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ORIGINAL ARTICLE

Retinal ganglion cell loss is associated with future disability worsening in early relapsing–remitting multiple sclerosis

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Abstract

Background and purpose: Thinning of the retinal combined ganglion cell and inner plexiform layer (GCIP) as measured by optical coherence tomography (OCT) is a common finding in patients with multiple sclerosis. This study aimed to investigate whether a single retinal OCT analysis allows prediction of future disease activity after a first demyelinating event.

Methods: This observational cohort study included 201 patients with recently diagnosed clinically isolated syndrome or relapsing–remitting multiple sclerosis from two German tertiary referral centers. Individuals underwent neurological examination, magnetic resonance imaging, and OCT at baseline and at yearly follow-up visits.

Results: Patients were included at a median disease duration of 2.0 months. During a median follow-up of 59 (interquartile range = 43–71) months, 82% of patients had ongoing disease activity as demonstrated by failing the no evidence of disease activity 3 (NEDA-3) criteria, and 19% presented with confirmed disability worsening. A GCIP threshold of ≤77 μm at baseline identified patients with a high risk for NEDA-3 failure (hazard ratio

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[HR] = 1.7, 95% confidence interval [CI] = 1.1–2.8, $p = 0.04$), and GCIP measures of ≤69 μm predicted disability worsening (HR = 2.2, 95% CI = 1.2–4.3, $p = 0.01$). Higher rates of annualized GCIP loss increased the risk for disability worsening (HR = 2.5 per 1 μm/year increase of GCIP loss, $p = 0.03$).

Conclusions: Ganglion cell thickness as measured by OCT after the initial manifestation of multiple sclerosis may allow early risk stratification as to future disease activity and progression.

KEYWORDS
disability, multiple sclerosis, optical coherence tomography, prognosis

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that may cause sustained both individual and professional disability during adulthood [1,2]. Although a growing therapeutic armamentarium allows effective therapy of both mild and aggressive disease courses, early initiation of a sufficient immunotherapy is crucial for favorable long-term outcomes [3]. The anticipation of future disease courses in early stages of the disease, however, is still challenging. Thus, reliable prognostic markers for assigning patients to individual therapeutic regimens are paramount.

Retinal optical coherence tomography (OCT) is a fast and well-tolerated imaging technique allowing accurate and reproducible quantification of different retinal structures [4]. In addition to inflammatory and neurodegenerative lesions of the brain and spinal cord, patients with MS may reveal subclinical alterations of the retinal architecture. During the past years, atrophy of the inner retinal layers, in particular of the peripapillary retinal nerve fiber layer (pRNFL) and the combined ganglion cell and inner plexiform layer (GCIP), have been linked to future disease activity and disability, suggesting that retinal OCT might have the capacity to predict the future disease course [5-10]. In particular, a macular GCIP thicknesses < 69 μm [9], 70 μm [5,8,10], and 77 μm [6] have been suggested as a risk factor of future ongoing disease activity and/or disability worsening in patients with relapsing–remitting MS (RRMS). Here, we investigated whether a single retinal OCT analysis after initial manifestation of MS allows prediction of future disease activity and whether longitudinal OCT assessments allow estimation of ongoing disability worsening in patients with newly diagnosed clinically isolated syndrome (CIS) and RRMS.

METHODS

Study design

Patients were retrospectively identified from two ongoing prospective observational cohort studies of patients with CIS and RRMS on the disease course of MS recruited between 2011 and 2018 at the university hospitals in Munich and Berlin (Munich TUM-MS cohort, Berlin CIS cohort NCT01371071) and were followed over up to 9 years. Diagnoses were retrospectively revised in all patients according to the McDonald criteria 2017 [11]. Inclusion criteria were a diagnosis of CIS or RRMS, age between 17 and 60 years, disease duration between 30 and 180 days after onset of first relapse at the time of study inclusion, and a follow-up period of at least 18 months. Exclusion criteria were optic neuritis (ON) in both eyes, any ophthalmologic comorbidity, a refractive error of >6 diopters, neurological comorbidities that could affect disability, and diagnosis of any other neuroinflammatory disorder.

