefficient was 0.77 and R-squared was 0.57.

DISCUSSION

This study provides evidence that a validated and regulatory-approved automated AI algorithm for macular fluid quantification provides insights from routine clinical practice and is able to predict treatment requirements in a 1-year follow-up and forecast the late-stage morphological development of nAMD in a 4-year follow-up based on conventional OCT images.

First, there is a controversial debate among experts about the management of different fluid compartments within the retina. Particularly regarding SRF, the correlation between treatment frequency and the impact of SRF quantity in the central macular region was previously highlighted in a randomised controlled trial (RCT) analysis.[20] The FLUID study (a comparison of treatment regimens using ranibizumab: Intensive [resolution of intra- and subretinal fluid] vs relaxed [resolution of primarily intraretinal fluid] treatment) concluded based on conventional central CRT values that SRF must not be targeted to reach SRF reduction while accurate SRF volume quantification using AI proved that with increasing SRF amounts BCVA loss will occur. In contrast to the FLUID results, the current real-world study reinforces that SRF in the central macula is the key factor to predict the number of anti-VEGF injections performed in clinical practice to control disease activity in a 1-year follow-up. Yet, the fact that clinicians are used to recognise and treat SRF does not necessarily imply that SRF extinction is needed for superior outcomes, but merely reflects 'treat all fluid' protocols. Despite reflecting a higher number of injections, the presence of SRF at baseline has been related to better visual outcomes when compared with IRF and PED.[21] It has been observed that not only fluid location, but also the dynamics of fluid fluctuation play a crucial role in the development of end-stage complications in nAMD.[6 22] Moreover, the presence of PED in the central 1 mm and 3 mm areas was additional key predictors of treatment frequency in our study, however, with less impact than SRF and a stronger correlation with worse visual outcomes.

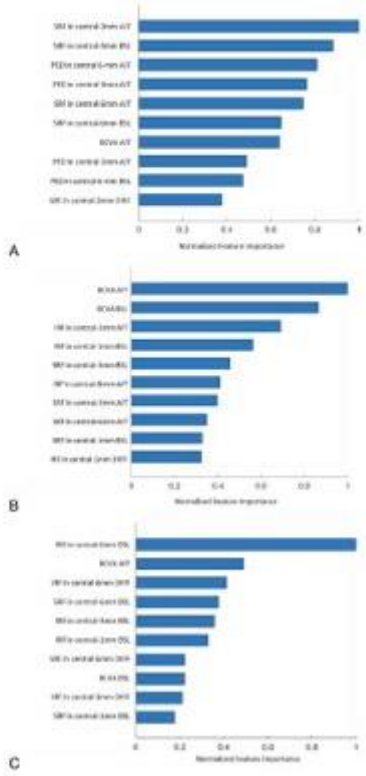

Figure 4 Ten-most important features for the prediction of (A) treatment requirement in 1-year follow up, (B) geographical atrophy development in 4 years follow-up and (C) fibrosis development in 4 years follow up. BSL, baseline; VA, visual acuity; DIFF, difference between baseline and after initial treatment; IRF, intraretinal fluid; AIT, after initial treatment (4 weeks after two anti-VEGF injections); PED, pigment epithelial detachment; SRF, subretinal fluid; VEGF, vascular endothelial growth factor; BCVA, best-corrected visual acuity.AIT, after initial treatment (4 weeks after two anti-VEGF injections); BCVA, best-corrected visual acuity; BSL, baseline; DIFF, difference between baseline and after initial treatment; IRF, intraretinal fluid; PED, pigment epithelial detachment; SRF, subretinal fluid; VA, visual acuity; VEGF, vascular endothelial growth factor.

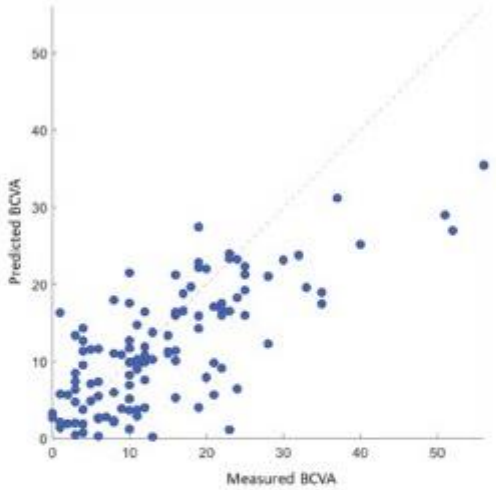

Figure 5 Scatter plot showing a close correlation of automated measurement with the ground truth measurement of best-corrected visual acuity (BCVA). VA, visual acuity.

As previously postulated, VA outcomes were dominantly influenced by VA at baseline and after initial treatment.[23–25] Clinical trials such as the CATT study and previous published manuscripts demonstrate this association, however, without quantification of fluid volumes. In a previous paper, we demonstrated that fluid volumes in each compartment impact BCVA independently of the drug and regimen with more fluid for each compartment leading to more visual loss.[26] Other studies showed that it is mostly IRF which reduces retinal function, as compared with SRF, yet this impact also depends on the volume. Although there is still no clear explanation for this common association, we believe that retinal fluid volumes play an important role in the loss of photoreceptor integrity and that the latter is strongly correlated with visual outcomes. Further studies are needed to better address these associations.

The lack of early functional recovery shows the importance of timely intervention at the beginning of the neovascular development with a rapid reduction of MNV activity to enable beneficial functional response to anti-VEGF treatment in the visual prognosis. The prognostic predominance of VA compared with the individual fluid condition at first presentation related to VA outcome is therefore not contradictory to the postulate that fluid is the event that initiates vision loss. The literature provides convincing evidence that VA loss occurs in presence of MNV activity and that retinal function may be irreversibly lost within weeks of delayed referral and treatment.[27–29] We have shown a tight correlation of IRF and BCVA loss and particularly persistent functional deficit when IRF persists during the loading dose referred to as degenerative fluid rather than active exudation.[30]

Real-world observations usually show lower injection frequencies compared with RCTs. The lower number of anti-VEGF injections poses the risk of an undertreatment resulting in poorer visual outcomes in nAMD.[31] The fluid monitor tool was able to distinguish these two groups of higher and lower retreatment need a priori and suggests a functional benefit when used in routine clinical practice.

The magnitude of reduction of CRT from baseline, a semiquantitative measurement for retinal fluid, at 12 months increased linearly with an increasing number of anti-VEGF injections as VA improved concomitantly.[27] Our group provided proof of principle that retinal fluid volumes as measured by AI-based tools are more precise parameters for evaluating disease activity in nAMD than CRT.[32]

We found 25.3% of eyes developing SF after 4 years of follow-up. SF development has been described in an even higher percentage (40%–45%) in nAMD patients from a 2 years follow-up RCT.[30] This difference could be related to more restrictive eligibility criteria and specific reading centre skills to analyse each image in clinical trials. In our study, the presence of IRF in the central 6 mm of the macula at baseline was the major feature related to SF development. This finding relates to using AI for capturing overall disease activity in nAMD, while

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Os principais resultados desse estudo foram descritos a seguir:

- Foram avaliados 202 olhos de 158 pacientes.

- 107 tiveram uma média mais baixa (≤7) e 95 olhos tiveram uma média mais alta (≥8) de injeções intravítreas para o tratamento no primeiro ano - precisão média da previsão de 0.77 (95% CI 0.71 to 0.83) área sob a curva ROC (AUC). (Figura 3 do artigo 1)
- FSR após o início do tratamento e no *baseline* foram os dois principais biomarcadores preditivos de resposta ao tratamento. (Figura 4 do artigo 1)
- A melhor acuidade visual corrigida no *baseline* foi o fator preditivo mais relevante para determinar os resultados visuais após 1 ano.
- Ao longo de 4 anos, 46,9% dos olhos progrediram para atrofia macular (AM), tendo o modelo sido capaz de distinguir olhos com AM de olhos sem AM com AUC de 0,70 (IC 95% 0,61 a 0,79).
- O desenvolvimento da atrofia esteve mais relacionado com as caraterísticas funcionais: acuidade visual após as duas doses de carregamento e no *baseline*, respectivamente, seguido de caraterísticas morfológicas: FIR nos 3 mm centrais após o tratamento inicial e no 1 mm central no *baseline* (Figura 4 do artigo 1).
- A predição de FS atingiu uma AUC de 0.74 (95% CI 0.63 to 0.81). FIR foi o principal biomarcador de evolução para FS. (Figura 4 do artigo 1)

Para uma melhor compreensão do impacto do FIR, FSR e DEP na acuidade visual e na evolução para atrofia macular, seria desejável analisar também informações sobre a integridade estrutural da retina neurosensorial ao longo do acompanhamento. Considerando estas demandas, um novo estudo foi planejado, com o objetivo de avaliar a eventual correlação do volume de fluido em diferentes compartimentos da retina com a integridade dos fotorreceptores e EPR. O artigo 2 a seguir intitulado **"Correlation of retinal fluid and photoreceptor and RPE loss in neovascular AMD by automated quantification, a real-world FRB! Analysis"** publicado recentemente na Acta Ophthalmologica.

Artigo 2

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ORIGINAL ARTICLE

Acta Ophthalmologica

Correlation of retinal fluid and photoreceptor and RPE loss in neovascular AMD by automated quantification, a real-world FRB! analysis

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Abstract

Purpose: To quantify ellipsoid zone (EZ) loss during anti-VEGF therapy for neovascular age-related macular degeneration (nAMD) and correlate these findings with nAMD disease activity using artificial intelligence-based algorithms.

Methods: Spectral domain optical coherence tomography (Spectralis, Heidelberg Engineering) images from nAMD treatment-naïve patients from the Fight Retinal Blindness! (FRB!) Registry from Zürich, Switzerland were processed at baseline and over 3 years of follow-up. An approved deep learning algorithm (Fluid Monitor, RetInSight) was used to automatically quantify intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED). An ensemble U-net deep learning algorithm was used to automated quantify EZ integrity based on EZ layer thickness. The impact of fluid volumes on EZ thickness and late-stages outcomes were calculated using Wilcoxon rank-sum tests, a linear mixed model and a longitudinal panel regression model.

Results: Two hundred and eleven eyes from 158 patients were included. The mean±SD EZ loss area in the central 6 mm was 1.81±2.68 mm^2 at baseline and reached 6.21±6.15 mm^2 at month 36. Higher fluid volumes (top 25%) of IRF and PED in the central 1 and 6 mm of the macula were significantly associated with more advanced EZ thinning and loss compared to the low fluid volume subgroup. The high SRF subgroup in the linear regression model showed no statistically significant association with EZ integrity in the central macula; however, the longitudinal analysis revealed an increased EZ thickness with no additional loss.

Conclusions: Intraretinal fluid and PED volumes and their resolution pattern have an impact on alteration of the underlying EZ layer. AI-supported quantifications are helpful in quantifying early signs of macular atrophy and providing individual risk profiles as a basis for tailored therapies for optimized visual outcomes.

KEYWORDS
anti-VEGF, artificial intelligence, geographic atrophy, image analysis, machine learning, neovascular AMD, optical coherence tomography, photoreceptor, retina

1 | INTRODUCTION

Optical coherence tomography (OCT) is the gold standard image modality for diagnosing and evaluating disease activity in neovascular age-related macular degeneration (nAMD) (Schmidt-Erfurth et al., 2017). Acquiring OCT volumes with high resolution enables a highly accurate identification of biomarkers for retinal diseases including not only fluid volumes, but also precise photoreceptors layers segmentation (Schmidt-Erfurth & Waldstein, 2016; von der Emde et al., 2023). Each OCT volume contains enormous amounts of data. Thus, artificial intelligence (AI)-based algorithms working as a tool to analyse many relevant biomarkers on OCT images open a new horizon for a more precise diagnostic and treatment approach in nAMD (Coulibaly et al., 2023; Keenan et al., 2021).

Anti-angiogenic therapy and in particular, anti-vascular endothelial growth factor (Anti-VEGF) are the current standard of care for nAMD (Jaffe et al., 2019). However, better results are more frequently seen early after treatment initiation and some patients may still have poor control of disease activity despite persistent treatment on the long-term (Nguyen et al., 2019). These findings show the variability in treatment response and in disease activity among different individuals. Moreover, real-world data compared to clinical trials have a higher variability in treatment outcomes since inclusion/exclusion criteria are less strict. In addition, treatment regimens, as well as retreatment decisions, are dependent on the treating ophthalmologist instead of a strict study protocol (Kiss et al., 2020).

Currently, there is an ongoing discussion about the contribution of intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelium detachment (PED) in developing degeneration of the photoreceptors and retinal pigment epithelium (RPE) in nAMD leading to macular atrophy (MA) and/or subretinal fibrosis (SF) (Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022; Roberts et al., 2022). It has been postulated that worst functional outcomes in nAMD show a higher correlation with IRF (Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022); however, any robust correlation between fluid volumes and visual outcome should contain information about the structural integrity of the neurosensory retina. Previous studies showed a strong and direct correlation between visual acuity and the integrity of outer retinal hyperreflective bands and retinal pigment epithelium (Coscas et al., 2015; Riedl et al., 2020). Long-term follow-up is essential to better understand disease progression and poorer outcomes despite anti-VEGF treatment. The CATT study showed a cumulative proportion of SF increasing from 32% to 56%, and of MA increasing from 12% to 38% from year 1 to year 5 under standardized anti-VEGF protocols (Daniel et al., 2018; Grunwald et al., 2017). Previous studies showed that photoreceptor damage may be the first step towards RPE degradation and subsequently poor late stage outcomes in AMD (Orlando et al., 2020). Progressive alterations of the ellipsoid zone (EZ) integrity and fluid volumes can now be automated and precisely quantified on OCT. Thus, this study is a proof-of-concept of AI-based EZ integrity quantification and its association with retinal fluid volumes at baseline in real-world nAMD patients over 3 years of follow-up.

2 | METHODS AND MATERIALS

2.1 | Participant inclusion and grading

This study presents a post hoc analysis of the Fight Retinal Blindness! Registry (FRB!) data including the respective OCT images from a single centre (Zurich, Switzerland). The study was conducted in compliance with the declaration of Helsinki and approval of the respective institutional review boards. Patients with ungradable scans, concomitant retinal sight-threatening disease and/or presence of MA or SF at baseline, as originally graded by the FRB! investigators, were excluded. Medical records regarding demographic data and best-correct visual acuity (BCVA) were reviewed. BCVA was measured using Snellen charts and converted to letters on the logarithm of the minimum angle of resolution (logMAR) visual acuity chart. Spectral-domain (SD) OCT (Spectralis, Heidelberg Engineering) images were processed at baseline and during the 3-year follow-up period. The OCT volumes were not standardized; however, the analysed images had to include at least 19 B-scans per volume. Treatment decisions, including regimen and drug of choice (ranibizumab or aflibercept) had been made by the attending physician. To evaluate the impact of fluid on EZ integrity loss during follow-up, a high fluid volume subgroup was defined for each compartment (IRF, SRF and PED) including patients with the highest 25% quartile of fluid volume at baseline in the central 6 mm. The remaining 75% of patients were classified as the low fluid volume subgroup for each respective fluid compartment (Schmidt-Erfurth et al., 2023).

