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Development of a Prognostic Model for Predicting Multiple Sclerosis After Optic Neuritis: A Secondary Analysis of Data From the Optic Neuritis Treatment Trial

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Background: Optic neuritis can be the initial manifestation of multiple sclerosis (MS). The purpose of this study was to develop a prognostic model for predicting the risk of MS development among patients with optic neuritis.

Methods: The data from 388 patients with optic neuritis were retrieved from the Optic Neuritis Treatment Trial (ONTT). Cox proportional hazards regression analysis was used to develop a prognostic model. The performance of the model was assessed by using Harrell's C-index and calibration curves. The rates of MS development were estimated using the Kaplan–Meier method.

Results: Among the enrolled subjects, a total of 154 (39.7%) patients developed clinically definite MS during a median follow-up period of 15.8 years (interquartile range, 7.2–16.9 years). The factors associated with the development of MS were the presence of brain lesions as on baseline MRI, previous nonspecific neurologic symptoms, commencing low-dose corticosteroids treatment, ocular pain, and absence of optic disc/peripapillary hemorrhage. After incorporating these 5 factors into the prognostic model, a C-index of 0.72 (95% confidence interval [CI], 0.69–0.76) and good calibration curves were obtained. The C-index of the model was significantly higher than the C-indexes of any single factor ($P < 0.001$ in all cases). The model was able to stratify the ONTT patient cohort into 3 risk groups with significantly different intergroup rates of developing MS (rates for developing MS within a 15-year period: high-risk group, 75.7% [95% CI, 65.6%–82.9%], intermediate-risk group, 44.7% [95% CI, 31.4%–55.4%]; and low-risk group, 20.8% [95% CI, 14.2%–26.8%]; log-rank $P < 0.001$).

Conclusions: This prognostic model had a better prediction ability when compared with the standard practice that relies solely on using brain lesions on MRI. It can, therefore, help guide decision-making to initiate earlier disease-modifying therapy for patients with optic neuritis at risk of developing MS.

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Optic neuritis is an acute condition that is caused by inflammation or demyelination of the optic nerve. It is usually associated with various degrees of visual loss, periorbital pain, and defects in color vision (1). Optic neuritis can be the initial manifestation of multiple sclerosis (MS) (2), which is a long-lasting disabling disease of the central nervous system with complex pathophysiology (3,4). Accumulating evidence suggests that the use of several disease-modifying therapies (DMTs) can reduce the frequency and severity of attacks and delay the development of MS after an optic neuritis episode (5,6). However, the use of DMTs might also lead to serious side-effects such as progressive multifocal leukoencephalopathy, cardiac arrhythmias, and hepatotoxicity (7). Similarly, the chance of developing MS after an episode of optic neuritis is not conclusive (2). Therefore, it is crucial to analyze the risk of developing MS among patients with optic neuritis to develop individualized treatment plans for those patients.

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The landmark Optic Neuritis Treatment Trial (ONTT) and several other studies have confirmed that the presence of brain demyelinating lesions on MRI is strongly associated with the development of clinically definite MS (CDMS) after optic neuritis (8–12). Accordingly, the presence of brain lesions on MRI is routinely used in clinical practice to predict the development of CDMS after optic neuritis (13). Nevertheless, information derived from a single predictor is not usually sufficient to assess the prognostic risk accurately (14). In fact, up to 20% of optic neuritis patients without brain lesions on the initial MRI scan still develop CDMS after long-term follow-up, while up to 40% of patients with brain lesions do not (2). Therefore, there is an urgent need to develop new and more accurate prognostic tools. In this study, we established a new prognostic model based on multiple factors including neuro-ophthalmic examination results in addition to brain lesions on MRI to predict the risk of CDMS among patients with optic neuritis. The prognostic model is presented as both a nomogram and an online calculator in this study. We compared the predictive accuracy of our model with single predictors.

METHODS

In this study, we used a publicly available ONTT data set which was obtained from http://lons.jaeb.org/. Details of the study were described previously (15,16). In short, the ONTT was a randomized controlled trial conducted from 1988 to 2006 to evaluate the effects of corticosteroids on acute optic neuritis and to determine the percentage of patients who subsequently developed CDMS. A total of 457 patients were enrolled from 15 clinical centers (14 academic centers and 1 community center) in the United States. The major inclusion criteria were a diagnosis of unilateral acute optic neuritis in patients aged between 18 and 46 years together with visual symptoms lasting 8 days or less before enrollment. The major exclusion criteria were a history of acute optic neuritis in the currently affected eye and evidence of systemic disease that can cause optic neuritis, other than MS.