At study inclusion and at follow-up, we took a detailed medical history including relapses and immunotherapies and performed a neurological examination including the Expanded Disability Status Scale (EDSS). At baseline, the presence of cerebrospinal fluid (CSF)-specific oligoclonal bands (OCB) was obtained from medical records. We performed brain magnetic resonance imaging (MRI) with quantification of T2-weighted lesions. Patients from the Munich center received additional annual retinal OCT analysis during study visits. Follow-up visits including MRI were performed at least yearly. Additional and unscheduled visits including assessment of EDSS, and cerebral MRI occurred in individual patients due to novel symptoms or the advice of the treating physician. The primary outcome parameter was failure of the no evidence of disease activity 3 (NEDA-3) criteria, defined as freedom from relapses, absence of sustained disability worsening, and stable radiographic parameters (no change in brain T2 lesion numbers) during the follow-up period. Secondary outcome parameters were sustained disability worsening defined as an at least 1.0-point increase in the EDSS score if the baseline EDSS score was ≥1 or an at least 1.5-point increase in patients with an EDSS of 0 at study inclusion, confirmed at a visit at least 3 months later. Further secondary outcome parameters were occurrence of relapses and radiological disease activity as measured by MRI (increase in T2 lesion number).

As a first step, we searched for OCT predictors of the primary and secondary outcome parameters. As a second step, we applied different GCIP thickness values (≤69 μm [9], ≤70 μm [5,8,10], ≤77 μm [6]) that have been suggested as risk factors of ongoing disease activity in RRMS in the literature to our cohort to test their predictive value on the future disease course. As a third step, we compared the

predictive value of OCT measures to established clinical and MRI risk factors on the primary and secondary outcome parameters. As a last step, we investigated associations of longitudinal alterations of OCT parameters and disability. The study was approved by the local ethics committees at Charité–Universitätsmedizin Berlin and the Technical University of Munich and was conducted in accordance with the Declaration of Helsinki. All participants gave informed written consent.

Magnetic resonance imaging

MRI sequences were derived from 3-T MRI scanners (Berlin: Magnetom Trio, Siemens Healthineers; Munich: Achieva, Philips). Imaging details are described elsewhere in detail [9]. In principle, the scanning protocol consisted of 3-dimensional (3D) whole brain MRI data (resolution 1 mm^3) with T2-weighted, T1-weighted, and fluid-attenuated inversion recovery sequences. T2 lesion count was assessed by the lesion growth algorithm implemented in the Lesion Segmentation Tool toolbox for Statistical Parametric Mapping [12]. The segmentation of automatic lesion masks was corrected manually by experienced raters according to predefined processes at the respective centers. The presence of infratentorial lesions was rated manually.

Optical coherence tomography

At both centers, OCT examinations were acquired for both eyes of each patient under normal lighting conditions using a spectral-domain OCT (Heidelberg Engineering Spectralis OCT2). OCT images were acquired as described elsewhere and included examination of the pRNFL by a 12° ring scan and assessment of the macular GCIP within the 6-mm-diameter Early Treatment Diabetic Retinopathy Study grid extracted from a 30°×25° macular volume scan [8,9,13]. We checked all scans for sufficient quality according to the OSCAR-IB criteria [14]. Retinal segmentation was performed automatically by an inbuilt software algorithm (HEYEX v2.5.4, HRA v6.9.a) and was manually corrected if necessary. Eyes with former clinical and suspected unilateral subclinical ON were excluded from the analyses. A history of unilateral subclinical ON was defined as an intereye difference of both the pRNFL and the GCIP of >5 and >4 μm, respectively [15].

To evaluate longitudinal annual changes of OCT measures, eyes with a history of clinical ON or suspected subclinical ON at baseline or during the study follow-up were completely removed from this analysis. In a first step and for every single time point, we calculated mean values of both eyes when both eyes were available or used values of the remaining eye if one eye was excluded. Furthermore, time intervals between different OCT follow-up and baseline examinations were calculated. In a second step, we performed a linear regression analysis of OCT time intervals (referenced to baseline, x-axis) and OCT measures (y-axis) using GraphPad Prism (v9.3.1) and calculated the best-fit value of the slope that reflected the linear change of the respective retinal layer thickness (μm) per time interval (year). We adhered to the APOSTEL 2.0 recommendations for reporting quantitative OCT studies [16].