2.2 | Automated quantification of retinal fluid and EZ segmentation

Macular fluid was automatically segmented and quantified using an extensively validated AI algorithm (Fluid Monitor, RetInSight) (Schlegl et al., 2018). The algorithm is approved by the medical device regulation (MDR) (EU) 2017/745 and uses a convolutional neural network (CNN) to identify retinal fluid on a pixel-level in each compartment (Schlegl et al., 2018). Absolute volume quantities were computed in nanolitres (nL) ($1\,nL = 0.001\,mm^3$) within the central 1 and 6 mm macular fields. PED was defined as a segmented region between the retinal pigment epithelium (RPE) and Bruch's membrane with a height > 200 µm, or alternatively, a width > 400 µm, as originally defined by professional reading centres (Vienna, Wisconsin, Duke) (Schmidt-Erfurth et al., 2023). Figure 1 shows a segmentation of PED. EZ integrity was defined as continued segmentation of the area between the top of the EZ and the outer boundary of the interdigitation zone. Automated segmentation of EZ thickness was performed by a

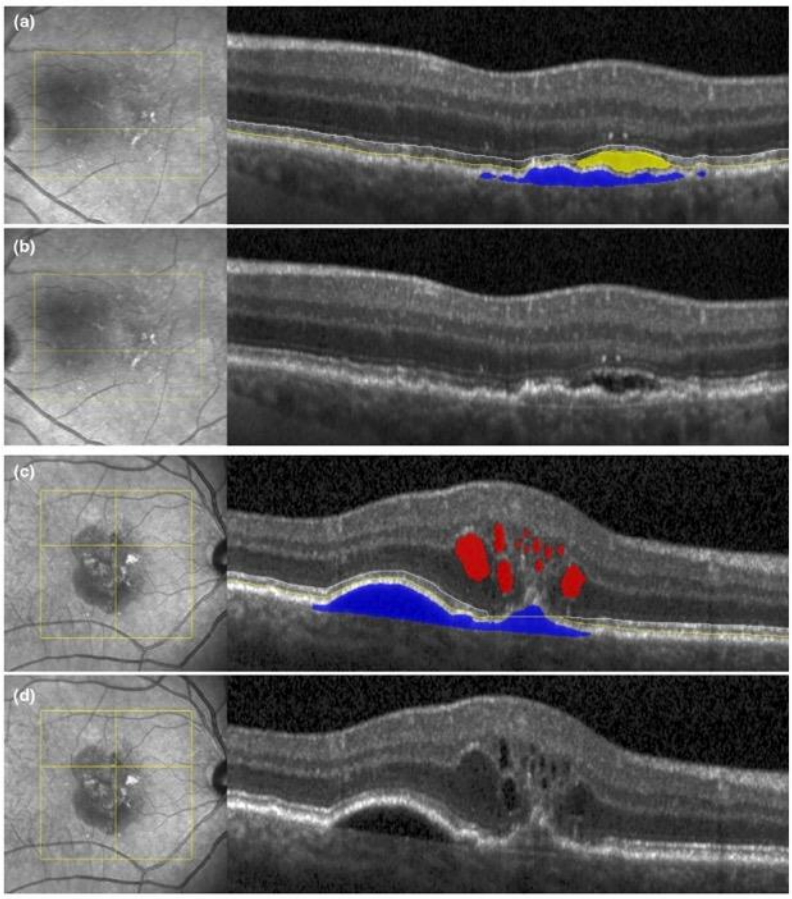

FIGURE 1 Automated segmentation of intraretinal fluid (red), subretinal fluid (yellow) and pigment epithelial detachment (blue), and ellipsoid zone (EZ) thickness. EZ thickness is reliably segmented when the fluid volume is below the threshold of 60 nL in the central 6 mm.

previously reported ensemble of U-Net-based fully CNN delineating layers on each individual B-scan of the entire SD-OCT volume (Orlando et al., 2020; Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022).

From the voxel-level binary segmentation, an en-face EZ thickness map was calculated, providing a thickness value for each single A-scan. In a postprocessing step, EZ integrity loss was defined as a discontinuity of the previously described segmented layer. For the automated EZ quantification, OCT scans with fluid volume over 60 nL in the central 6 mm area or over 10 nL in the central 1 mm area were excluded. Figure 1 shows examples of segmentation with less than 60 nL of fluid in the macula. High fluid volumes will distort adjacent structures to a level that the EZ layer cannot be reliably segmented on OCT. The following time points were used in the analysis: month 3 (M3), M6, M12, M15, M24, M27 and M36. Spatiotemporal correlation of fluid volumes in nL with EZ loss in mm^2 and µm was performed to identify early signs of atrophy development and progression in nAMD in dependence on the fluid compartments and their respective volume.

2.3 | Statistics and mathematical analysis

Data were split between high (top 25%) and low (bottom 75%) of the macular fluid volumes groups in each compartment at baseline. A comparison between high versus low macular fluid volumes impact on EZ loss was performed using a Wilcoxon rank-sum tests with bootstrapped confidence intervals. EZ thickness and integrity loss and their association with the development of MA and/or SF were calculated using a linear mixed model in which the fixed effects were the time points and development of MA or SF within the 36 months. The random effect in these calculations was patient (eye). A longitudinal panel regression model was also performed to correlate fluid volumes to EZ thickness and EZ loss. For all statistical tests, a *p*-value below the significance level 0.05 was considered significant.

3 | RESULTS

Four hundred and thirty eyes from 215 treatment-naïve patients were initially evaluated. Ungradable scans,

and eyes with other concomitant macular disease and/or presence of geographic atrophy or fibrosis at baseline were excluded. The final sample consisted of 211 eyes from 158 patients with nAMD. The mean number of injections were 18.57±8.74 over the 3 years of follow-up.

3.1 | EZ thickness and EZ integrity loss measurements

There was a progressive increase in the EZ loss area during follow-up. In the total cohort, the mean±SD of EZ loss area in the central 6 mm at baseline was 1.81±2.68 mm^2, increased to 4.88±5.4 mm^2 after initial treatment (month 3), reached 5.19±5.43 mm^2 at month 24 and 6.21±6.15 mm^2 at month 36.

There was a continuous thinning of the EZ layer (measured from top of the ellipsoid zone to the outer boundary of the interdigitation zone) during follow-up. The mean EZ thickness in the central 6 mm at baseline was 26.9±4.7 µm, decreased to 22.71±5.77 µm at month 3, reaching 22.04±5.38 µm at month 24 and 21.4±5.8 µm at month 36 as shown in Table 1. No significant change in EZ integrity loss area was detected in the central 1 mm from baseline to month 36.

Overall, the continuous thinning on the EZ layer was followed by a progressive loss of its integrity from month 6 until month 36 (Figure 2). Related visual acuity showed more impressive improvement from baseline to month 3, and then maintained a modest improvement until month 15. Thereafter, a progressive worsening on visual acuity was noted (Figure 2). The Spearman correlation between EZ loss and visual acuity at month 36 was moderate to high with −0.61 ($p<0.0001$).

3.2 | Fluid correlation with EZ affection

At baseline, SRF was present in 87.68% and IRF was present in 60.19% of all scans. The median volumes of SRF and IRF at baseline in the central 6 mm were 133.38 nL (interquartile range [IQR]: 7.79–441.71) and 1.18 nL (IQR: 0–80.5), respectively. Higher fluid volume subgroup (top 25%) of IRF in the central 1 and 6 mm of the macula were significantly associated with more EZ thinning in the analysed time points ($p=0.001$, 95%CI 2.51–8.85 and $p=0.01$ 95%CI 0.44–5.17 at month 36, respectively). Higher volume of PED in the central 1 and 6 mm also showed significant association with EZ thinning in the analysed time points ($p=0.003$, 95% CI 2.12–8.85, $p=0.001$, 95% CI 2.14–6.27, respectively, at month 36). Higher IRF volume subgroup also showed a significant correlation with the EZ loss area in the central 1 mm ($p=0.0002$, 95% CI −5.45 to −1.96 at month 36). However, after Bonferroni correction, this correlation was not significant in the central 6 mm. High PED volumes in the central 6 mm were significantly correlated with EZ loss in the analysed time points ($p=0.0001$, 95% CI −5.46 to −2.25 at month 36). In contrast, high volume of SRF showed no statistically significant association with EZ thinning in the central 1 and 6 mm or EZ loss in the central 1 mm during follow-up ($p=0.94$, 95% CI −3.40 to 3.89; $p=0.18$, 95% CI −0.49 to 3.84; and $p=0.64$, 95% CI −1.47 to 2.40, respectively, at month 36). These correlations are shown in Figure 3.

A longitudinal panel analysis confirmed a significant correlation between PED volume and EZ thinning ($p=0.01$), as well as with an increase in the area of EZ loss within the central 6 mm ($p=0.004$). IRF showed a clear correlation with EZ thinning in the central 1 mm ($p=0.01$), which was not statistically significant in the central 6 mm, but still showed a trend towards a thinning effect ($p=0.05$). The difference may be due to the fact that most of the IRF is present within the central 1 mm and the effect may be less when the entire 6 mm area is included. Regarding EZ loss, IRF volume showed no significant correlation with EZ loss in the central 1 and 6 mm. SRF was significantly correlated with an increase in EZ thickness and showed a negative correlation with the area of EZ loss ($p<0.001$ and $p=0.002$, respectively).

3.3 | EZ loss with development of macular atrophy (MA) and subretinal fibrosis (SF)

Despite regular treatment in clinical practice, 34.1% (72 eyes) converted to late stages of the disease (MA and SF) over 3 years of follow-up. Thirty-six eyes developed MA, 10 eyes developed SF and 26 eyes developed combined MA and SF. When analysing the impact of EZ behaviour during the late-stage outcomes in this cohort, we found that eyes which developed MA and SF (converters to late-stage of nAMD) had a significant correlation with

TABLE 1 Ellipsoid zone loss, EZ thickness, subretinal fluid, intraretinal fluid and pigment epithelium detachment changing at baseline and months 3, 6, 12, 24 and 36.

	BSL 6 mm	M3 6 mm	M6 6 mm	M12 6 mm	M24 6 mm	M36 6 mm
EZ loss (μm^2)	1.81±2.68	4.88±5.4	4.56±5.43	4.21±4.45	5.19±5.43	6.21±6.15
Mean EZ thickness (µm)	26.9±4.76	22.71±5.77	22.71±5.43	22.74±4.96	22.04±5.38	21.45±5.82
Median SRF (nL)	133.38 (IQR 7.79–441.71)	0.99 (IQR 0.05–17.18)	3.89 (IQR 0.13–23.75)	3.64 (IQR 0.33–30.8)	1.5 (IQR 0.0–14.95)	1.29 (IQR 0.17–16.87)
Median IRF (nL)	1.18 (IQR 0.0–80.5)	0.0 (IQR 0.0–1.83)	0.0 (IQR 0.0–5.06)	0.13 (IQR 0.0–5.43)	0.0 (IQR 0.0–23.28)	0.29 (IQR 0.0–8.05)
Median PED (nL)	0.0 (IQR 0.0–720.27)	0.0 (IQR 0.0–405.31)	0.0 (IQR 0.0–755.04)	0.0 (IQR 0.0–503.11)	0.0 (IQR 0.0–678.3)	0.0 (IQR 0.0–750.66)

Abbreviations: BSL, baseline; EZ, ellipsoid zone; IRF, intraretinal fluid; M, month; nL, nanolitre; PED, pigment epithelium detachment; SRF, subretinal fluid; µm, micometre.

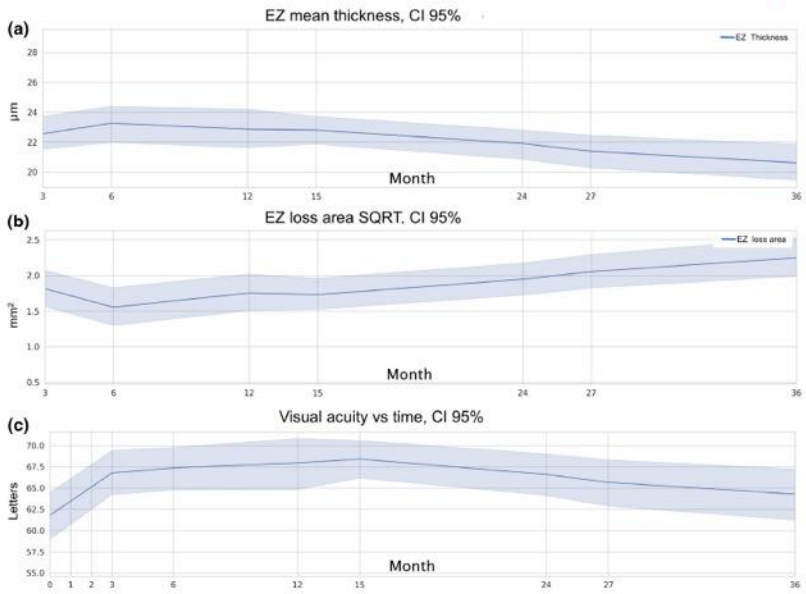

FIGURE 2 The plots show a continuous thinning on the ellipsoid zone (EZ) (a), a progressive increase in the EZ loss area (b) and a decrease in visual acuity particularly after month 15 (c).

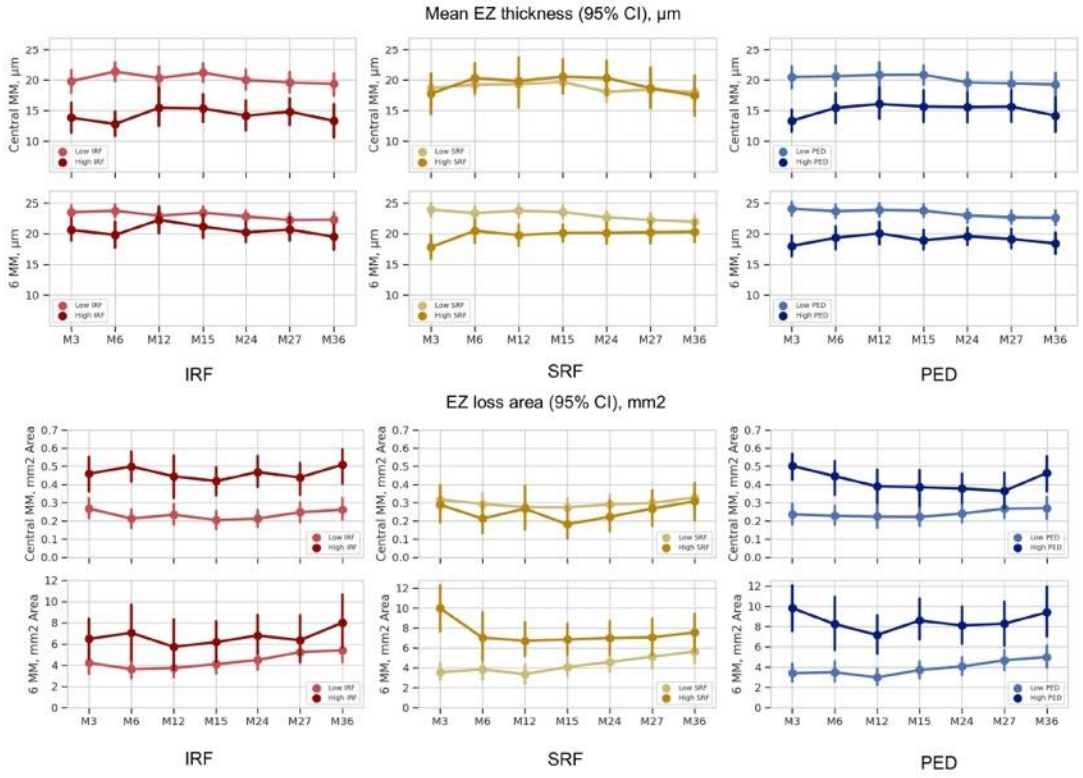

FIGURE 3 A comparison between higher fluid volume subgroup (top 25%) in each compartment (intraretinal and subretinal fluid and pigment epithelial detachment) and bottom 75% fluid volume subgroup regarding ellipsoid zone (EZ) thickness and EZ loss during follow-up.

faster progression of the EZ loss area (steeper curve slope) in the central 1 and 6 mm ($p=0.01$ and $p=0.001$, respectively). Furthermore, EZ thinning in the central 1 mm was significantly correlated with MA and SF development ($p=0.04$), but this was not seen on the central 6 mm ($p=0.50$).

4 | DISCUSSION

High-resolution optical coherence tomography (OCT) is a non-invasive imaging modality with close correlation with retinal histology (Cheng et al., 2018). The detailed analysis of OCT scans may provide an accessible opportunity to analyse the behaviour of the neurosensory layers in vivo during AMD progression. As observed in both trials and clinical practice, late-stage outcomes in nAMD involving photoreceptor damage persist despite continued treatment with anti-VEGF. The presence of fluid remains a significant contributing factor in these outcomes. Our overall results showed a progressive decrease in EZ thickness and a progression in EZ loss in close correlation with visual acuity changes after 6 months and thereafter (Figure 2). Although macular atrophy origins remain unclear, photoreceptor integrity loss is clearly a key feature in the early stage of atrophy development, and therefore, an important biomarker of disease progression (Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022). The effect of ageing on the retinal tissue is heterogeneous and closely related with areas of higher energy demands. Thus, the macula and specially the outer retina and choroid are major targets in age-related retinal diseases (Elsner et al., 2022; Zouache, 2022). Photoreceptor and posterior RPE degradation with development of macular atrophy is important for long-term results of visual acuity in non-neovascular AMD as well as in nAMD.