Patients were randomly assigned to 3 treatment groups: (1) low-dose oral prednisone (1 mg/kg/day for 14 days), (2) high-dose intravenous methylprednisolone (IVMP) (1g/day for 3 days) followed by oral prednisone (1 mg/kg/day for 11 days), and (3) oral placebo (for 14 days). These patients were followed up for their visual outcomes and the development of CDMS. Standardized ophthalmic and neurological examinations were performed at the time of enrollment, at 6 and 12 months, and then annually for up to 5 years after enrollment and then at years 10 and 15.

Standardized unenhanced MRI of the brain (2.5-mm gap and 5-mm slice thickness) was performed at the time of enrollment (baseline). The number of white matter lesions of at least 3 mm in diameter on T2-weighted MRI was determined (17). Oligoclonal bands (OCB) were analyzed in cerebrospinal fluid (CSF) samples collected at the time of initial enrollment as described previously (18). In this study, we included patients without probable or definite MS at the time of initial enrollment to build a prognostic model for predicting MS after optic neuritis.

Our study outcome was the development of CDMS. Diagnoses were derived from the ONTT through application of Poser's criteria during the study follow-up period (19). The potential predictive variables associated with CDMS conversion were selected from the demographic and clinicoradiological features at the time of enrollment before modeling based on the clinical importance, professional opinion of the physician involved, and previously published evidence (2,12,20,21).

The ONTT followed the principles of the Declaration of Helsinki, and the study was approved by the institutional review boards of the performing institutions. All ONTT participants provided informed consent at the time of enrollment. The current study relies on deidentified data derived from the ONTT data set, and thus, it is exempt under 45 CFR 46.101(b) (4) from 45 CFR part 46 requirements.

Statistical Analysis

Categorical variables were expressed as the exact number and the corresponding proportions, whereas continuous variables were expressed as mean values with SDs or as medians with interquartile ranges (IQRs) based on the normal or non-normal distributions of the data. The rates of CDMS development in the study population were estimated using the Kaplan–Meier method, and differences in CDMS development rates were compared using the log-rank test. In this study, we used all available cases from the ONTT data for the development of the prognostic model and therefore did not need to recalculate the sample size (14).

Variables with $>50\%$ missing data (e.g., OCB) or binary variables (positive or negative) with a prevalence of $<5\%$ were excluded before the modeling process. For categorical variables with ≥ 3 categories, categories with similar effects or with a prevalence of $<5\%$ were combined (22). On this basis, we combined the placebo and low-dose oral prednisone treatment into a single category. For exploring the effect of high-dose IVMP on CDMS development, a sensitivity analysis including the uncombined treatment regimen categories was performed.

Missing data analysis indicated a random pattern of missingness for brain lesions on MRI. Missing data were imputed with multivariate imputations by chained equations using the *mice* package (version 3.6.0) in R. Consequently, 20 imputed data sets were generated.

The associations between the relevant clinicoradiological variables with CDMS development were assessed using the Cox proportional hazards regression models. A "stacked" data set combining multiplied imputed data sets was used for selection of predictors (23). Backward stepwise selection

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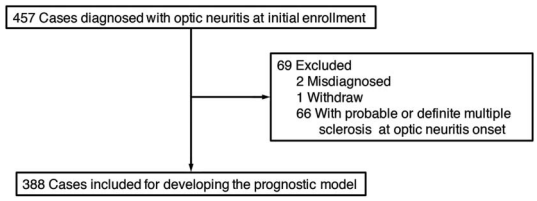

FIG. 1. Study flowchart.

was used to identify predictors for the multivariable Cox proportional hazards regression model based on the Akaike information criterion (24). The selected predictors were incorporated into a multivariable Cox proportional hazards regression model so as to predict the conversion rates for each imputed data set. The final estimates were pooled with Rubin's rule (25).

A nomogram and an online calculator for predicting the probability of CDMS development were created using the *rms* (version 5.1–3.1) and *Shiny* (version 1.4.0.2) packages in R, respectively. The performance of the prognostic model was assessed using Harrell's C-index (26) and calibration curves. The potential model optimism was evaluated by bootstrap validation with 1,000 resamplings. The prediction strength of our prognostic model was compared with the strength of single predictors using C-index and time-dependent area under the curve (tAUC) values. The *compareC* (version 1.3.1) and *timeROC* (version 0.4) packages were used to compare C-index and tAUCs, respectively. A larger C-index or tAUC indicates a better distinguishing capacity. Kaplan–Meier survival curves were used to assess the cumulative CDMS conversion rates among the different tertile risk groups stratified by the individual's predicted total points. The Kaplan–Meier survival curves were plotted for the overall cases, as well as for cases with or without brain lesions, respectively. All tests were two-sided, and a P value of <0.05 was considered to be statistically significant. Data were analyzed using R 3.6.1 (http://www.r-project.org).