Statistical analysis

We performed statistical analysis with GraphPad Prism (v9.3.1). To account for inter-eye correlations, mean values of both eyes were used as one data point when both eyes were available. If one eye was excluded, values of the remaining eye were used. We applied Fisher exact test for contingency analysis of gender, diagnosis, center, infratentorial lesions, and OCB. Quantitative differences between two groups were calculated using an unpaired *t*-test if normally distributed or a nonparametric Mann–Whitney *U*-test if not. Differences between more than two groups were calculated by an ordinary one-way analysis of variance with Tukey multiple comparisons if normally distributed or a nonparametric Kruskal–Wallis test with Dunn multiple comparisons if not. To analyze the association of baseline clinical and OCT parameters and primary and secondary outcome measures, we applied adjusted Cox proportional hazards regression models. Multiple linear regression models were used to test the association of longitudinal OCT measures with EDSS values. We adjusted both Cox proportional hazards regression and linear regression models for age, sex, center, disease duration, and disease-modifying therapy (DMT) during the follow-up period if not otherwise stated. Here, DMT exposure was categorized as a dichotomous variable (yes, no). We provide adjusted HR measures for Cox models and the respective estimates (ß-value) as regression parameters. Values are provided as mean ± SD if normally distributed, otherwise as median (25%–75% interquartile range [IQR]). The statistical significance threshold was $p < 0.05$.

RESULTS

Study cohort

As shown in Figure 1, a total of 1381 patients (Munich, 1208; Berlin, 173) with CIS and RRMS were screened, and 206 patients (Munich, 128; Berlin, 78) met the inclusion criteria. Five patients (Munich, 4; Berlin, 1) were excluded due to the exclusion criteria. Furthermore, we excluded a total of 70 eyes due to a clinical history of ON, six eyes due to suspected unilateral subclinical ON, and 18 eyes due to quality issues. Thus, a total of 201 patients (Munich, 124; Berlin, 77) with 308 eyes (Munich, 188; Berlin, 120) were included in the final analysis. Hereof, 96 patients (Munich, 66; Berlin, 30) have already been reported in other studies [8-10].

At baseline OCT, patients were overall just mildly affected (median EDSS = 1.0, 25%–75% IQR = 0–2.0) and had a very short disease duration (median = 2.0, IQR = 1.5–4.0 months; Table 1). Most patients (90%) had CSF-specific OCB during the initial diagnostic

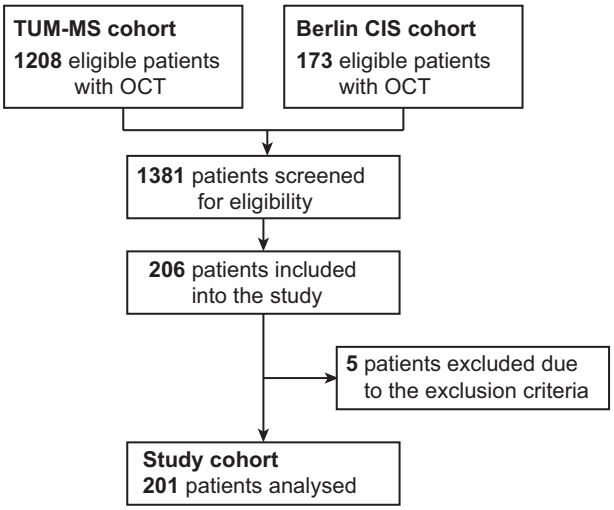

FIGURE 1 Study profile and number of participants. CIS, clinically isolated syndrome; OCT, optical coherence tomography; TUM-MS, Technical University of Munich multiple sclerosis

workup, and 49% had at least one infratentorial lesion on cerebral MRI at study enrollment. There were differences between the centers regarding disease duration, diagnosis, DMT at baseline, T2 lesion counts, and infratentorial lesions (Table S1).

Follow-up

Median clinical follow-up duration was 59 (43–71) months. A total of 165 (82%) patients met the primary outcome parameter by failing NEDA-3 criteria. Concerning secondary outcome parameters, 39 (19%) patients showed confirmed disability worsening and 89 (44%) patients suffered from a second clinical relapse during follow-up. One hundred forty-seven (73%) patients showed disease activity on MRI. Occurrence of primary and secondary outcomes were comparable between the centers, whereas follow-up duration and times to NEDA-3 violation, disability worsening, and MRI disease activity differed between the centers (Table S2).