In this cohort, SRF was the most prevalent fluid component at baseline and 87.68% of all scans had SRF while 60.19% had IRF in the central 6 mm. These rates are similar to related data from clinical studies with even larger populations such as the HARBOR trial (Sadda et al., 2022). The larger amount of total retinal fluid present at baseline can cause distortions in the outer retinal bands as well as transitory worsening of visual acuity. Therefore, the quantification of EZ integrity loss at baseline and its correlation with visual acuity may be not reliable at this time point. Yet, a follow-up quantification of EZ thickness and the comparison between the higher and lower fluid volume subgroups can be more reliably performed from month 3 to month 36.

The direct correlation between retinal fluid volumes and visual acuity may be unreliable, due to varying pre-existing damage to the underlying neurosensory compartment. However, EZ loss and visual acuity are closely related which was demonstrated in this study. A progressive EZ loss followed by a continuous decrease in visual acuity after month 15 was observed. Therefore, photoreceptor layer analysis on OCT can be used not only as a biomarker in intermediate AMD (Zekavat et al., 2022) and GA, but also in nAMD. Furthermore, a binary classification of presence or absence of ellipsoid zone does not completely meet the actual interest in automated quantification of outer retinal bands on OCT.

Photoreceptor thinning has been described preceding their complete loss in histological studies, nevertheless the pathophysiology remains unclear (McHugh et al., 2019; Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022). Yet, photoreceptor thinning has also been correlated with loss of visual function using microperimetry measurements in drusen areas (Acton et al., 2012). The possibility of real-time correlation of retinal fluid behaviour and neurosensory disease progression is clearly providing a missing link in the understanding of fluid/function correlation. In real world, automated segmentation is mandatory, since manually segmentation and quantification of retinal layers and fluid volumes are time consuming and not realistic in clinical routine.

Currently, automated tools such as central retinal thickness (CRT) have been used in clinical practice as a marker of disease activity or recurrence and to guide treatment decisions in nAMD. However, this measurement does not provide any detailed information about location and extension of disease-specific activity, and also presented a weak correlation with visual acuity and fluid volumes (Nanegrungsunk et al., 2022; Pawloff et al., 2022). Previous studies have postulated that the severity of CRT fluctuation is related with visual acuity outcomes (Chakravarthy et al., 2021; Lai and Lai, 2021; Sheth et al., 2022); thus, an automated tool capable of measuring and analysing fluid fluctuation in each compartment for each patient during follow-up may provide more accurate and personalized information about functional and anatomical outcomes. The comparison between high and low fluid volume subgroups showed that the central macula is particularly vulnerable to damage caused by high IRF volumes, leading to EZ thinning and loss. This is in accordance with previous analysis in the FRB! Registry dataset that indicates higher IRF volumes associated with increased atrophy onset (Nguyen et al., 2021). Since photoreceptor damage may be the first step to RPE degradation and persistent macular atrophy (Orlando et al., 2020), this analysis becomes crucial. The longitudinal analysis confirmed statistically significant correlation between IRF and EZ thinning in the central 1 mm. In the central 6 mm area, $p=0.05$, indicating a trend that did not reach statistical significance. Regarding IRF and EZ loss correlation, the longitudinal analysis showed no statistically significant correlation. Since the IRF volumes are mainly located in the central macula, both models presented more significant damage in the 1 mm area.

The subgroups analysis showed that high SRF volumes were neither significantly associated with EZ thinning in the central 1 or 6 mm, nor with EZ loss. Interestingly, the longitudinal panel analysis suggests that SRF correlates with an increase of EZ thickness and presented a negative correlation with EZ loss. Supporting this finding, previous analysis have shown that inactive persistent SRF volumes may be tolerated and may also be related to better visual outcomes (Bogunović et al., 2022; Guymer et al., 2019). However,

when the residual volume of SRF is higher and actively increases, it does lead to worse visual acuity outcomes (Grechenig et al., 2021; Sadda et al., 2022). Furthermore, there might be an increase in the number of injections needed to achieve disease control in the first year of follow-up (Bogunović et al., 2022; Mares et al., 2023). Higher PED volumes in the central 1 and 6 mm of the macula were also significantly associated with EZ thinning and integrity loss during follow-up. Schuman et al. (2009) have demonstrated an association of large drusen with the loss of photoreceptor and outer segments in 2009 and so, it is expected that in larger PEDs that would also be noted.

The relentless progression of photoreceptor degeneration in nAMD despite regular treatment remains a clinical unmet need. In previous studies, IRF has been linked to deteriorating visual acuity outcomes and the onset of atrophy (Reiter et al., 2023; Riedl, Vogl, Mai et al., 2022; Riedl, Vogl, Waldstein et al., 2022). Our analysis comparing EZ behaviour on eyes that developed late stages of nAMD such as atrophy and fibrosis, during a 3-year follow-up with those that did not, supported previous findings in the literature. A faster increase of the EZ loss area in both the central 1 mm and 6 mm area were found to be significantly associated with further development of clinical signs of atrophy and/or fibrosis. Thus, understanding the impact of retinal fluid volumes on the outer retina segments may be the key to better understand and maybe prevent late-stage outcomes of nAMD. In times of the first pharmacological treatments for GA being approved, combination therapies may be an option, although having to take into account MNV formation under GA therapy.

A possible association of fluid compartment, MNV type and late-stage outcomes in nAMD has been suggested in the literature (Ernest et al., 2020). Type 3 MNV has been more frequently associated with IRF and macular atrophy. Type I MNV showed predominantly SRF and a protective effect for macular atrophy has been postulated (Fukuyama et al., 2022). In our analysis, MNV type showed no significant correlation with increased EZ thinning and/or loss during follow-up. However, type 3 MNV was presented in only six cases, and this must be noted as a limitation, thus no final conclusions can be taken from such a small subgroup.

This is a retrospective real-world study and therefore has some inherent limitations such as retrospective chart analysis, non-standardized treatment decisions and different scan mode imaging between different patients and within patients and between all visits.

However, this is a large sample size of treatment-naïve patients, from the well-curated FRB! Registry platform, which offers high-quality data from routine disease management (Gillies et al., 2014). Furthermore, OCT images were collected from one single device (OCT Spectralis, Heidelberg Engineering) avoiding technical variability among device types. Yet, the AI algorithms used in the analysis were previously tested, human ground truth was provided and the tools were validated. EZ automated segmentation was only possible in the absence of large fluid volumes or with low amounts of fluid at the defined timepoints (less than 60 nL in the 6 mm area, as described in the methods). Neovascular AMD comes with the dilemma of a fast, devastating and usually irreversible loss of retinal function without treatment (Kiss et al., 2020). Retinal fluid particularly intraretinally may cause permanent damage to the EZ in the central macula with resulting irreversible visual loss. Interesting is also the notion that PED is associated with a decline of EZ integrity. As demonstrated in this study, volumes and location of retinal fluid compartments are important for neurosensory layer anatomy and, consequently, for visual outcomes. Prompt detection of photoreceptor early changes associated with fluid dynamics may be the most impactful method to optimize anti-VEGF treatment and try to prevent long-term visual loss due to nAMD. Advanced OCT image analysis shed more light into the complex patterns of nAMD and AMD in general. A precise quantitative analysis of fluid by type and volume in nAMD and knowing about the pathognomonic impact of fluid on EZ and RPE as correlate for visual function may empower health care providers to develop a comprehensive approach to vison-saving therapy. The portfolio of relevant biomarkers and parameters guiding therapeutic strategies is increasing as we speak and is ready to be used in the hands of thousands of ophthalmologists treating millions of patients which are threatened by a blinding disease. In times of AI-based precision measurements, fluid volumes and neurosensory destruction can be visualized in every individual patient to improve his/her outcome and throughout populations to understand the associations of markers of nAMD and AMD disease in general. Macula-wide EZ integrity assessment work is certainly a most useful candidate endpoint to monitor nAMD treatment and progression.

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CONFLICT OF INTEREST STATEMENT

GSR: Research funds from RetInSight. Consultant for Apellis, Bayer, Boehringer Ingelheim and Roche. HB: Research funds from Heidelberg Engineering and Apellis. DB: Research grants and travel expenses from Bayer and Novartis. (b) Scientific consultant for Alcon. US-E: Scientific consultant for AbbVie, Annexon, Apellis, Aviceda, Complement Therapeutix, Genentech, Heidelberg Engineering, Kodiak, RetInSight, Novartis, Roche and Topcon. OL: Employee of RetInSight. VM, MG and MBN report nothing to declare.

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Os principais resultados desse segundo artigo estão descritos a seguir:

- Foram analisados 211 olhos de 158 pacientes com DMRI neovascular.
- No geral, houve um aumento significativo na área de perda da ZE, de 1,81 ± 2,68 mm² no início do estudo para 5.19 ± 5.43 mm^2 no mês 3 e atingiu 6,21 ± 6,15 mm² no mês 36. (Figura 1, artigo 2)
- Houve também um afinamento contínuo da ZE ao longo dos 3 anos de acompanhamento. A espessura média dos fotorreceptores nos 6 mm centrais na linha de base era de 26,9 ± 4,7 µm, diminuiu para 22,71 ± 5,77 µm no mês 3, atingindo 21,4 ± 5,8 µm no mês 36. (Figura 1, artigo 2).
- Maiores volumes de FIR e DEP foram significativamente associados ao afinamento e perda da ZE ao longo do acompanhamento de 3 anos. Maior volume de FSR não foi correlacionado com o afinamento ou a perda da ZE nas regiões centrais de 1 mm e 6 mm.
- Como esperado, a perda da ZE esteve relacionada à redução na acuidade visual. Foi possível identificar uma clara correlação na Figura 1, particularmente após 15 meses de acompanhamento. A análise estatística também mostrou uma correlação de Spearman de -0,61 no mês 36. (Figura 1, artigo 2)
- Maiores volumes basais de FIR e DEP tiveram maior probabilidade de desenvolver AM e FS ao final do acompanhamento, quando comparados com o subgrupo de menor volume.

A análise longitudinal, utilizando modelo de regressão em painel, confirmou uma correlação significativa entre o volume do DEP e o afinamento ou perda da ZE, nos 6 mm centrais da mácula (p=0,01, p=0,004 respectivamente). O FIR teve uma correlação clara com o afinamento da ZE quando analisado 1 mm central (p=0,01) e indicou uma forte tendência de afinamento (p=0,05) nos 6 mm, apesar do p não ter sido estatisticamente significativo. A diferença pode ser atribuída ao fato de que a maior parte do FIR está presente na região central da mácula, e o efeito pode ser menor quando toda a área de 6 mm é incluída. Em relação à perda de ZE, o volume de FIR não mostrou correlação significativa nas regiões centrais de 1 mm e 6 mm. Houve uma correlação estatisticamente significativa do FSR com um aumento da espessura da ZE e menor área de perda de ZE (p<0,001 e p=0,002, respectivamente). A IA foi útil para a quantificação dos fluidos em nanolitros, bem como para mensurar

a espessura da ZE em micra. Mudanças sutis nesses parâmetros seriam dificilmente vistas, quantificadas e comparadas sem o auxílio dos algoritmos.

Expandindo a pesquisa no intuito de avaliar o funcionamento do algoritmo de quantificação automatizada de fluido retiniano numa coorte brasileira de vida real, bem como avaliar a resposta dos pacientes dessa coorte ao tratamento durante 2 anos de acompanhamento, desenvolvemos um estudo envolvendo pacientes com DMRI neovascular atendidos em um hospital terciário de Belo Horizonte. O artigo abaixo intitulado **"Automated fluid monitoring to enhance patient follow-up with neovascular age-related macular degeneration (nAMD) in the Brazilian population",** fruto dessa análise, está em revisão com os co-autores.

Artigo 3

Automated fluid monitoring to enhance patient follow-up with neovascular age-related macular degeneration (nAMD) in the Brazilian population

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Abstract:

Purpose: To investigate the efficacy of an automated medical device regulation (MDR)-approved fluid monitoring tool in enhancing the monitoring of neovascular age-related macular degeneration (nAMD) patients in a Brazilian cohort.

Methods: This is a retrospective real-world study performed in a tertiary center in Brazil, including patients with nAMD in a treat-and-extend treatment regimen. Spectral-domain optical coherence tomography (Spectralis, Heidelberg Engineering, Germany) images were processed at baseline and over 2 years of follow-up. Demographic and clinical data were collected. An MDR-approved deep learning algorithm (Fluid Monitor, RetInSight, Austria) was used to automatically quantify intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED). A longitudinal panel regression model and Log-Rank test were performed to assess the correlation between fluid volumes and treatment frequency, visual outcomes, macular atrophy (MA) and subretinal fibrosis (SF) development.

Results: Ninety-nine eyes from 84 patients were included, whereof 66.7% were female, mean age was 76.5 ± 9.8 years. Fifty-eight eyes were treatment naïve. Higher fluid volumes of IRF, SRF and PED in the 6mm area were correlated with worse visual outcomes over a 2-year follow-up (p=0.01, p=0.002, p<0.001, respectively). Elevated IRF and PED volumes were significantly associated with an increased risk of SF development (p<0.001 for IRF in 1 and 6 mm, and p=0.02 for PED in both compartments), while the higher SRF subgroup was significantly associated with SF only in the central 6 mm, p=0.049. MA development showed no significant correlation with higher IRF, SRF nor PED in this analysis. Higher SRF volume correlated with a greater number of required intravitreal injections over 2-years.
Conclusion: This study demonstrated the efficacy of using an AI-based fluid monitoring tool to analyse nAMD activity and late-stage outcomes in a Brazilian cohort. Fluid dynamics in each compartment impacts differently functional and anatomical outcomes. Further studies that highlight the significance of using newly validated technologies across diverse populations worldwide is still necessary.

Introduction:

Age-related macular degeneration (AMD) stands as one of the leading cause of irreversible vision impairment worldwide, particularly affecting individuals aged 50 and older.[63,64] Among its subtypes, neovascular AMD (nAMD) presents a major threat to vision due to the rapid progression and for its macula targeting location. Macular neovascularization is responsible for fluid leakage into intraretinal and subretinal space and the advent of intravitreal anti-VEGF therapy was a paradigm shift for controlling disease activity.[65,66] Optical coherence tomography (OCT) has become the primary imaging device for detecting and monitoring retinal fluid.[67] A retrospective study performed in a large tertiary center in London, the Moorfields Eye Hospital, showed more than 10-fold increase in numbers of anti-VEGF injections from 2009 to 2019, with nAMD being the foremost condition on injections demand, and consequently, the inherent costs.[68] In Brazil, the prevalence of AMD and its treatment mirrors the global trend. A previous study using the Brazilian public health system database showed an increase of 1.088% in prevalence of anti-VEGF injections in the country from 2010 to 2019.[69] Yet, anti-VEGF injections still represent an important burden to public and supplementary health care systems worldwide, and with the ageing population and the advent of anti-complement intravitreal therapy for geographic atrophy the numbers may rise significantly.[70,71]

Brazil is a multi-ethnic continental country with over 200 million people and is one of the few countries worldwide to offer a free universal coverage health care system to all its citizens, covering from primary to tertiary care.[72] More than 75% of the population relies exclusively on this system to access clinical appointments, exams, and surgical procedures, including

ophthalmology care.[73] Furthermore, the distribution of eye care professionals in the country is not uniform across the vast and diverse population. The last census reported by the Brazilian Ophthalmology Council (CBO) from 2021 showed a clear concentration of eye doctors in the southeast region, with a median of 20.2 ophthalmologists per 100,000 inhabitants, while in the northern region, for example, the median density was 6.9 ophthalmologists per 100.000 inhabitants.[74] The dynamic nature of retinal diseases such as nAMD demands close monitoring of patients to detect early signs of disease recurrence, treatment demand, and/or progression to late stages such as macula atrophy (MA) and subretinal fibrosis (SF), which can be challenging to patients and to the health system.[75] Yet, a combination of large population, unbalanced resources and high monitoring demand may pose a significant challenge to the eye care health system and professionals in a daily practice.