RESULTS

Demographic and Clinicoradiological Features

A total of 391 among the 457 cases were diagnosed with optic neuritis without probable or definite MS at the time of initial enrollment into the ONTT. Two patients had a misdiagnosis of optic neuritis subsequent to the study entry, and 1 patient withdrew from the study before having undergone a baseline neurologic examination. Consequently, the number of patients enrolled into the current study was reduced to 388 (Fig. 1).

The mean age at baseline was 31.7 years (SD, 6.6 years), and 77% (299/388) of the patients were women. Most subjects (85% [330/388]) were Caucasian. Approximately 34% (133/388), 33% (129/388), and 33% (126/388) of the subjects were randomized into the high-dose IVMP treatment, low-dose oral prednisone and placebo groups, respectively. In addition, 46% (160/351) of subjects had at least 1 brain lesion at the baseline on MRI, and 20% (76/388) of the patients had previous nonspecific neurologic symptoms (self-reported symptoms but did not meet the criteria for MS attack). Finally, ocular pain and optic disc/peripapillary hemorrhage were observed in 92% and 5.9% of subjects, respectively. Among those enrolled, a total of 154 (39.7%) patients developed CDMS in a median follow-up period of 15.8 years (IQR, 7.2–16.9 years). The 5-, 10-, and 15-year CDMS conversion rates were 27.5% (95% confidence interval [CI], 22.8%–32.0%), 39.6% (95% CI, 34.1%–44.6%), and 43.0% (95% CI, 37.3%–48.1%), respectively.

Predictors in the Prognostic Model

The potential predictors evaluated using the univariable Cox proportional hazards regression model are shown in Figure 2. Brain lesions on MRI, previous nonspecific neurologic symptoms, treatment regimen used, optic disc/peripapillary hemorrhage, and ocular pain at onset were all included in our novel prognostic model (Fig. 3A). The multivariable Cox proportional hazards regression model (Fig. 3A) and a sensitivity analysis (Fig. 3B) showed that high-dose IVMP was associated with a reduced CDMS development rate. The nomogram of the model for predicting CDMS conversion probability after optic neuritis is shown in Figure 4. An online calculator of the probability is also available at https://drduyi.shinyapps.io/cdms.

Prognostic Model Performance

The C-index of the new model was 0.72 [95% CI, 0.69–0.76], with an optimism of 0.01. The 1,000 resampling bootstrapped calibration curves for the prognostic model for the CDMS development are shown in Figure 5.

Every imputed data set showed a high degree of similarity with each other. Therefore, we randomly selected 1 data set using R to analyze tAUC, cutoff values, conversion possibilities, and Kaplan–Meier curves for different risk groups of patients. The predicted conversion risk was stratified by the tertile and calculated from the nomogram (cutoff values of total points: low-risk group: 0 to <168, intermediate-risk group: ≥ 168 to <235, and high-risk group: ≥ 235) (Fig. 6A). Patients with the lowest predicted 15-year risk of CDMS development (20.8% [95% CI, 14.2%–26.8%]) (low-risk group) had a substantially better prognosis compared with patients in intermediate- and high-risk groups (44.7% [95% CI, 31.4%–55.4%] and 75.7% [95% CI, 65.6%–82.9%], respectively) ($P < 0.001$). Furthermore, Kaplan–Meier curves also demonstrated that the proposed prognostic model facilitates further risk stratification for CDMS development in patients with or without brain lesions (Fig. 6B, C).