Identification of OCT measures associated with disease activity and disability

In a first step, we searched for predictors of the primary and secondary outcomes. Using unadjusted Cox proportional hazard regression models, we found an association of higher age, immunotherapy, lower pRNFL, and lower GCIP thickness with a higher risk for violation of NEDA-3 criteria. Moreover, lower GCIP thickness was associated to a higher risk for disability worsening. Higher age and the application of DMT was linked to higher relapse rates and female sex, and center (Berlin) was connected to a higher risk for subclinical MRI disease activity (Table S3). When correcting unadjusted Cox proportional hazards regression models for age, sex, center, and DMT, a thinner GCIP still remained

TABLE 1 Baseline characteristics at study baseline, $N = 201$

Demographics	
Age, years, median (IQR)	32 (27–37)
Sex, female, *n* (%)	137 (68)
Disease duration, months, median (IQR)	2.0 (1.5–4.0)
EDSS, median (IQR)	1.0 (0–2.0)
History of ON, *n* (%)	70 (35)
Diagnosis, *n* (%)	
CIS	28 (14)
RRMS	173 (86)
Disease-modifying therapy, *n* (%)	37 (18)
MRI measures	
T2 lesion count, median (IQR)	12 (6–19)
Presence of ≥1 infratentorial lesion, *n* (%)	98 (49)
CSF measures	
Presence of oligoclonal bands, *n* (%)	161 (90)[a]
OCT measures	
pRNFL μm, mean ± SD	101.9 ± 10.2
GCIP μm, mean ± SD	71.4 ± 6.1
INL μm, mean ± SD	34.7 ± 2.3

Note: RRMS is according to the 2017 McDonald criteria. T2 lesion count and presence of infratentorial bands are as measured by cerebral MRI. Oligoclonal bands are as measured in the CSF. pRNFL, GCIP, and INL are as measured by OCT. Values are provided as mean ± SD if normally distributed or median (IQR) if not normally distributed, if not otherwise stated.Abbreviations: CIS, clinically isolated syndrome; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; GCIP, ganglion cell and inner plexiform layer; INL, inner nuclear layer; IQR, 25%–75% interquartile range; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ON, optic neuritis; pRNFL, peripapillary retinal nerve fiber layer; RRMS, relapsing–remitting multiple sclerosis.
[a]CSF data were only available in 178 of 201 patients.

associated with NEDA-3 failure and disability worsening (Table 2). Lower pRNFL measures were associated with a higher hazard for NEDA-3 failure (Table 2). We did not find any adjusted effects of pRNFL, GCIP, and inner nuclear layer (INL) on occurrence of relapse and MRI disease activity and did not see an impact of INL on NEDA-3 failure and of pRNFL and INL on disability worsening (data not shown).

In a second step, we aimed to validate different cutoff measures of GCIP thickness for prognosis of NEDA-3 failure and disability worsening in our cohort of patients with very early MS. In the literature, GCIP thicknesses < 69 μm [9], 70 μm [5,8,10], and 77 μm [6] have been suggested as markers of future disease activity in patients with RRMS. When applying these values to the present cohort, a GCIP threshold of 77 μm significantly differentiated between patients with high and low rates of NEDA-3 failure (Figure 2a, Table S4). Patients with GCIP measures of ≤69 μm (Figure 2b, Table S4) and by trend ≤70 μm (HR = 1.87, 95% CI = 0.99–3.59, $p = 0.055$; data not shown) revealed higher rates for disability worsening as compared to patients with the respective higher values.

TABLE 2 OCT measures associated with disease activity and disability

	NEDA-3 violation		Disability worsening		Relapse		MRI disease activity	
Variable	**aHR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**aHR (95% CI)**	***p***
pRNFL[a]	1.02 (1.00–1.04)	**0.03**	1.00 (0.97–1.03)	0.94	0.99 (0.97–1.01)	0.27	1.00 (1.00–1.03)	0.05
GCIP[a]	1.03 (1.00–1.06)	**0.03**	1.05 (1.00–1.12)	**0.04**	1.02 (0.99–1.06)	0.20	1.02 (1.00–1.05)	0.11
INL[a]	1.04 (0.97–1.12)	0.30	1.06 (0.92–1.22)	0.45	1.08 (0.98–1.19)	0.13	1.01 (0.94–1.09)	0.71

Note: Multivariate Cox proportional hazard models for OCT predictors on violation of NEDA-3 criteria (primary outcome parameter) and disability worsening, occurrence of relapse, and MRI disease activity (secondary outcome parameters) are adjusted for age, sex, center, and disease-modifying therapy. Values are provided as aHR with 95% CI and respective *p*-value; *p*-values marked in bold indicate significance.Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; GCIP, ganglion cell and inner plexiform layer; INL, inner nuclear layer; MRI, magnetic resonance imaging; NEDA-3, no evidence of disease activity 3; OCT, optical coherence tomography; pRNFL, peripapillary retinal nerve fiber layer.