In the past recent years, there has been a notable increase of artificial intelligence (AI)-based tools capable of identify and quantify retinal imaging biomarkers.[3] The integration of deep learning algorithms in AMD patients follow-up is promising for enhancing decision-making processes and optimizing treatment strategies.[76–78] One limitation of the recent published studies regarding AI-based technology is the predominance of Caucasian population in validating and testing the algorithms, which can lead to a lack of generalization of the results. The Brazilian society was initially formed by a confluence of European, African and Indigenous ethnicities.[79] Currently, according to the Brazilian Institute of Geography and Statistics (IBGE), the population can be classified, based on ethnicity as white, black, brown (multiracial), indigenous and yellow (east Asian). The purpose of this study is to investigate the use of an automated medical device regulation (MDR)-approved fluid monitoring tool to enhance nAMD patients control in a real-world Brazilian cohort.

Methods:

Participants

This is a retrospective study performed in a tertiary center in Minas Gerais, Brazil, including patients with nAMD treated in a treat-and-extend regimen with Aflibercept or Ranibizumab over 2 years of follow-up. The study was conducted in compliance with the declaration of Helsinki and had approval from the institutional review board (CAAE 58850622.4.0000.5149). Patients' informed consent was exempted because of the retrospective nature of this study using fully anonymized retinal images. Electronic medical records regarding age, sex, best-corrected visual acuity (BCVA), number of injections, and presence of MA or SF were collected. Anonymized spectral-domain (SD)-OCT (Spectralis, Heidelberg Engineering, Germany) images were segmented at baseline and every visit during 2 years of follow-up. Patients with ungradable scans, less than 1 year follow-up, visual acuity worse than 20/200 in Snellen chart at baseline, history of cataract surgery during the

follow-up period, concomitant retinal sight-threatening disease such as advanced glaucoma, epiretinal membrane or vitreo-macular traction, and/or presence of central MA or SF at baseline were excluded. The OCT volumes were not standardized, however the analysed images had at least 19 B-scans per volume. To evaluate the impact of retinal fluid volumes in each compartment at baseline in the number of injections and final BCVA the patients were divided into two groups. The highest 25% quartile of fluid volume in each compartment (intraretinal fluid [IRF], subretinal fluid [SRF], and pigment epithelial detachment [PED]) at baseline in the central 6 mm were classified as high fluid volume subgroup. The remaining 75% of patients were classified as low fluid volume subgroup for each respective fluid compartment.[47,80,81]

Visual acuity, macular atrophy and subretinal fibrosis determination

BCVA was tested every visit using Snellen chart and converted to early treatment of diabetic retinopathy study (ETDRS) score. MA and SF were graded from the attending physician and extracted from the medical records. This assessment was based on either OCT images, fundoscopy, fundus photography and on fundus autofluorescence images when available. Further, all the included baseline OCT images were analysed by a retinal specialist (VM) to exclude baseline central MA and SF, in case it was not mentioned in the chart, for the MA and SF development analysis. Retinal pigment epithelium (RPE) loss with associated retinal ellipsoid zone loss more than 250 µm in diameter detected in the central 3 mm area were excluded as MA. OCT images showing a compact multilaminar hyperreflective material situated above or below RPE, with indistinct RPE layer, in the central 3 mm area was excluded as SF.[82] Subretinal hyperreflective material (SHRM) was not excluded.

Automated quantification of retinal fluid

IRF, SRF and PED volumes within the central 1 mm and 6 mm macular subfields were automatically segmented and quantified using the MDR-certified deep learning algorithm (Fluid Monitor, RetInSight, Vienna, Austria) in all time points. The algorithm uses a convolutional neural network (CNN) to identify retinal fluid in each compartment and PED on a pixel-level (Figure 1). The number of assigned pixels can be computed into an estimation of fluid volumes in nanoliters ($1\ nL = 0.001\ mm^3$) and their respective compartments. [36,83]

Statistical analysis and fluid function correlation

Statistically significant Lagrange Multiplier Breusch-Pagan and Chow test demonstrated that a longitudinal time-series data analysis would be better suited to correlate fluid volume in each compartment with BCVA over a 2-year follow-up. Panel regression with fixed or random effect model was chosen based on Hausman and Sargent-Hansen chi-squared test for each variable. A Log-Rank test with Kaplan Meier curve was used to analyse the correlation between fluid volumes in both subgroups in each compartment and new onset MA and SF, as well as MA and SF development over treatment naïve and pre-treated patients. Spearman

correlation was used to analyse the association between fluid volume in each compartment at baseline and number of intravitreal injections after 12 and 24 months.

Results

Ninety-nine eyes from 84 patients with nAMD were included, whereof 56 (66.7%) patients were female, mean age was 76.5 ± 9.8 years and 58 eyes (58.5%) were treatment-naïve (Table 1). In the central 1 mm area fluid volumes measurements showed IRF with a median of 0 (IQR 0-11.26), SRF presented a median of 1.84 (IQR 0-19.49) and PED with a median of 44.91 (IQR 16.66-102.45). In the central 6mm area, the median of IRF volume was 1.04 (IQR 0.0 - 61.94), SRF was 66.54nL (IQR 1.98-292.8) and PED achieved 446.24nL (IQR 135.7-1025.6).

The overall behavior of each of the 99 eyes included in this analysis regarding BCVA over the follow-up time is shown in the supplementary material. As demonstrated in the IQR numbers, the highest 25% quartile in each compartment at baseline in the central 6 mm corresponded to eyes with IRF ≥ 61.94nL, SRF ≥ 292.85nL and PED ≥ 1025.65nL. These baseline volumes are higher than reported in a previous analysis from a European cohort.[84]

The statistically significant chow test showed that a multivariate regression analysis with fixed timepoints would not be the most appropriate method for assessing visual acuity impairment in this cohort. Therefore, a panel regression analysis was performed showing that higher IRF and PED volumes subgroup in the central 6 mm had a statistically significant impact on the LogMar BCVA measurements, meaning worsening of BCVA over 2 years of follow-up ($p=0.01$, $p<0.001$ respectively). Higher SRF volume subgroup was significantly correlated with worse BCVA when fluid volume was higher than 19.49 (Q3) in the central 1 mm, ($p=0.02$), as shown in figure 2.

To further analyze late-stage outcomes, SF and MA development, 11 eyes were excluded after imaging evaluation due to presence of MA or SF in the central 3 mm at baseline. Of 88 eyes, 16 (18.1%) developed MA and 21 eyes (23.8%) developed SF over the 2 years of follow up. The higher IRF and PED subgroups showed increased risk of developing SF when compared to the lowest 75% subgroups. IRF analysis showed a hazard ratio (HR) of 6.6 (IC95% 2.8 - 15.5) and $p<0.001$ in the central 1 mm and HR of 6.6 (IC95% 2.8 - 15.9) and $p<0.001$ in the central 6 mm area of the macula. PED showed HR of 2.5 (IC95%1.1 - 5.9) and $p=0.02$ for the central 1 mm, and HR of 2.6 (IC95% 1.1 - 6.1), $p=0.02$ for the central 6 mm, as shown in Figure 3. The higher SRF subgroup in the central 6 mm was significantly associated with SF, HR of 2.3 (IC95% 1.0 - 5.3), $p=0.049$ but this was not significantly in the central 1mm analysis. Regarding MA, higher fluid volumes did not show statistically significant correlation with its development in any of the compartments (Figure 4). However, higher IRF (> 61.94nL in the central 6 mm) presented a decreased in average survival time until atrophy development from 22.7 months (95%CI: 21.7 - 23.7) to 19.8 months (95%CI:

16.8 - 22.7), p=0.07 in the Log-Rank test. The overlap within the CIs across volume subgroups and p>0.05 associated with a small sample size makes it difficult to determine whether this result is clinically meaningful. However, this result fits previous findings that strongly correlate type III MNV, which is known to have predominantly more IRF, with MA development.[85] Furthermore, the development of MA and SF showed no significant difference between treatment naïve and pre-treated patients in this cohort.

Overall, the mean number of injections per eye was 5.9 ± 2.6 over 12 months and 13.6 ± 4.2 over 24 months. An analysis between the total volume of IRF, SRF and PED and treatment needed (number of injections) using Spearman test showed that SRF has a positive, despite weak, correlation on increased number of intravitreal injections after 12 months (r=0.3, p=0.02 in the central 1mm and r=0.38, p<0.001 in the central 6mm) and 24 months (r=0.2, p=0.01 in the central 1mm and r=0.2, p=0.02 in the central 6mm). IRF and PED were not significantly correlated with the number of injections. When comparing between higher and lower SRF subgroups using a t-test, the results was consistent with previous analysis[48,80] showing that higher 25% of SRF was associated with higher mean number of injections after 12 months (mean 7.1 ± 2,7, while lower 75% mean of 5.4 ± 2,4) and 24 months (mean 15.0 ± 4.4, while lower 75% mean of 13.0 ± 3.9), p=0.005 and p=0.04 respectively.

Discussion

AI-based technologies have been described with the potential to bridge some gaps between patients and health care providers with cost-effective and scalable solutions such as automated disease screening, biomarkers segmentation, and risk prediction for late stages outcomes.[30,48,86,87] Minas Gerais is the second most populous state in Brazil with a total population of 20,539,989 inhabitants.[88] It is located in the Southeast, the most populous macro-region and responsible to the highest concentration of ophthalmologists in the country. However, despite the increased number of ophthalmologists, inside of the state there is also an important unbalance of personal and material resources in the health care system by microregions. Furthermore, Minas Gerais' ethnical distribution (self-declared) in the last census showed that the state population is composed by 46.76% brown (multiracial), 41.08% white, 11.84% black, 0.16% indigenous and 0,15% east Asian population.[89] Thus, a study that effectively used an AI-based fluid monitor in a real-world sample from a Latin population highlights the importance of testing newly algorithms worldwide.

This cohort is composed of patients in a treat-and-extend regimen, whereof 41.5% were non-treatment naïve. Visual acuity at baseline is the most important predictor to BCVA in a long term follow-up, however, retinal fluid is still the most important biomarker in visual and anatomical outcomes, as well as for retreatment decisions in nAMD.[90] Thus, the volume, location, and its fluctuation play an important role in disease progression.[77] The results from our analysis demonstrated that higher fluid volumes in all three compartments were

significantly corelated with worsening BCVA. According to the literature, IRF and PED have been more associated with visual impairment. The topographic distribution of fluids with IRF more concentrated in the central fovea and SRF more distributed across the macular region may contribute to this statement.[91] A previous analysis conducted in the Caucasian population of the FRB! Zürich dataset showed that only IRF was associated with worse BCVA, however in the cited study fluid volumes were quantified after initial treatment and SRF volume in this present cohort is significantly higher.[80] Furthermore, individual responses to available treatment needs to be also taken into consideration. Regarding SRF behaviour there is an open question if a correlation with better visual outcomes is pertinent,[92,93] or even if a residual tolerable volume threshold can be settle. Previous analysis using data from the FLUID study showed that tolerating SRF had similar BCVA after 24 months of follow up than those treated in order to dry out the fluid.[94] On the other hand, a post hoc analysis also in the FLUID study data using the SRF-tolerant arm showed that 50% of the eyes with residual SRF increased the volume in the central 1 mm at the consecutive visit. The increase in SRF in the central mm was correlated with significant decrease in BCVA in the next visit when compared with the non-tolerant group.[95] In addition, SRF fluctuation was found to be correlated with worse photoreceptor integrity in the OCT on the analysis from the OCTAVE clinical trial dataset, and there is a positive correlation between photoreceptor integrity and visual outcomes.[96]

The limited period of follow-up associated with the exclusion criteria of presence of MA and SF in the central 3 mm area at baseline likely underestimates the rate of MA and SF development in this cohort when compared to the literature.[97–99] Furthermore, treat-and-extend regimen usually presents higher treatment frequency than pro-re-nata (PRN) which could also be associated with lower rates of these late-stage outcomes. Our results showed that higher IRF and PED volumes were associated with increased risk of developing SF. SRF was also associated with SF, but only when analysing the whole 6mm area. Fluid location may play a role in this finding since, as mentioned, SRF is often more present parafoveal than centrally.[100] Higher fluid volumes in any compartment did not show statistically significant correlation with MA development. MA pathophysiology remains unclear, however, previous findings showed that almost 100% of eyes with previous non-foveal atrophy will evolve to central atrophy over 10-years of follow-up.[98] This findings demonstrates the multifactorial components of MA development, possibly including genetic factors.

In this study we have founded a mean number of injections per eye of 5.9 over 12 months and 13.6 over 24 months. A previous report using DATASUS database showed a way lower number of 2.37 (1.35-3.43) as an annual median of injection in Brazilian public health care from 2014 until 2020.[73] It is important to state that although anti-VEGF drugs were approved

by the Brazilian federal agencies since 2007, only in 2018 the treatment was incorporated into the guideline of the Brazilian public health system, which surely impacted the median reported in this database over the years. Furthermore, if the supplementary system numbers were included, the real mean number of injections in the Brazilian population per year would significantly increase and probably get closer to what was founded in this study and it is reported in the literature worldwide.

In a daily basis clinical practice, anti-VEGF treatment can follow monthly, treat-and-extend or PRN regimens. In the PRN regimen, the decision is mainly driven by the dichotomous parameter of presence or absence of retinal fluids. In this study, higher SRF volume proved to be the most important driving force for an increased number of injections at one and two years. Previous studies from our group have also shown that SRF was the most important anatomic biomarker for predicting treatment need,[47,48] despite not being the most impactful fluid compartment in worse anatomical and visual outcomes. Certainly, IRF is actively treated in all regimens, since is the fluid compartment with the strongest correlation with worse BCVA and late-stage outcomes. Nevertheless, it seems to present a faster response to anti-VEGF treatment. Until now, PED is not an isolated target to anti-VEGF therapy, despite some previous studies have shown an anatomical response to the treatment and possible visual improvement.[101] Our study showed an association of higher volumes of PED with worse visual outcomes and faster development of SF, however further prospective studies are necessary to address this question.

The ageing population has continuously increased AMD prevalence and, consequently also increased anti-VEGF intravitreal injections demand.[68] Despite all effort in the nAMD research subfield, the available treatments demand continuous monitoring and injections, which means a high burden for the patient and for the health care system. The DATASUS report showed that OCT and anti-VEGF procedures were mainly done in the Southeast macro-region (87%). As previously stated, the higher population concentration in this area certainly contributes to this finding, but a higher density of professional ophthalmologists is another contributor to these statistics.[74,88]

This study has inherent limitations for being a retrospective analysis performed on real-world patients and with only 2-years duration which is however in accordance with many randomized controlled trials. First, treatment was not standardized, despite mainly followed a treat-and extend regimen. Second, the images were not acquired specifically for this analysis, but as a clinical routine, thus number of B-scans are not uniform. However, a minimum of 19-Bscan was performed, which showed to be reliable for fluid quantification. Finally, there are other biomarkers such as SHRM and ellipsoid zone segmentation with a strong impact on visual acuity outcomes in AMD, which should be considered for future investigations in a prospective manner.

The possibility of monitoring patients using a real-time automated tool and assisting non-retinal specialists' doctors can shorten some gaps regarding the health care unbalance between regions. This study investigates the multifaceted landscape of nAMD in a tertiary center in the Southeast Brazil, considering the country's epidemiology and particular context, pointing the potential benefits of AI-driven technologies on patient's care. Further studies that highlight the significance of using newly validated technologies, especially deep learning algorithms across diverse populations worldwide is still necessary.

Table 1: Demographic data from the 99 eyes from 84 patients included in the study.

Variable		Frequency	
		N	%
Gender	Male	28	33.3
	Female	56	66.7
Age	Mean ± SD	76.5 ± 9.8	
Eye	Unilateral	69	82.1
	Bilateral	15	17.9
Treatment naïve	Yes	58	58.5
	No	41	41.5
Injections (12 months)	Mean ± SD	5.9 ± 2.6	
Injections (24 months)	Mean ± SD	13.6 ± 4.2	
Macular atrophy development during follow-up	Yes	16	18.2
	No	72	81.8
Subretinal fibrose development during follow-up	Yes	21	23.9
	No	67	76.1

Figure 1: Automated segmentation of intraretinal fluid (red), subretinal fluid (yellow) and pigment epithelial detachment (blue).

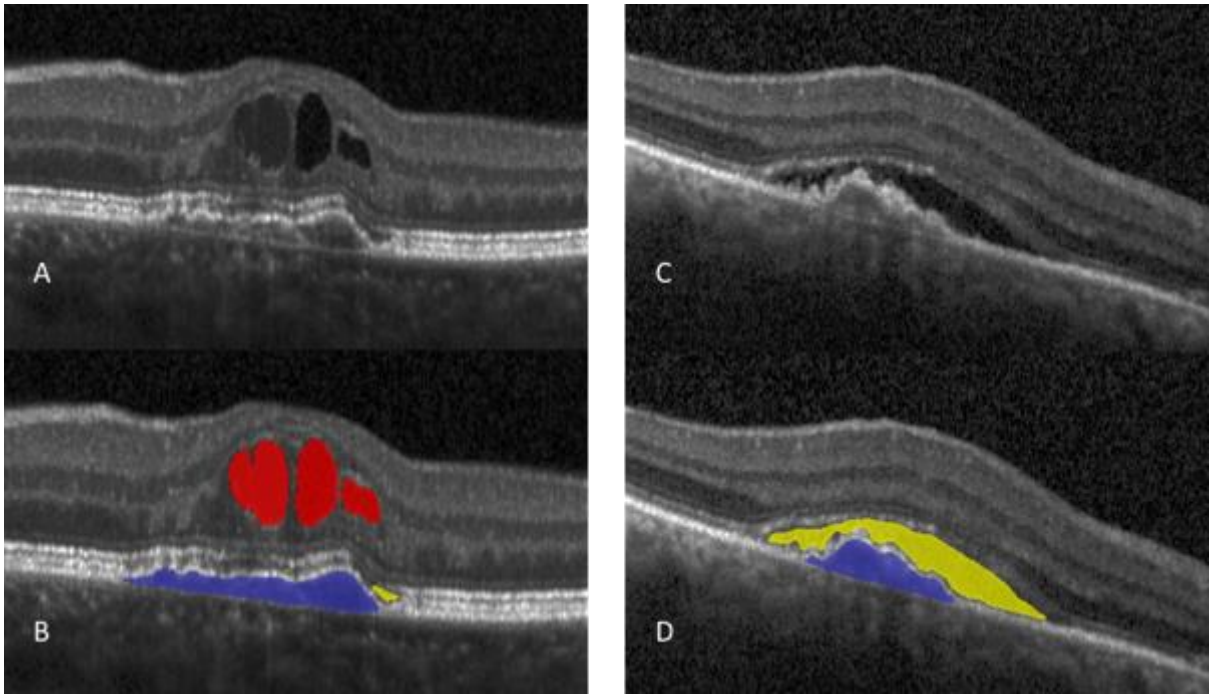


Figure 2: BCVA over time in the higher 25% and lower 75% volume subgroup in the central 6mm of the macula during follow-up. SRF correlation was statistically significant when fluid volume in the central 1mm was included in the model. The dotted lines graphic showed that when fluid volumes in the central 1mm was above 19.49 (Q3) the worst BCVA in the higher fluid volume subgroup (>292.85nl) was clearer to be seen.

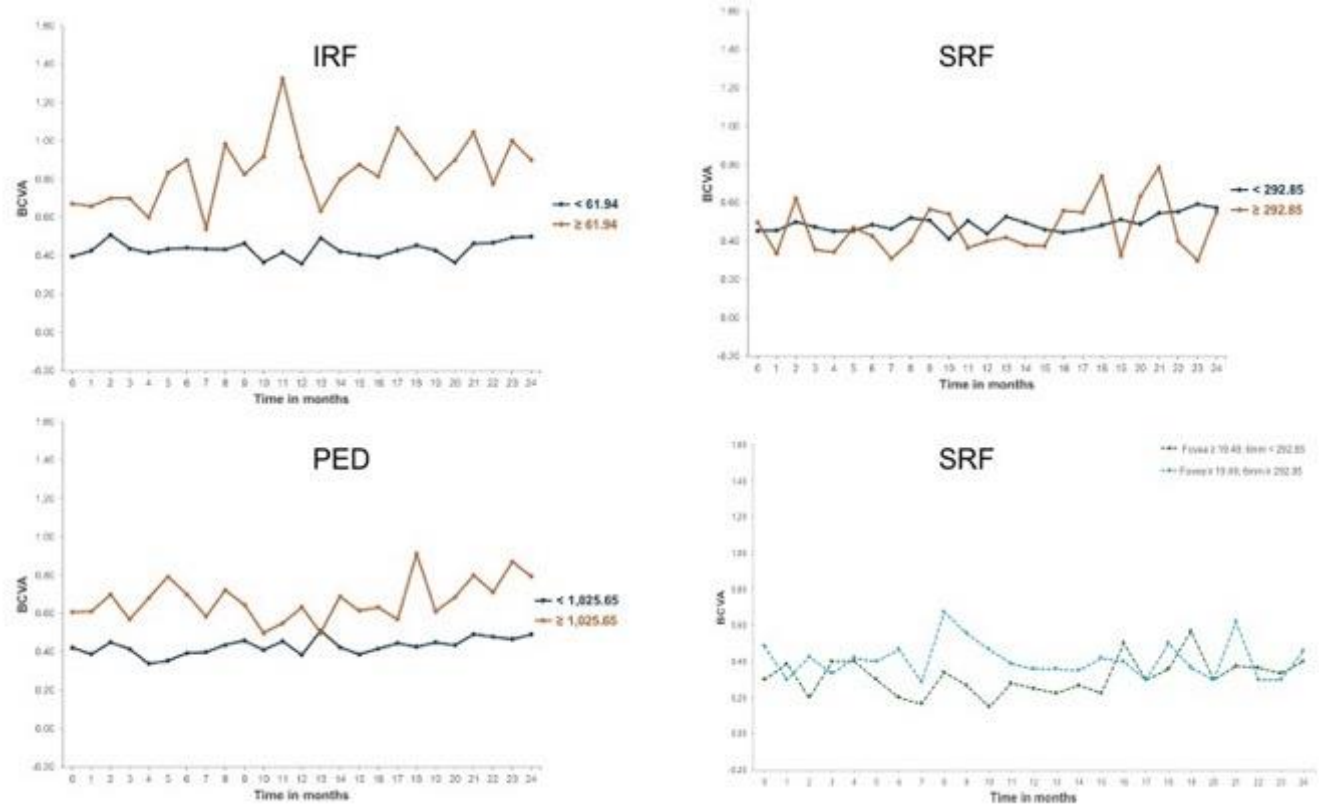


Figure 3: Kaplan-Meier survival curve showing significant higher subretinal fibrosis development in the higher fluid volume subgroup. Hazard ratio (HR), Intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED).
during follow-up.

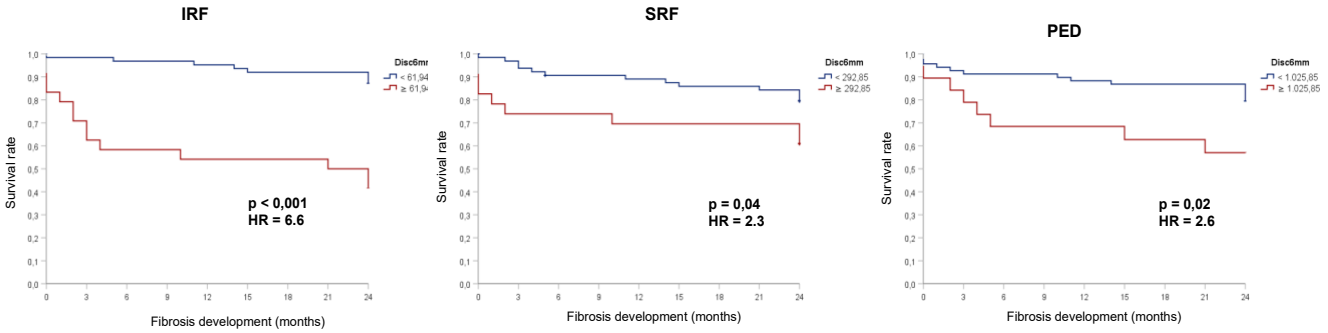
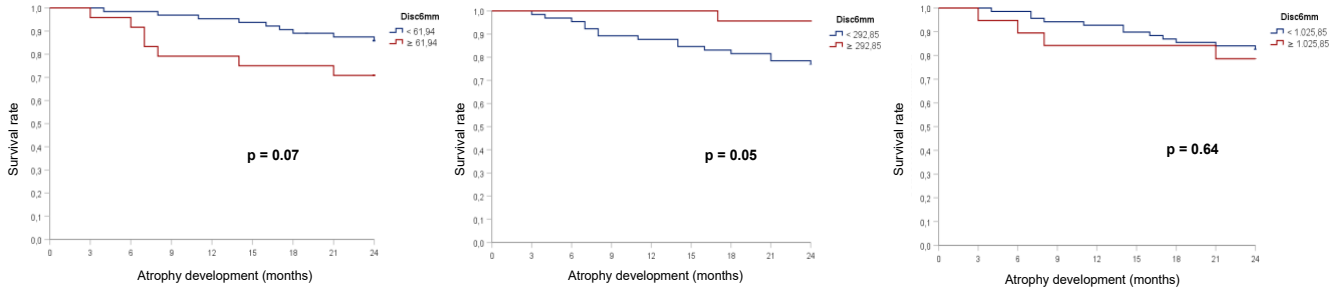
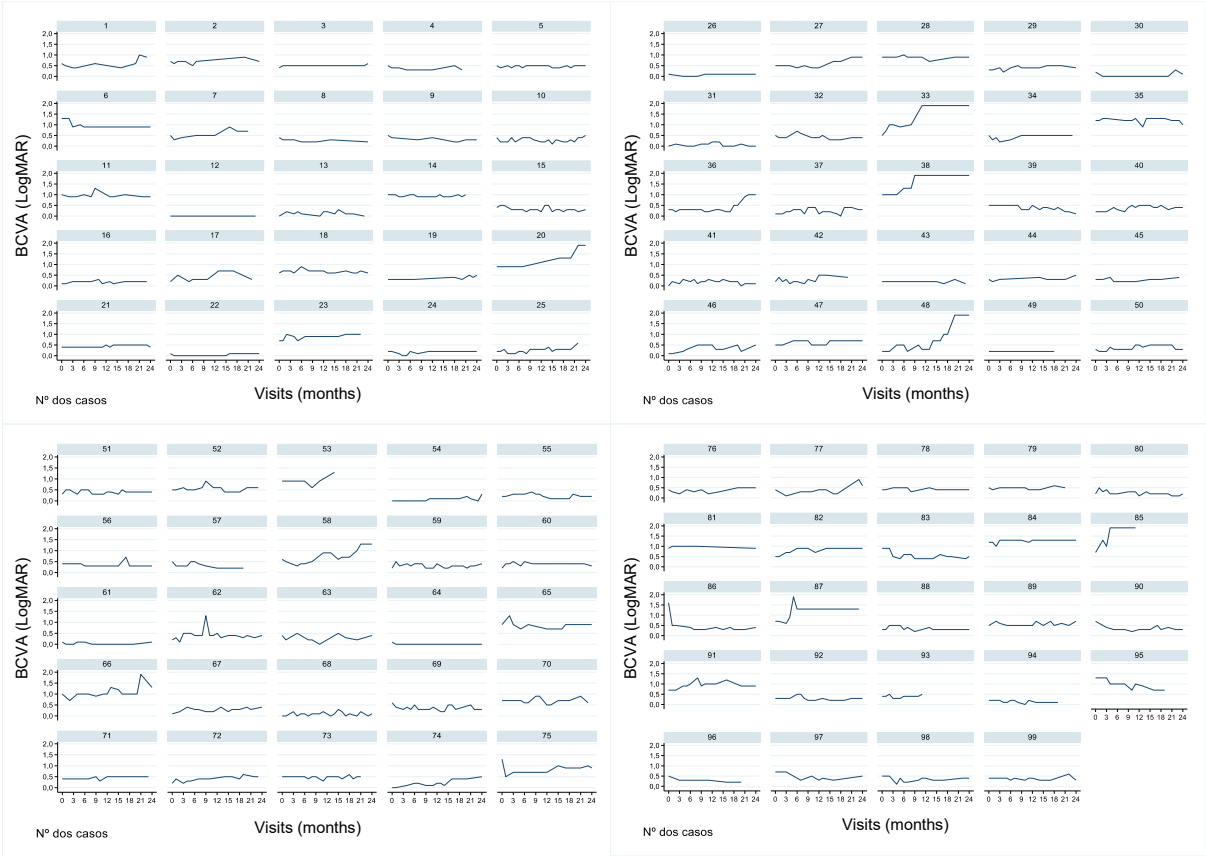


Figure 4: Kaplan-Meier survival curve of macular atrophy development did not show statistically significance difference between the two groups. Intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED).



Supplementary material: Visual acuity variation curve on each of the 99 eyes over the follow-up time.



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Os principais resultados desse trabalho estão resumidos abaixo:

- Foram estudados 99 olhos de 84 pacientes.
- Volumes basais mais altos de FIR, FSR e DEP no *baseline* nos 6 mm centrais da mácula mostraram impacto significativo na piora da acuidade visual ao longo de dois anos.
- 16 olhos (18,1%) desenvolveram AM e 21 olhos (23,8%) desenvolveram e FS em dois anos.
- Subgrupos com maiores volumes de FIR e DEP apresentaram maior risco de desenvolver FS tanto no 1 mm central quanto nos 6 mm centrais.
- O subgrupo com alto volume de FSR teve maior risco de desenvolver FS apenas nos 6 mm centrais.
- Não houve diferença significativa entre os grupos em relação à ocorrência de AM.

- O volume de FSR apresentou correlação estatisticamente significativa com o aumento de injeções necessárias para o controle da doença ao longo dos 2 anos de acompanhamento.

6 DISCUSSÃO

Os estudos desenvolvidos durante a elaboração desta tese fornecem evidências de que o algoritmo de monitoramento de fluido automatizado, o *Fluid monitor*, da RetInsight, Vienna, Austria, baseado em IA e aprovado pelo órgão regulamentador de equipamentos médicos da União Européia (*Medical Device Regulation*) oferece ferramentas úteis para o acompanhamento de pacientes com DMRI neovascular na prática clínica. Além disso, a quantificação e a localização automatizadas dos FIR, FSR e DEP podem ser utilizadas para predizer o prognóstico visual e anatômico, necessidade de tratamento e tendência a desenvolvimento de estágios avançados da doença.

Apesar dos avanços substanciais no diagnóstico e tratamento para DMRI, a prevalência estimada de comprometimento visual leve ou grave devido à essa doença aumentou globalmente em 10% entre 2000 e 2020.[102] Além disso, a cegueira relacionada à DMRI é um problema crescente diante do progressivo envelhecimento populacional. Sendo assim, o investimento em tecnologias de alta precisão para monitoramento da DMRI tanto na sua forma neovascular quanto na forma não neovascular representa um tópico de extremo interesse da comunidade científica.

O primeiro artigo dessa tese destaca o potencial de ferramentas baseadas em IA na identificação de padrões de fluidos e criação de modelos preditivos que podem estimar não apenas a necessidade de tratamentos futuros, mas também desfechos morfológicos tardios, como AM e FS. Um estudo desenvolvido pelo nosso grupo anteriormente elaborou um modelo preditivo para desfechos visuais e necessidade de tratamento aplicados a uma coorte padronizada do ensaio clínico TREND.[47] A aplicação de um modelo preditivo numa coorte de vida real, com as limitações inerentes a esse tipo de estudo, incluindo menor padronização do número de cortes

por imagem de OCT e a heterogeneidade no acompanhamento dos pacientes permitiu testar a segmentação do algoritmo e demonstrar a efetividade do modelo. Esse estudo identificou os 10 principais biomarcadores, funcionais e anatômicos, relacionados ao maior número de tratamento e maior progressão para estágios mais avançados da doença (Figura 4, artigo 1)[48]. Como previamente mencionado, o volume de FSR está mais relacionado a uma maior quantidade de injeções necessárias para “secar” a retina. O segundo biomarcador mais importante foi o DEP. Entretanto, já foi previamente publicado na literatura que o DEP responde de forma insatisfatória ao tratamento com anti-VEGF, não sendo um bom indicador, de forma isolada, para o tratamento.[103,104] Na predição para o desenvolvimento de AM, os principais biomarcadores foram funcionais (acuidade visual após o tratamento inicial e no *baseline,* respectivamente) seguido pelo FIR. Respostas piores após o tratamento inicial podem estar relacionadas a um dano prévio aos fotorreceptores que, por sua vez, podem preceder o desenvolvimento de atrofia.