[a]Continuous decrease per micrometer. pRNFL, GCIP, and INL are as measured by optical coherence tomography.

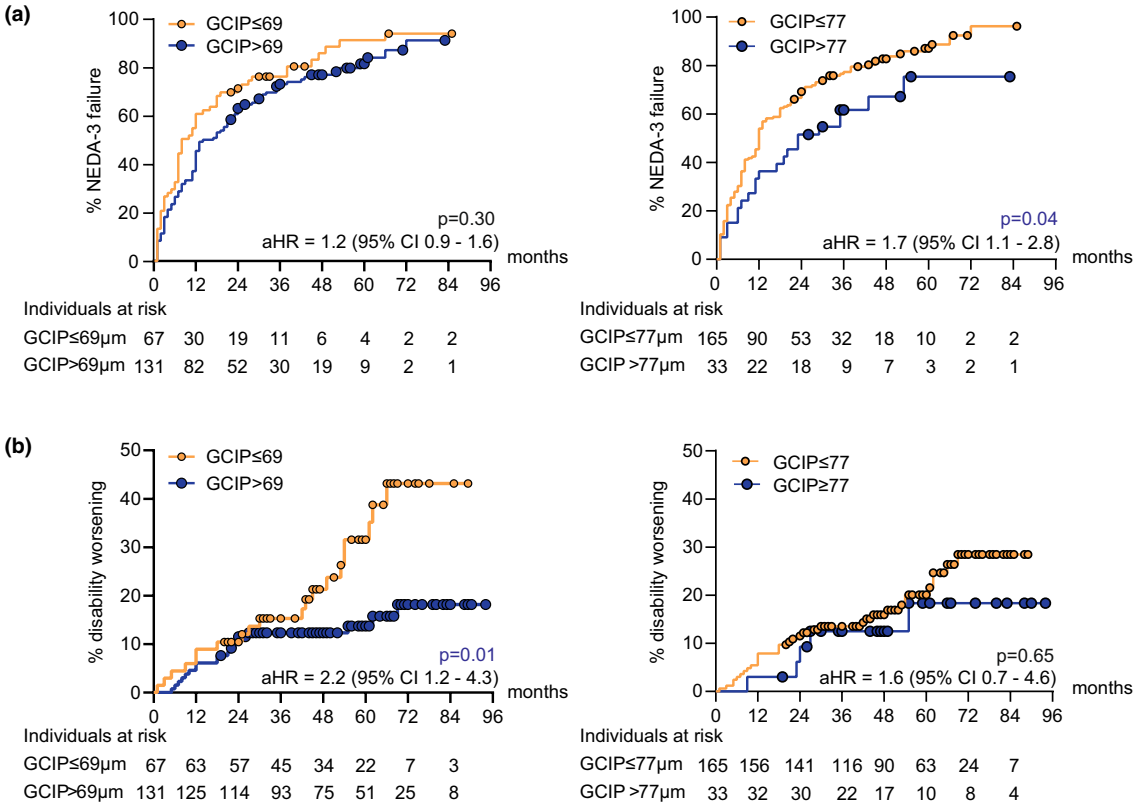

FIGURE 2 Kaplan–Meier plots for patients suffering from ongoing disease activity and disability worsening. (a) Cumulative fraction of patients with ongoing disease activity by failing the no evidence of disease activity 3 (NEDA-3) criteria stratified by ganglion cell and inner plexiform layer (GCIP) thickness of ≤69 µm and >69 µm (left) and ≤77 µm and >77 µm (right) at baseline. (b) Cumulative fraction of patients with disability worsening stratified by GCIP thickness of ≤69 µm and >69 µm (left) and ≤77 µm and >77 µm (right) at baseline. Kaplan–Meier analysis with Cox proportional hazards regression was adjusted for age, sex, center, and disease-modifying therapy. aHR, Adjusted hazard ratio; CI, confidence interval

Comparing OCT markers to clinical, MRI, and CSF risk factors

Having validated GCIP as a predictor for disease activity and disability worsening in patients with very early MS, we aimed to compare its diagnostic value on disease activity and disability to other established clinical, CSF, and MRI parameters [17,18]. As shown in Figure 3 and Table S4, a diagnosis of RRMS, CSF-specific OCB at first diagnostic workup, and a T2 lesion count of >9 [17] were associated with violating NEDA-3 criteria during the study follow-up, in addition to GCIP measures of ≤77 µm. A diagnosis of RRMS, presence of infratentorial lesions, and T2 lesion counts >9, but not OCT measures, were associated with MRI disease activity. There was no influence of any measure on relapse occurrence. Notably, GCIP thickness of ≤69 µm, but not MRI lesion distribution or presence of OCB within the CSF, predicted future disability worsening in our study (Figure 3, Table S4). This remained robust when additionally correcting for the presence of infratentorial lesions or T2 lesion