Além disso, a não recuperação funcional, muitas vezes presente após o início do tratamento com anti-VEGF, mostra o potencial de agressividade da atividade neovascular e a importância de uma intervenção imediata para o melhor prognóstico visual. A literatura fornece provas convincentes de que o volume de fluido retiniano se correlaciona com acuidade visual e de que a função retiniana pode ser irreversivelmente perdida em semanas em caso de atraso no encaminhamento e no tratamento do paciente.[48,105,106] Sobre o desenvolvimento de FS, o FIR foi o biomarcador que mostrou uma correlação mais forte. A correlação estreita entre o FIR e a perda de acuidade visual e, em particular, com o desenvolvimento de FS foi também evidenciada nos artigos subsequentes desta tese.

Apesar da maior demanda de tratamento, o volume do FSR nem sempre apresenta correlação com o resultado funcional final.[49] Sabemos que o tratamento com injeções intravítreas de anti-VEGF mensais representa uma sobrecarga financeira para o sistema de saúde público e suplementar, bem como uma sobrecarga financeira e emocional para os pacientes. Individualizar esse tratamento pode representar uma oportunidade de diminuir o número de injeções, mantendo o controle adequado da doença para determinados casos. Entretanto, esse acompanhamento de forma precisa (em nanolitros) e personalizada se torna inviável de forma manual na rotina

diária atribulada das clínicas oftalmológicas. A quantificação automatizada de fluidos retinianos, como a utilizada nos estudos desta tese, pode auxiliar no monitoramento individualizado dos pacientes de forma a melhor compreender a dinâmica da doença e individualizar o esquema de tratamento no intervalo de poucos minutos. Um estudo prospectivo, realizado pelo nosso grupo nos últimos 3 anos, mostrou a viabilidade da aplicação desse modelo no dia-a-dia clínico do ambulatório de mácula do Hospital Geral de Viena e teve os resultados iniciais apresentados no congresso anual da ARVO 2024 *(Association for Research in Vision and Ophthalmology)*. [76,107]

Embora ainda não exista uma explicação clara que faça a corelação direta entre fluido e acuidade visual, acreditamos que os volumes de fluido retiniano desempenham um papel importante na perda de integridade dos fotorreceptores e que esta última está fortemente correlacionada com os resultados visuais. Sendo assim, o estudo reportado no artigo 2 foi realizado de forma a enfatizar a relação entre os volumes de FIR, FSR e DEP com a integridade da ZE. Os resultados mostraram que volumes maiores de FIR e DEP foram significativamente correlacionados com o afinamento e a perda da ZE o que impacta a integridade dos fotorreceptores e consequentemente compromete desfechos visuais. O FSR, por outro lado, não apresentou correlação significativa com o afinamento da ZE, sugerindo até um efeito protetor em determinados contextos. Essa observação é relevante pois corrobora a hipótese, previamente discutida na literatura, de que o FSR pode, em alguns casos, não ser tão prejudicial e contribuir para melhores resultados visuais a longo prazo. Entretanto, o volume de FSR e a sua flutuação podem ser a chave para melhor compreender quando ele se torna uma ameaça à visão.

Entendendo a necessidade de generalização dos algoritmos de IA, foi desenvolvido o estudo 3 que teve como foco uma análise longitudinal utilizando o *Fluid Monitor* em uma coorte brasileira de pacientes com DMRI neovascular. Os resultados mostraram que volumes mais altos de FIR, DEP e FSR nos 6mm centrais da mácula correlacionaram-se com pior desfecho visual e maior risco de desenvolvimento de FS. Esses achados se correlacionam parcialmente com os resultados encontrados na coorte do FRB! de Zurique. Entretanto na coorte europeia o subgrupo de maior volume de FSR não foi correlacionado com piora da AV. Para melhor discutir essa diferença nos resultados, é importante ressaltar que a quantidade de fluido intra e

subretiniano e volume do DEP no *baseline* da coorte brasileira foram consideravelmente mais altos. Sendo assim, essa diferença nos resultados reforça a importância de se avaliar o impacto dos fluidos retinianos por volume e por compartimento. Como citado anteriormente, e reforçado nos resultados dessa análise, pode haver um possível limiar de tolerância para o FSR, mas que necessita de estudos adicionais, prospectivos para a sua comprovação.

Uma vez analisado o real valor da IA, e a sua validação como ferramenta segura e útil para o manejo da DMRI neovascular, amplia-se grandemente o leque da sua aplicação. A sua utilidade para o diagnóstico e acompanhamento da forma atrófica da DMRI tem sido confirmada por publicações recentes, incluindo os estudos do nosso grupo. É muito provável que ela possa também desempenhar um papel muito importante no monitoramento domiciliar da DMRI, assim como de outras afecções retinianas. Ela poderá ainda ser de grande auxílio no planejamento de ensaios clínicos, permitindo, por exemplo, otimizar o processo de recrutamento e de seleção dos pacientes. As discussões desses tópicos, assim como as novas aplicações da IA, embora muito relevantes, fogem ao escopo deste trabalho.

Naturalmente, a implementação de algoritmos baseados em IA no diagnóstico e tratamento da DMRI apresenta limitações. A demanda por grandes conjuntos de dados para treinar modelos de IA pode introduzir vieses, já que certas populações ou variações nas características da doença podem estar sub-representadas. As considerações éticas em torno da privacidade do paciente, segurança dos dados e a interpretabilidade das decisões de IA também levantam preocupações e devem estar em conformidade com diferentes órgãos reguladores em cada nação. Outro aspecto a ser considerado são modelos de reembolso adequados em caso de sistemas de saúde suplementar. A diversidade de dispositivos, o constante lançamento de novos equipamentos e as variações nos protocolos de imagem em diferentes abordagens clínicas podem dificultar o desenvolvimento de algoritmos universalmente aplicáveis.

Esta tese contém trechos traduzidos do artigo de revisão, escrito pela própria autora e co-autores durante a elaboração da tese. Este artigo, intitulado **“AI-based support for optical coherence tomography in age-related macular degeneration”** , foi recentemente publicado e está anexado a essa tese como apêndice.[90]

7 CONCLUSÃO

Os modelos baseados em IA podem ser ferramentas úteis no acompanhamento individualizado da progressão da DMRI utilizando a quantificação de biomarcadores clínicos e subclínicos na prática clínica.

O FSR é um forte fator preditivo da necessidade de tratamento, mas nem sempre está significativamente relacionado com a piora da BCVA.

O FIR é o fator preditivo mais importante da perda de visão e do desenvolvimento de FS. Volumes maiores de DEP também foi correlacionada com piores resultados visuais e com o desenvolvimento mais rápido de FS.

O volume mais elevado de FIR e DEP no *baseline* (subgrupo com 25% mais fluido nos dois compartimentos) foi associado ao afinamento e perda mais avançadas da ZE nos 1 mm e 6 mm centrais da mácula, quando analisados os pontos temporais selecionados.

A identificação de sinais precoces de atrofia na prática clínica é um passo importante para um tratamento preciso e personalizado, minimizando o risco de sub-tratamento.

O algoritmo *Fluid monitor*, RetInsight, Viena, mostrou eficácia na segmentação e quantificação do fluido retiniano na coorte brasileira. Ainda são necessários mais estudos que enfatizem a importância do uso de tecnologias recentemente validadas, especialmente algoritmos de DL em diversas populações em todo o mundo.

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APÊNDICES

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: O uso da inteligência artificial para análise de biomarcadores nas doenças oculares do segmento posterior.

Pesquisador: Márcio Bittar Nehemy

Área Temática:

Versão: 3

CAAE: 58850622.4.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.709.728

Apresentação do Projeto:

Trata-se de um estudo observacional e retrospectivo, com análise dos prontuários e exames complementares e de imagem dos pacientes atendidos no departamento de retina do Hospital São Geraldo e do Instituto da Visão de Belo Horizonte de 2002 a 2022, em que serão estudados aspectos epidemiológicos (sexo e etnia), clínicos (acuidade visual) e de imagem (Retinografia, autofluorescência e tomografia de coerência óptica) das doenças do segmento posterior. A análise será realizada com o auxílio de algoritmo de inteligência.

Objetivo da Pesquisa:

São apresentados na Plataforma Brasil (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1924069.pdf):

"Objetivo Primário: O objetivo primário desse estudo é analisar retrospectivamente componentes funcionais e estruturais da retina com o auxílio de um algoritmo de inteligência artificial a fim de reconhecer biomarcadores, modelos, processos e subgrupos.

Objetivo Secundário: O objetivo secundário do estudo é predizer possíveis resultados visuais, necessidade de mais ou menos tratamento e fatores de risco para desenvolvimento de atrofia e fibroses (estágios avançados das doenças retinianas), utilizando inteligência artificial, em população brasileira portadora de doenças do segmento posterior. A primeira doença a ser estudada será a degeneração macular neovascular relacionada à idade."

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Avaliação dos Riscos e Benefícios:

São apresentados na Plataforma Brasil (PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1924069.pdf):

"Riscos: A avaliação retrospectiva dos dados dos prontuários não traz riscos, respeitada a confidencialidade dos dados e sua análise sigilosa e anônima, dentro dos padrões da boa prática científica.

Benefícios: Os benefícios advêm da melhor compreensão dessas doenças na nossa população, principalmente a DMRI e retinopatia diabética relacionadas à perda irreversível da visão com grande impacto social e econômico. Além disso, pode aumentar a assertividade e a qualidade da assistência, melhorando o planejamento e a adesão ao tratamento."

Comentários e Considerações sobre a Pesquisa:

A pesquisa possui mérito com aprovação da Câmara Departamental da FM/UFMG.

Considerações sobre os Termos de apresentação obrigatória:

Os documentos foram analisados em PB_PARECER_CONSUBSTANCIADO_CEP_5543945.pdf, Número do Parecer: 5.543.945, de 25 de Julho de 2022. Em resposta ao CEP, foram adicionados os documentos nesta submissão para análise:

CartaaprovacaoGEPHCUFMG.pdf: aprovação do GEP-UFMG/EBSERH de 10 de outubro de 2022.

CartarespostaaoCEP2.docx: carta resposta às solicitações deste CEP referente ao Número do Parecer: 5.680.395 de 03 de Outubro de 2022 (PB_PARECER_CONSUBSTANCIADO_CEP_5680395.pdf). Esclarece: "Foi esclarecida a faixa etária de inclusão dos pacientes como descrito abaixo:
Pag. 6, linha 154: "Serão incluídos no estudo os pacientes acima de 18 anos, atendidos ..." Pag. 7, linha 175 "Dados de imagem totalmente anônimos ou pseudonomizados existentes de pacientes acima de 18 anos." Sendo assim, o TALE e o TCLE do responsável não se aplicam e o TALE foi retirado dos documentos anexos."

Conclusões ou Pendências e Lista de Inadequações:

Aprova-se a pesquisa.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de

notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1924069.pdf	16/10/2022 16:27:11		Aceito
Outros	CartarespostaaoCEP2.docx	16/10/2022 16:26:06	Márcio Bittar Nehemy	Aceito
Outros	CartaaprovacaoGEPHCUFMG.pdf	16/10/2022 16:21:10	Márcio Bittar Nehemy	Aceito
Outros	CartarespostaaoCEP.docx	19/08/2022 07:27:49	Márcio Bittar Nehemy	Aceito
Outros	parecercamaradepartamental.pdf	19/08/2022 07:25:01	Márcio Bittar Nehemy	Aceito
Projeto Detalhado / Brochura Investigador	ProtocolodePesquisa_IA.docx	19/08/2022 07:22:19	Márcio Bittar Nehemy	Aceito
Outros	TCUD_IV.pdf	17/08/2022 12:16:48	Márcio Bittar Nehemy	Aceito
Declaração de Instituição e Infraestrutura	CartadeAnuencia_IV.pdf	17/08/2022 12:10:08	Márcio Bittar Nehemy	Aceito
Outros	cartaanuencia.pdf	17/08/2022 12:04:43	Márcio Bittar Nehemy	Aceito
Cronograma	cronograma.docx	17/08/2022 12:00:53	Márcio Bittar Nehemy	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_IA.doc	17/08/2022 11:58:23	Márcio Bittar Nehemy	Aceito
Folha de Rosto	folhaDeRostoIAassinada.pdf	03/05/2022 10:21:55	Márcio Bittar Nehemy	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Continuação do Parecer: 5.709.728

BELO HORIZONTE, 19 de Outubro de 2022

Assinado por:
Críssia Carem Paiva Fontainha
(Coordenador(a))

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REVIEW Open Access

AI-based support for optical coherence tomography in age-related macular degeneration

Virginia Mares[1,2], Marcio B. Nehemy[2], Hrvoje Bogunovic[1], Sophie Frank[1], Gregor S. Reiter[1] and Ursula Schmidt-Erfurth[1*]

Abstract
Artificial intelligence (AI) has emerged as a transformative technology across various fields, and its applications in the medical domain, particularly in ophthalmology, has gained significant attention. The vast amount of high-resolution image data, such as optical coherence tomography (OCT) images, has been a driving force behind AI growth in this field. Age-related macular degeneration (AMD) is one of the leading causes for blindness in the world, affecting approximately 196 million people worldwide in 2020. Multimodal imaging has been for a long time the gold standard for diagnosing patients with AMD, however, currently treatment and follow-up in routine disease management are mainly driven by OCT imaging. AI-based algorithms have by their precision, reproducibility and speed, the potential to reliably quantify biomarkers, predict disease progression and assist treatment decisions in clinical routine as well as academic studies. This review paper aims to provide a summary of the current state of AI in AMD, focusing on its applications, challenges, and prospects.

Keywords Age-related macular degeneration, Anti-VEGF, Artificial intelligence, Choroidal neovascularization, Deep learning, Drusen, Geographic atrophy, Optical coherence tomography

Introduction

Artificial intelligence (AI) spans a wide range of techniques within computer science, executing tasks that were traditionally performed by humans [1]. Machine learning (ML) is a branch of AI firstly described by Arthur Samuel in 1959 as the combination of computational science and mathematical concepts used to perform specific tasks without being explicitly programmed [2]. Deep learning (DL) is a class of machine learning techniques dedicated towards developing artificial neural networks with multiple levels of abstraction in which task-specific features are not prespecified by human engineers, but they are learned directly from data using a general-purpose learning procedure [3]. The integration of AI into the field of medicine is not a recent phenomenon. The MYCIN system was developed at Stanford University in the 1970s to assist in diagnosing and treating bacterial infections [4]. From there, the amount of automated algorithms multiplied and more advanced AI-based systems were developed including risk prediction scales that are currently used in clinical practice [5–7]. AI has emerged as a transformative technology across various fields, and its applications in ophthalmology have gained significant attention due to the availability of large

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digital datasets from retinal imaging. The exponential growth of interest from the scientific community can be easily identified when analysing the raising numbers of publications in recent years. Using "artificial intelligence" and "ophthalmology" as keywords in PubMed there are 3187 publications from 1900 to 2023, 2820 (88%) of them were published in the last 5 years.

Due to the large potential of multi-modal imaging utilized for diagnostics and monitoring of vision-threatening conditions in clinical routine, the retina emerged as the most promising field for application of AI. Age-related macular degeneration (AMD) is one of the leading causes of severe visual loss worldwide and is described as a multifactorial interaction of metabolic, functional, genetic, and environmental factors [8, 9]. Late-stage AMD is characterized by vision-impairing lesions in the macula such as geographic atrophy (GA) in non-exudative AMD or macular neovascularization (MNV) in neovascular AMD (nAMD) [10]. Over the past 20 years, there were significant advances in diagnostic tools, ultimately spectral-domain (SD) optical coherence tomography (OCT) has become the gold standard imaging modality in AMD [11, 12]. 10–15% of all AMD cases advance to nAMD and often suffer from fast progressing devastating visual impairment. Thus, the introduction of intravitreal vascular endothelial growth factor (VEGF) inhibition in 2006 for treating nAMD was a landmark event in disease management [11, 12]. However, the half-lives of these biological drugs are short and in the context of chronic treatment over lifetime, may represent an important burden to the patient and to the health care system [13, 14]. Clinical trials such as PULSAR, TENAYA and LUCERNE analyzed treatment efficacy of more extended regimens in order to address this problem [15, 16]. Furthermore, the first intravitreal complement system inhibitors were approved by the US Food and Drug Administration (FDA) in 2023 to treat patients with GA, [17] representing an additional burden on already stressed health care systems.

Fortunately, efficient AI algorithms relying on high resolution imaging have the potential to reduce time effort and improve quality standards in evaluating disease activity in clinical practice. OCT images are characterized by their high-resolution depiction of retinal structures, containing many millions of pixels in each volume, providing the most critical parameters for guiding treatment decisions in AMD [18]. This review paper aims to provide an overview of the current state of AI in OCT in AMD focusing on its applications, challenges, and prospects.

AI in retinal imaging

Before the advent of AI-based tools, management of retinal pathologies relied mostly on dichotomous parameters, meaning subjective assessment of presence or absence of specific biomarkers. A binary approach often underestimates biomarker dynamics and the intricate nature of all retinal conditions, including AMD. The multi-modal approaches lead to an enormous amount of information for each patient at each visit. However, traditional methods struggle to capture the subtle variations in pathology, such as atrophy progression, fluid volume and fluctuation. Moreover, novel biomarkers of relevance are subclinical in nature such as photoreceptor layer loss consistent with the ellipsoid layer attenuation. Hence, advanced AI detection tools are needed to reliably inform the clinician about the state of the disease in GA. Nevertheless, the ageing population causes a continuous growth in the prevalence of AMD worldwide, demanding novel strategies capable of screening as well as precisely following disease progression in a faster and reliable manner. AI enables a prompt analysis by quantifying various parameters, that are usually challenging to assess comprehensively by humans in a busy clinical practice [19, 20].

Early detection is paramount in managing retinal diseases as it allows for timely intervention in case of conversion to sight-threatening stages of the disease. For example, the presence of large confluent drusen, subretinal drusenoid deposits, refractile deposits, large and central pigment epithelial detachment (PED) and vitelliform material on intermediate AMD were described as phenotype precursors for GA development [21, 22]. Multimodal imaging is a praised gold standard to identify retinal biomarkers. Historically, color fundus photography (CFP) played an important role in screening due to its non-invasive and fast acquisition and broader availability of devices, including the recent emergence of portable handheld devices or applications on smartphones. Due to lower complexity of this imaging modality potentially less intricate algorithms are able to automatically analyze the images [23]. AI-based technology applied on CFP enables the detection of biomarkers such as drusen, haemorrhages and pigment abnormalities and may classify the eye following a binary (referable or non-referable) or multi-class scale (no AMD, early, intermediate, or advanced AMD) [24, 25]. A previous study showed sensitivity and specificity of AI-based screening for intermediate and advanced AMD using CFP achieving 93.2% and 88.7%, respectively [26]. However, limitations including real-world applicability and generalizability as well as demonstrating the long-term benefits on functional outcomes still need further prospective studies. So far, CFP has not been able to provide other than descriptive epiphenomena of AMD.

Fundus autofluorescence (FAF) emerged as a non-invasive imaging modality able to detect light emission from fluorophores such as lipofuscin, supposedly present within the outer segment of photoreceptors and the RPE. This property allowed FAF to further distinguish retinal lesions such as pseudo-drusen and atrophic regions [27]. Usually, blue-light FAF (488 nm excitation wavelength) is most commonly used for imaging AMD, however longer wavelengths, such as green or near infrared, have shown advantages in detecting subtle changes. Recently, AI-based algorithms applied on FAF imaging were developed with the potential of automated segment macular lesions in GA [28, 29]. However, FAF devices are not readily available in clinical practices. Furthermore, the perilesional patterns such as diffusely or focal granular, branching or reticular lipofuscin deposits can be subjectively interpreted and do not reliably correlate with GA lesion progression as neurosensory structures such as photoreceptors are not depicted by FAF.

The amount of information increases by millions due to the pixel-wise extraction when using AI on OCT images [30, 31]. OCT is a non-invasive real-time high-resolution imaging tool of the retina, which, combined with robust algorithms, has the potential to diagnose retinal disease and predict advanced stages, treatment response and visual outcomes in AMD [32].

De Faw et al. from the Google group presented the use of automated algorithms in the triage of retinal diseases at Moorfields Eye hospital, determining therapeutic referral need of a patient's condition. One of the algorithms presented referral recommendations reaching or exceeding the performance of eye care professionals for a range of sight-threatening retinal diseases [33]. The use of this technology on screening and referral pathways may open a cost-effective solution and could increase accessibility in areas of imbalance between caregivers and patients.

Since safety is a key issue in the AI field, the performance of human specialists and algorithms are compared to test and validate automated algorithms. For detection of retinal fluid in AMD patients, an AI-based algorithm showed higher accuracy than eye care professionals, [34] reinforcing the power of these automated measurement tools.

Post hoc analyses offer a good opportunity to validate and refine AI algorithms. However, the utilization of large-scale datasets, such as the Intelligent Research in Sight (IRIS) Registry, may be instrumental in prospectively evaluating AI systems in real-world scenarios [35]. The integration of AI with big real-world datasets not only facilitates the validation of AI technologies, but also contributes to the evolution of precision medicine by tailoring interventions based on the complexities observed in diverse patient populations. Nevertheless, in IRIS, image collection has not yet been integrated into AI and the variability of multiple devices and scan patterns used will present an important obstacle in performing a uniform image analysis.

AI techniques in OCT analysis

AI-based OCT analysis typically rely on different DL methods including convolutional neural networks (CNNs) and generative adversarial networks (GANs). CNNs in particular have been at the forefront of AI-driven image analysis in ophthalmology and in retina [36]. They exploit the fact that adjacent pixel values in the image are correlated and they excel at extracting hierarchical features from images, making them particularly effective for the vast amount of high-resolution image data present on OCT. In the context of AMD, CNNs can automatically learn and detect relevant retinal features to perform diverse tasks, such as layer segmentation and fluid quantification (Fig. 1) [37]. For example, Mishra et al. used CNNs to develop a shortest-path algorithm of 11 retinal layers, drusen and subretinal drusenoid deposits in SD-OCT based on probability maps (Fig. 2) [38]. Transfer learning, which involves fine-tuning pre-trained CNN models on OCT data, has proven beneficial

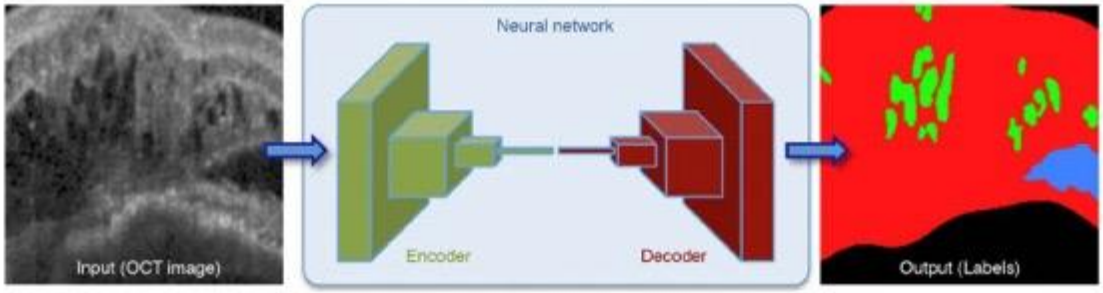

Fig. 1 Convolutional neural network with an *encoder-decoder* architecture to identify intraretinal fluid (green) and subretinal fluid (blue). The retinal tissue is marked in red. Reproduced with permission from Schlegl et al., 2022 [37]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article)

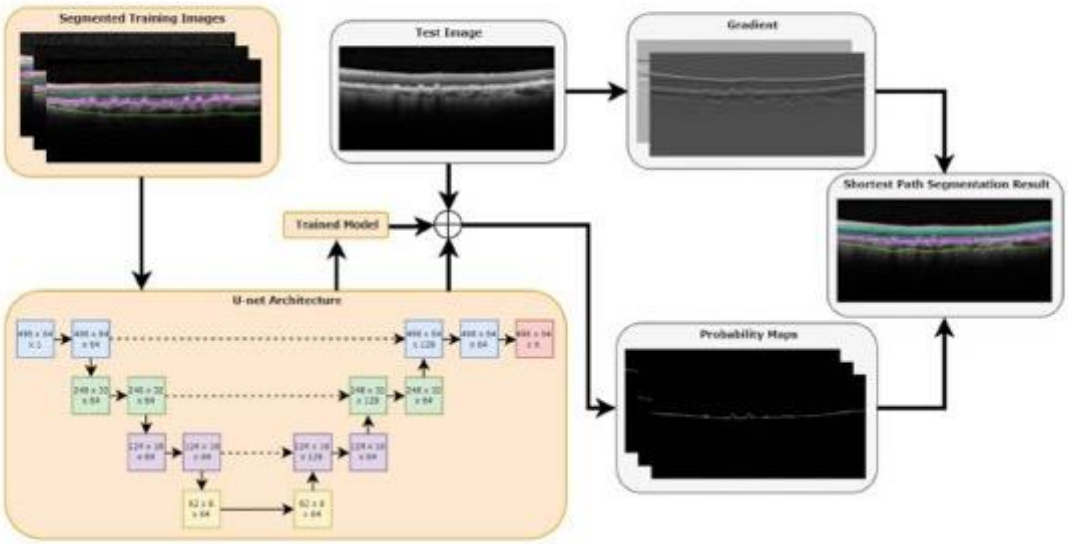

Fig. 2 Deep learning utilizing a short-path approach for segmenting retinal layers. Orange boxes represent training steps and gray boxes represent evaluation steps. Reproduced with permission from Mishra et al., 2020 [38]

for small datasets by leveraging knowledge gained from larger related datasets.

Layer segmentation is a critical step in extracting anatomical structures from OCT images. AI-powered segmentation algorithms employ techniques like U-Net, a convolutional network architecture tailored for segmentation tasks. Indeed, a precise segmentation aids in identifying disease-specific features such as photoreceptor integrity, defined as continued segmentation of the area between the top of the ellipsoid zone and the outer boundary of the interdigitation zone, and RPE layer disruption, enabling more accurate diagnosis and disease progression assessment [39–41].

Furthermore, GAN is a deep learning method that consist of two neural networks, a generator, and a discriminator, automatically working in tandem to produce high-quality synthetic data. In OCT analysis for AMD, GANs can aid in data augmentation for addressing the challenge of imbalanced datasets and for training models to detect abnormalities on OCT without the need for manual labelling [42]. GAN-generated images can also be applied for super-resolution and denoising in OCT images [43].

The foundation model's ability to leverage vast datasets for nuanced pattern recognition can play an important role in the early detection of retinal diseases [44]. A self-supervised learning-based foundation model was recently described as capable of training on unlabelled retinal images and showing satisfactory performance in detecting ocular disease and predicting systemic disease based on retinal imaging. Furthermore, it holds promise for democratizing access to medical AI and advancing clinical implementation by providing a publicly available resource for further research and applications [44].

AI in OCT in Intermediate AMD

Patients with early and intermediate AMD frequently show few to no symptoms. The speed of progression to advanced stages varies widely, hence it is of great importance to accurately identify key biomarkers and to predict the patient's conversion, as vision loss occurs only in advanced stages with foveal destruction. Since early interventions with intravitreal therapies are more beneficial in preserving visual function of patients, there is a strong drive towards early detection of converters [45]. Multiple prognostic markers have been identified preceding conversion to advanced AMD including demographics, genotype and structural features. For example, the location, volume and size of drusen indicated the progression to nAMD, whereas outer retinal thinning led to GA [46]. However, the features are confluent suggesting a common mechanism among the different types of AMD.

Subretinal drusenoid deposits (SDD) have been shown to be a significant biomarker, associated with a higher risk for developing type 3 MNV, outer retinal atrophy and GA [47, 48]. Therefore, it is desirable to automatically quantify them and implement in predictive progression models. However, segmentation of SDD can be challenging. A previous study showed an overall substantial inter-reader agreement regarding the presence of SDD, but a

slight and moderate inter-reader agreement for presence of type 1 and type 2 SDD on selected OCT B-scans [49]. Furthermore, a larger difference between human graders and AI was reported for SDD when compared to drusen [38]. With targeted efforts in this field, automated SDD detection is advancing.

The ongoing PINNACLE trial consisting of multimodal imaging including over 400.000 OCT images from AMD patients with a follow-up of up to 3 years is conducted to characterize and validate biomarkers for conversion and, as secondary outcome, develop predictive risk models [50]. Recently, a DL classifier was developed using data from the PINNACLE study identifying normal eyes and the onset of early and intermediate AMD, GA and nAMD automatically. It consists of a two-stage CNN categorizing disease stages with an AUC of 0.94 in a real-world test set [51]. Based on multiple risk factors for conversion identified, ML algorithms were developed to predict nAMD or GA conversion in fellow eyes of nAMD patients [52, 53]. Using the HARBOR trial dataset, an algorithm showed that converters to nAMD present different patterns than GA converters such as thickening of the RPE drusen complex, increased drusen area, HRF and outer nuclear layer (ONL) thickening in areas with hyperreflective foci. GA-converters on the other hand show global ONL thinning, RPE and inner segment/outer segment junction (IS/OS) thinning and hyperreflective foci in the ONL. This predictive model achieved an AUC of 0.68 with 0.46 specificity and 0.80 sensitivity for nAMD and a higher AUC of 0.80 with 0.69 specificity and 0.80 sensitivity for GA prediction [53].

AI in OCT in nAMD

Automated tools for guiding anti-VEGF therapy in nAMD is not new. Central subfield thickness (CST) is an automated measurement tool, widely used as endpoint and guide for treatment decisions in many clinical trials [14, 54]. However, this parameter does not provide any detailed information about location and extension of disease-specific activity and is often not adequately aligned in diseased macula. Furthermore, it does not distinguish between neurosensorial layers, retinal fluid compartment and pigment epithelial detachments. Previous studies have shown a weak correlation between CST and visual acuity as well as between CST and retinal fluid volumes [55, 56]. Moreover, in recent clinical studies comparing durability of the novel substances CRT values were used in various and irreproducible combinations making an objective comparison of the novel therapeutics impossible.

The most recent AI-based algorithms developed for OCT involve biomarkers such as fluid volume quantification in each compartment (intra- and subretinal), fibrovascular PED, subretinal hyperreflective material (SRHM) and hyperreflective foci [10, 19]. Despite the importance of all high-order biomarkers on disease classification and progression, [57, 58] post hoc analysis from TREND study and from the Fight Retinal Blindness! dataset using DL and ML showed that retinal fluid is still the most important anatomical biomarker for predicting disease activity, treatment demand and visual outcomes in nAMD [59, 60]. Indeed, recent analysis showed that not only the location of fluid is important for disease progression, however the dynamic fluctuation of each retinal fluid has a high impact on the outomes [61]. Volumes and changes in volumes of retinal fluid have a substantial impact on vision outcome. Higher IRF and PED were associated with worse visual outcomes, despite IRF being the fluid type with faster response to anti-VEGF therapy. SRF showed slower resolution, intuitively leading to an increased number of injections during the first year in a pro-re-nata regimen, however no significant correlation with worse functional outcomes was found presumably due to the predominant location of SRF outside of the central 1 mm of the fovea [59, 60, 62]. This highlights the notion that traditional treatment patterns have to undergo a reality check by a rigorous structure/function correlation. In long-term follow up, retinal fluid volumes and visual acuity are not generally, but individually correlated, indicating a concomitant neurodegenerative process [63]. Furthermore, despite "regular" treatment, most of nAMD patients are prone to develop subretinal fibrosis and macular atrophy with time [64, 65]. Higher amounts of fluid, particularly volume fluctuations, the presence of subretinal hyperreflective material and MNV type revealed to be correlated with atrophy or fibrosis development [61, 66–68]. Photoreceptor loss and RPE loss were strongly correlated with development of macular atrophy [69]. Thus, to better understand late anatomical outcomes, early changes on the photoreceptor layers in association with fluid behaviour may be further investigated through precise in vivo measurments [70]. Furthermore, there is still an open question if SRF, overall or dependent on its dynamics, might be protective against macula atrophy development in patients with nAMD [71].