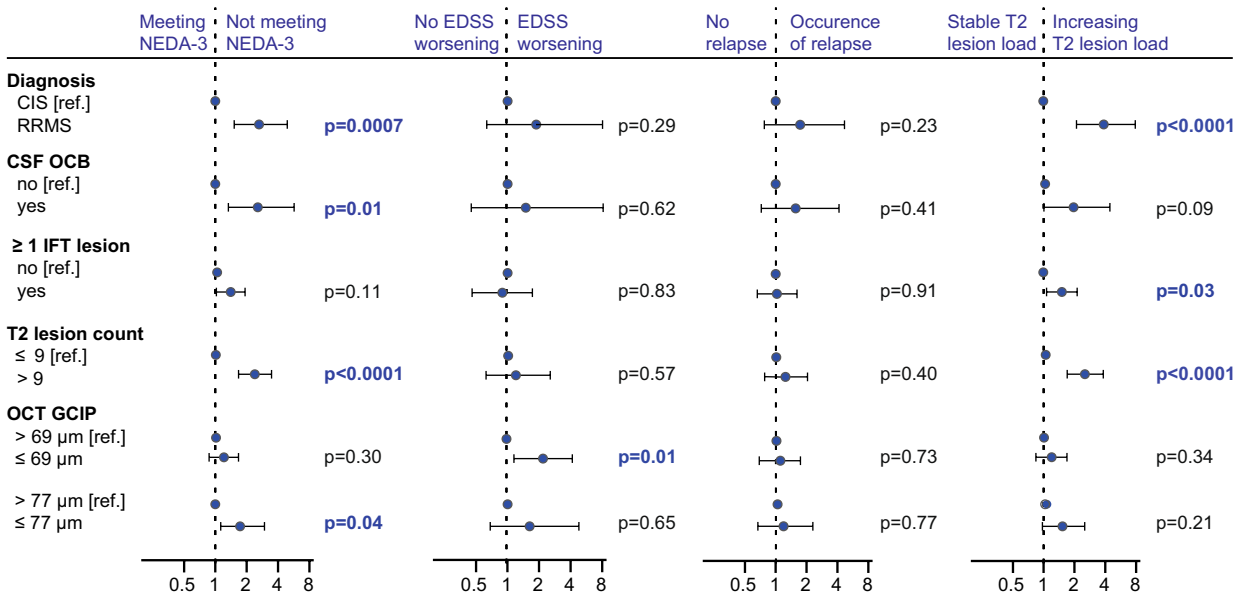

FIGURE 3 Association of diagnosis and measures from cerebrospinal fluid (CSF), cerebral magnetic resonance (MRI), and optical coherence tomography (OCT) with disease activity. Forest plots represent multiple Cox proportional hazards regression models of the effect of diagnosis at study enrollment (as defined by the McDonald 2017 criteria), presence of oligoclonal bands within the CSF during initial workup (CSF OCB), presence of at least one infratentorial lesion (≥1 IFT lesion) or T2 lesion count as measured by cerebral MRI at baseline, and thickness of the common ganglion cell and inner plexiform layer (GCIP) as measured by OCT at baseline on not meeting no evidence of disease activity 3 (NEDA-3) criteria, Expanded Disability Status Scale (EDSS) worsening, occurrence of relapse, and increasing T2 lesion load during follow-up; the shown data indicate adjusted hazard ratios (circles) with 95% confidence intervals (bars) as compared to the respective reference (ref.); *p*-values marked in bold indicate significance. CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis

count (disability worsening: GCIP thickness of ≤69 µm as compared to >69 µm, HR = 2.25, 95% CI = 1.14–4.45, $p = 0.01$; multiple Cox proportional hazards regression models corrected for age, sex, center, DMT, presence of infratentorial lesions, and T2 lesion load).