OCT angiography (OCTA) represents a powerful non-invasive technology able to analyse choroidal and retinal vessels, including MNV characteristics in nAMD. A previous study analysing MNV characteristics using OCTA found a correlation between higher vessel tortuosity within the MNV area and worse visual outcomes as well as stronger trend to atrophic changes, despite lower exudation at baseline [72]. In the other hand, Sulzbacher et al. reported no significant correlation between OCTA patterns such as vessels density of the neovascular lesion and BCVA [73]. An automated and precise tool applied to choroidal flow, vessel density and other MNV

characteristics may open new perspectives on vascular biomarkers.

Home monitoring OCT

Home monitoring OCT has emerged as an innovative technological paradigm aimed at optimizing the surveillance of individuals affected by chronic sight-threatening pathologies, notably those requiring recurrent monitoring and fast intervention, such as nAMD [74]. Home screening tests for nAMD are not a novelty. Amsler grid and preferential hyperacuity perimetry has been previously proposed to detect metamorphopsia as an early sign of choroidal neovascularization in AMD patients [74, 75]. The current development of an AI-based fluid monitoring algorithm implemented on a home OCT device (The Notal Vision Home OCT system) showed promising results with feasible self-scan rates. This technology is not yet available on the market, however it showed feasibility in early detection of biomarkers and advanced stages of AMD such as neovascularization [76]. Home monitoring OCT may bring advantages including a decreased number of visits to the eye hospital and close monitoring of disease progression. However, there are challenges such as quality of data acquisition, safety of data transfer and integration of the acquired data into a local healthcare system. A previous economic evaluation based on a simulation showed that a home visual-field monitoring system for early CNV detection was cost-effective compared with scheduled examinations alone on patients at risk of developing nAMD [77]. Further cost-effective simulations should be conducted for new devices. Additionally, the concomitant escalation in data volume stemming from increased imaging monitoring frequencies is a major issue. Also, compliance has always prevented reliable and long-term self-monitoring in chronic disease. Shared-care as already implemented in Great Britain with community-based monitoring "around the corner" by fully equipped opticians may be a more realistic model, particularly if supported by standardized AI-based detection tools.

AI in geographic atrophy

GA is characterized by degeneration of the photoreceptors and RPE, accompanied by degeneration of the subjacent choriocapillaris, leading to irreversible vision loss [78, 79]. The literature mentions that GA affects around 5 million people worldwide, [80] however this number might be underestimating the total number of patients, as it primarily accounts for fovea-centered lesions. Consequently, it overlooks a significant spectrum of the disease in earlier stages all arising from the perifoveal area and being non-symptomatic. The diagnosis of GA was initially based on fundus photography [81]. Blue-light fundus autofluorescence (FAF) emerged as a valuable tool in diagnosing GA, since the degeneration of the RPE results in a clearly demarcated area of hypo-autofluorescence. Near-infrared reflectance (NIR) imaging, which has a longer wavelength, has also provided a benefit for visualization of GA lesions with lower interference caused by the macular luteal pigments [28, 82]. Therefore, the number, location and size of GA lesions as well as other disease-specific biomarkers could be measured easier with FAF [83]. Therefore, FDA and European Medicines Agencies accepted FAF-based measurements of changes in GA area as anatomical endpoint in the early clinical trials [84, 85]. Availability of high-resolution three-dimensional OCT imaging together with AI tools detecting the pathognomonic neurosensory, yet subclinical features not accessible to human specialists by retinal images alone, but accurately visualized on OCT-based AI analysis represent the novel horizon of precision medicine [28, 29, 86].

In clinical practice, OCT devices are widely available and are the gold standard in monitoring AMD. SD-OCT provides a more detailed information of the condition of the outer retinal layers, including the degeneration of photoreceptors in the lesions' active junctional zone [47, 87]. Therefore, OCT might provide more insights into progression patterns due to the detailed visualization of photoreceptor alteration. In a post-hoc analysis of the FILLY phase 2 clinical trial data set, findings from OCT imaging were consistent with FAF results measuring the RPE defect. Both imaging modalities could prove the superiority of treated patients regarding RPE loss, but only three-dimensional assessment in OCT was able to reveal early superior maintenance of photoreceptor integrity with complement inhibition [88]. To precisely measure these parameters, a DL algorithm segmenting A-scan regions on SD-OCT was clinically validated and tested using study datasets as well as real world images (Fig. 3) [88]. The GA monitor computes topographic maps and measurements of RPE and photoreceptor integrity loss based on 3D imaging and is accessible by a simple upload of a standard OCT image to the Heidelberg engineering Spectralis AppWay [41]. In the consecutive phase 3 studies, Oaks and Derby, high statistical significance with $p<0.0001$ was provided demonstrating that disease activity, i.e. GA growth correlated with the ratio between photoreceptor integrity loss and RPE loss, i.e. the PR/RPE loss ratio. The PR/RPE ratio also strongly determined the level of therapeutic benefit in the study results qualifying as a most reliable clinical parameter for treatment indications in GA (Fig. 4) [89, 90].

As the question remains unclear which patients should be treated, clinicians search for predictors of disease activity. For this purpose, a validated algorithm was used to predict topographic progression of GA by analysing RPE loss, photoreceptor integrity and hyperreflective foci

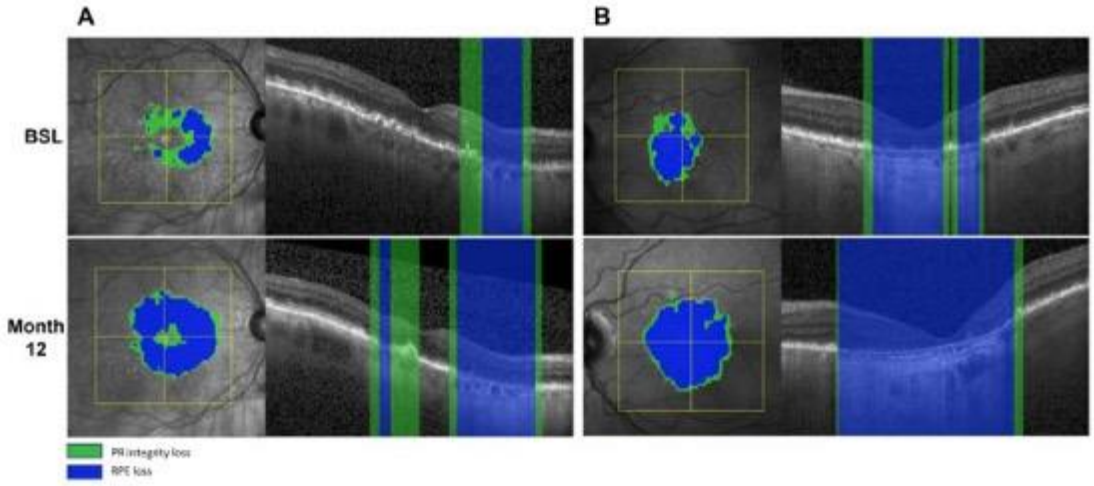

Fig. 3 Geographic atrophy (GA) lesion from two patients at baseline (BSL) (upper row) and at month 12 (lower row) from OAKS clinical trial dataset automated segmented with the AI-based GA monitor. Retinal pigment epithelium (RPE) loss (blue) and photoreceptor integrity loss (green) are shown as en face visualizations (left) and example B-scans (right). RPE loss extends into regions of preexisting PR loss

(HRF) [53]. Higher progression rates of GA were associated with atrophies closer to the fovea, HRF at the junctional zone and thinner photoreceptor layers. These tools could help in identifying progression patterns, which would support clinicians to better identify patients, who would benefit from a potentially life-long treatment.

AI-based OCT tools in clinical trials

Despite the previously mentioned potential of using AI in clinical practice, another evident application pertains to the recruitment processes in clinical trials for AMD. Developing a new drug presents a financial challenge, attributable to regulatory requirements, extensive data collection and usually prolonged timelines associated with clinical trials. The use of ML and DL models exhibit substantial promise in accelerating the enrolment of participants who are more likely to present faster progression to advanced stages of the disease, may present stronger response to specific novel therapies, and demonstrate a reduced likelihood of premature withdrawal from a trial [91]. An efficient selection process can increase sample size and consequently the detection of statistically significant differences between groups on a trial [53]. On the other hand, selecting patients with higher disease activity and possibly stronger response to a specific therapy could improve patient enrolment in clinical trials. Additionally, automated algorithms can assess morphological endpoints in a precise and reliable manner, most importantly in real-time for all clinical sites providing highest image quality as the images immediately undergo analysis control. Especially in GA, functional endpoints such as best-corrected visual acuity are frequently insufficient to describe all aspects of visual impairment [83]. Structural biomarkers are less influenced by patient compliance than functional endpoints. Clinical trials have been performed to study how disease activity assessment is influenced and supported by AI-based enrichment of OCT images. RAZORBILL (NCT04662944), Notal Vision Home OCT study (NCT04642183), and a prospective study using fluid monitoring (NCT05093374) are examples of ongoing trials using automated segmentation of retinal fluid volumes. A clinical trial using a DL algorithm on OCTA (NCT05969418) to analyze neovascular membrane vessel characteristics has started and as previously mentioned in this review the PINNACLE clinical trial cohort is being conducted for AI-based segmentation of early atrophy and fluid-related biomarkers on OCT (NCT04269304). Less intricate algorithms based on CFP segmentation are also under investigation for screening purposes such as iPredict (NCT04863391) and VeriSee AMD (NCT05593913).

The limitations of AI-based algorithms

The implementation of AI-based algorithms in AMD diagnosis and treatment comes with the known limitations of innovative approaches. The demand of large datasets for training AI models may introduce biases, as certain demographics or variations in disease characteristics may be underrepresented. The ethical considerations surrounding patient privacy, data security, and the interpretability of AI decisions also raise concerns and must comply with different regulations in each nation. Another aspect to consider are adequate reimbursement models. Furthermore, the diversity of devices, launch of

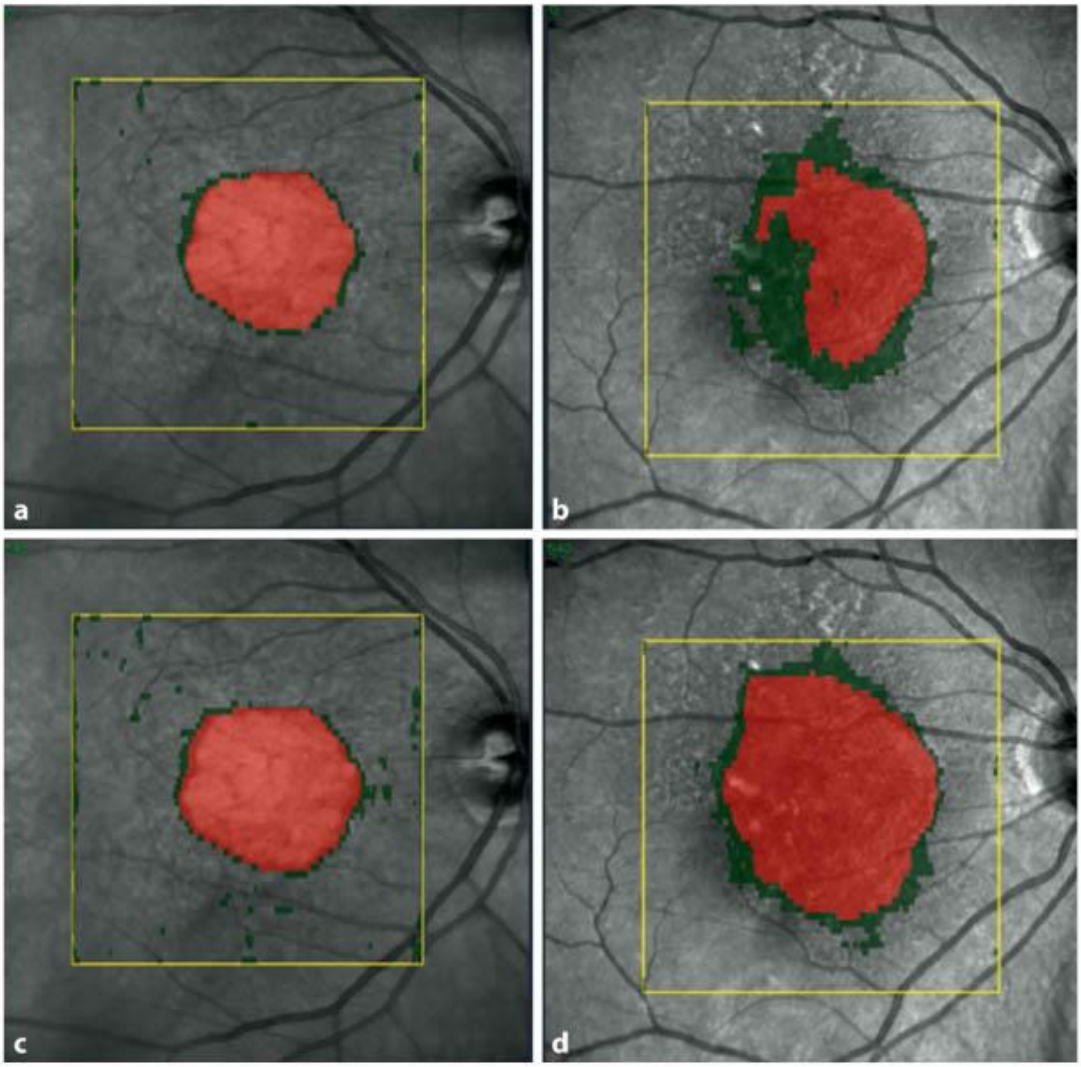

Fig. 4 Example of 2 lesions with geographic atrophy and different PR/RPE loss ratios. PR loss is marked in green and RPE loss in red. (**a**) shows a lesion with a small PR/RPE loss ratio and (**b**) a lesion with a large PR/RPE loss ratio at baseline. Letters (**c**) and (**d**) show the respective lesions at month 12 with significantly faster growth in the lesion with the higher ratio (**d**). Reproduced with permission from Schmidt-Erfurth et al., 2023 [90]

new imaging machines, and variations in imaging protocols across different clinical settings can hinder the development of universally applicable algorithms. While AI in retinal images holds promise, addressing these limitations is crucial to realizing its full potential in enhancing diagnostic accuracy and ensure its effective and ethical integration into clinical practice. The overwhelming introduction of OCT imaging hand-in-hand with anti-VEGF therapy using OCT hardware as a "fluid meter" clearly serves as a potent role model for the introduction of OCT-based AI analysis in times of GA management, an even bigger responsibility, 20 years later.

Conclusion

AI-based models can strongly benefit clinical practice and research in AMD. Multimodal imaging, the conventional standard for diagnosing patients with AMD, is being replaced by OCT imaging. Furthermore, DL and ML algorithms showed the potential of reliably quantifying biomarkers, predicting disease progression and

assisting treatment decisions. The next steps have to be taken for bringing AI from clinical research to its clearly needed application in everyday clinical practice, however, ongoing advances in the field are steadily narrowing this gap.

Author contributions
VM: Major contributor in writing the manuscript. MBN: Writing/reviewing the manuscript. HB: Writing/reviewing the manuscript. SF: Writing the manuscript. GSR: Writing/reviewing the manuscript. US-E: Writing/reviewing the manuscript and supervisor of the project. All authors read and approved the final manuscript.

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Declarations

Conflict of interest
No conflicting relationship exists for any author.

Competing interests
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