Association of longitudinal GCIP loss and disease activity

Finally, we searched for associations of longitudinal retinal measures with disease activity and disability. Here, OCT measurements obtained from 108 patients during 498 OCT examinations (median = 5, IQR = 4–6 OCT examinations per patient) were used. Longitudinal retinal ganglion cell thinning was associated with increasing EDSS values (Figure 4). Moreover, a higher rate of annualized ganglion cell loss increased the risk for disability worsening in patients with early RRMS and CIS (HR = 2.5, 95% CI = 1.1–6.3, $p = 0.03$ per 1 µm/year increase of GCIP loss; Cox proportional hazard regression corrected for age, sex, center, DMT). We did not detect a significant association between longitudinal alterations of the pRNFL and INL and any predefined outcome measure.

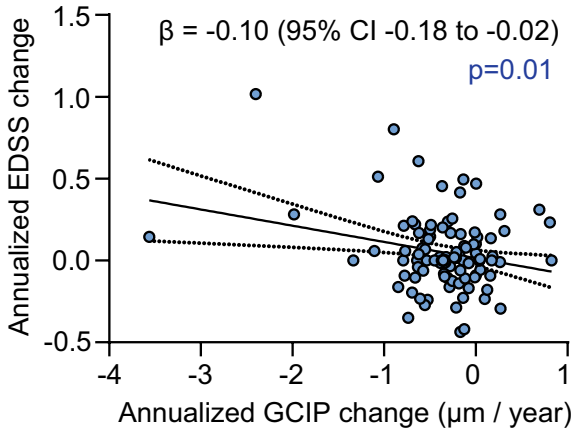

FIGURE 4 Association of longitudinal ganglion cell loss and Expanded Disability Status Scale (EDSS) measures. Annualized changes of the common ganglion cell and inner plexiform layer (GCIP) thickness and their association with annualized changes of the EDSS in $n = 108$ patients (all from the Munich cohort) are shown. The multiple linear regression model corrected for age, sex, and disease duration. Dotted lines indicate the 95% confidence interval (CI) of the β regression variable (line)

DISCUSSION

In the present study, we show that the GCIP thickness as measured by OCT might have the capacity to predict future disease activity and disability worsening in patients with early MS. Patients with GCIP thicknesses <77 µm had a 1.7-fold increased risk of suffering from future disease activity, and patients with GCIP measures <69 µm faced a 2.2-fold increased risk of disability worsening during the subsequent 9 years as compared to individuals with the respective higher measures. These findings might have implications for

clinical and therapeutic management in patients with a recent CIS and RRMS diagnosis.

As summarized here [4,19], GCIP loss is a frequent finding in patients with MS. Compared to healthy individuals, GCIP thickness is reduced by 6.3 μm on average in eyes from patients with RRMS without a history of ON [4]. It is assumed that subclinical ganglion cell loss during MS might result—in addition to subclinical optic neuropathy—from retrograde transsynaptic degeneration and might be a measure for chronic CNS neurodegeneration [20-22]. In line with this concept, GCIP thinning has been shown to correlate with both brain and spinal cord atrophy and disability in patients with MS [23-29]. Similar associations have been reported in individuals with CIS and radiologically isolated syndrome [13,28,30,31].

The prognostic value of GCIP on future disease activity has been recently evaluated by others. Applying a longitudinal prospective study design, GCIP thickness <70 μm in patients with MS was associated with fourfold increased odds of EDSS worsening during a median follow-up duration of 10 years as compared to patients with GCIP thicknesses ≥70 μm [5]. The investigated patient cohort, however, included both patients with RRMS and patients with progressive MS with significantly longer disease durations (>10 years disease duration in patients with GCIP <70 μm). Another study with a follow-up duration of 2.9 years detected a higher risk for disability worsening in MS patients with GCIP thicknesses of <77 μm [6]. Again, patients with both relapsing and progressive MS and a mean disease duration of 6.3 years were included, limiting the significance of their findings for patients with early MS. A recently published multicenter prospective study did not find an association of any OCT measures and disability progression during a follow-up of 3 years [26]. Here, mean disease durations were longer (7.3 years) than in the present study, and the proportion of MS patients with confirmed EDSS progression was only 7%. Given that in our study the majority of EDSS worsening occurred after 3–4 years, the follow-up of their study might have been too short to detect a robust impact of GCIP thickness on disability worsening.

Moreover, we found a robust association of GCIP thickness and future disease activity as measured by the NEDA-3. In a former study from 2017 including 66 patients from the current cohort, GCIP thickness <70 μm was associated with increased hazard for not meeting NEDA-3 criteria in RRMS patients with very short (median = 1.0 months) but not in those with longer disease durations (median = 36 months) up to 3 years after OCT analysis [8]. In another previous study from our groups from 2018 including 59 patients from the present cohort, GCIP values ≤74 μm were linked to higher rates of failing NEDA-3 criteria in patients with CIS during a median follow-up of 729 days [9]. After applying different GCIP thresholds to the current cohort, we could not detect a general GCIP threshold that identifies individuals with a high risk for ongoing (inflammatory) disease activity and disability worsening. Thus, and in line with the literature, very thin GCIP values of ≤69 μm (representing the lowest tertile in our study) might predict disability worsening, whereas thicker GCIP values of >77 μm (representing the top 15% in our cohort) might be associated with a stable disease course [5].

Several other risk factors for future disease activity have been described in the literature. Focusing on early stage MS, both cerebral lesion count and the presence of infratentorial and spinal cord lesions have been described as predictors for ongoing inflammatory disease activity and clinical progression [17,32]. In line with the literature, both cerebral lesion load and infratentorial lesions predicted ongoing disease activity as measured by NEDA-3 in our cohort, whereas this effect was mainly driven by predicting paraclinical inflammatory disease activity as detected by MRI. GCIP thinning, however, was the only parameter to identify patients with a high risk for disability worsening in the future.

We could also show that longitudinal GCIP thinning is associated with increasing disability. This finding is in line with the literature, where longitudinal GCIP loss has been described as associated with disability progression, disability progression independent of relapse activity, failure of applied immunotherapy, active MS lesions within the cerebral MRI, and brain atrophy [23,33,34,35,36].

Our study has several limitations. First, we only provide OCT measures derived from one type of OCT device. Measurements are not completely comparable between devices. Nevertheless, we could validate GCIP thresholds that have been detected by different devices (Heidelberg Engineering, Zeiss) in the past, suggesting that our findings might be robust independent of the OCT manufacturer. Second, although the data were derived from two ongoing prospective observational cohort studies, the outcomes have been defined retrospectively. Moreover, diagnostic criteria for MS have changed during the study, and we adjusted the diagnoses of patients afterward. Third, patient visits and MRI examinations occurred in different time intervals between the study centers. Fourth, although we included established markers for risk stratification as derived from MRI and CSF in the study, we were not able to include biomarkers like neurofilament light chain measures due to our study protocol [10].

CONCLUSIONS

This study shows that GCIP thickness as measured by retinal OCT, but not cerebral lesion load as measured by MRI, is associated with future disability worsening in patients with recently diagnosed CIS or RRMS. Thus, GCIP analysis could support risk-adjusted patient stratification. As a next step, we suggest applying OCT-derived GCIP thickness measures to randomized controlled interventional studies to prove their prognostic value and applicability for therapeutical decision-making.

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CONFLICT OF INTEREST

S.A. has received speaker's honoraria from Alexion, Bayer, and Roche. K.R. has received research support from Novartis Pharma, Merck Serono, German Ministry of Education and Research, European Union (821283-2), Stiftung Charité, and Arthur Arnstein Foundation, and travel grants from Guthy Jackson Charitable Foundation. T.S.-H. is funded by the institution from Celgene/BMS and Roche Pharma. She receives speakers' honoraria from Bayer and Biogen. C.C. has received speaking honoraria from Bayer, and research funding from Novartis, unrelated to this current study. A.B. has received personal fees and nonfinancial support from Alexion, Biogen, Celgene, Merck, Novartis, Roche, and Sandoz/Hexal, all outside the submitted work. A.U.B. is cofounder and hold shares of medical technology companies Motognosis and Nocturne. He is named as inventor on multiple patents and patent applications describing retinal image analysis methods, multiple sclerosis serum biomarkers, motor function analysis using 3D pose estimation, and myelinating treatments using modulation of N-glycosylation. F.P. reports research grants and speaker honoraria from Alexion, Bayer, Teva, Genzyme, Merck, Novartis, MedImmune, and Roche, and is a member of the steering committee of the OCTIMS study (Novartis). B.H. has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Sandoz, Polpharma, and TG Therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron for multiple sclerosis research. He holds part of two patents: one for the detection of antibodies against KIR4.1 in a subpopulation of patients with multiple sclerosis and one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study. H.G.Z. has received research grants from Novartis Deutschland and speaking honoraria from Novartis Deutschland and Bayer Healthcare. B.K. has received travel support and a research grant from Novartis and speaker honoraria from Teva. All remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. We will share raw imaging OCT data in an anonymized way upon request by any qualified investigator. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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