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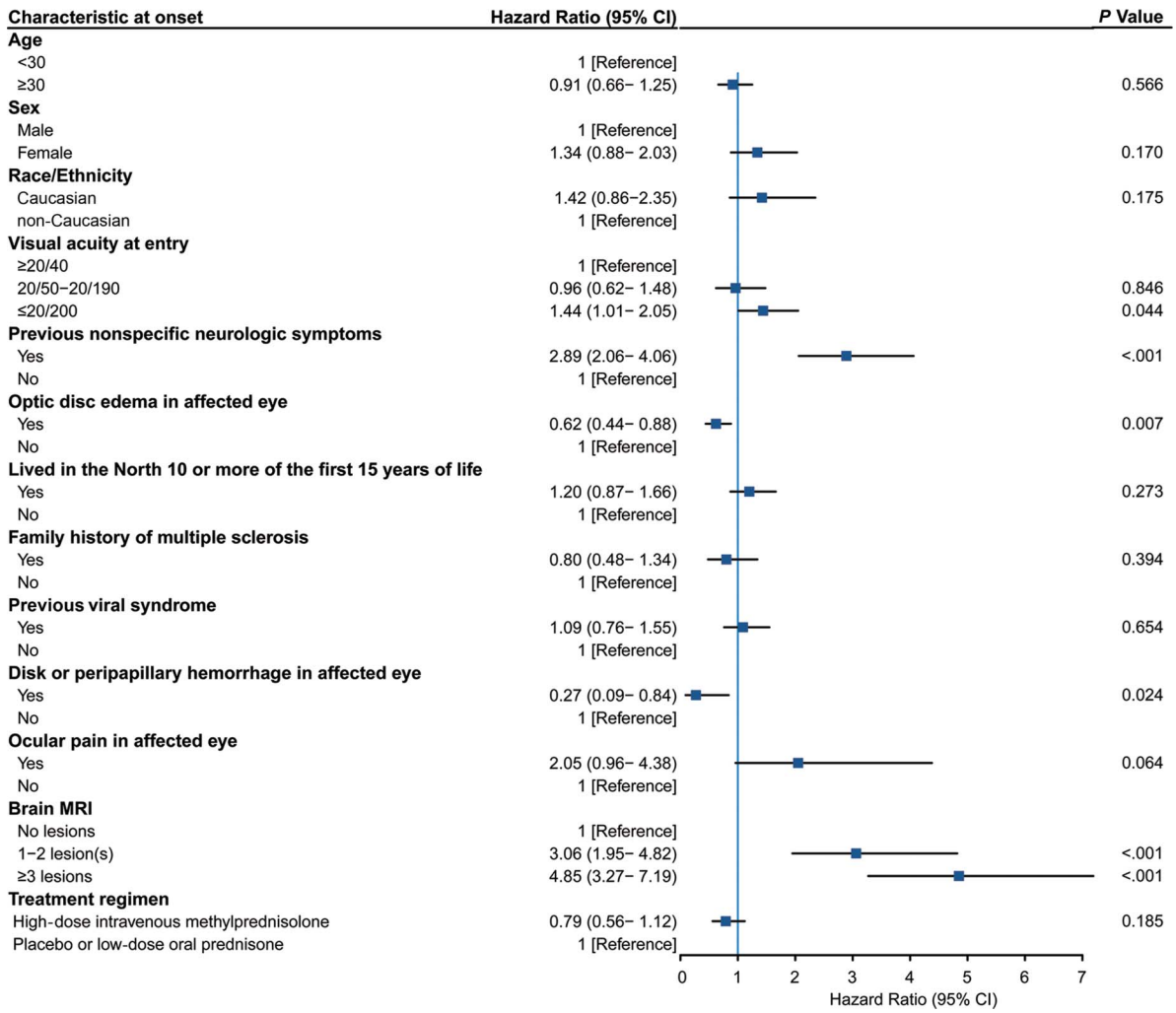

FIG. 2. The univariable Cox proportional hazards regression model demonstrating the association of different variables with the development of clinically definite multiple sclerosis after optic neuritis. Error bars indicate 95% CIs.

Comparison With Single Predictors

The C-index of the proposed model was significantly higher than those of the single predictors included in the model ($P < 0.001$ in all cases). Compared with the tAUC values for the single predictors, those for the proposed prognostic model were significantly higher ($P < 0.05$ in all cases; Fig. 7).

DISCUSSION

In this study, we developed a prognostic model for the prediction of CDMS development after an optic neuritis episode. Using the nomogram or the online calculator of this model, we divided the ONTT patient cohort into low-, intermediate-, and high-risk groups with respect to CDMS development. When patients with or without brain lesions were evaluated, the model allowed further risk stratification to be performed.

Previous studies have reported several risk factors, such as the presence of molecular biomarkers in CSF, which are associated with the development of CDMS after optic neuritis (2,13,27,28). However, in clinical practice, MRI is the main procedure that is routinely used for assessments. In the ONTT, 45.6% (160/351) of the optic neuritis patients without MS at the time of initial enrollment had brain lesions consistent with a more widespread demyelinating disease. In agreement, other studies demonstrated that brain lesions are associated with a higher risk of MS development (8–12). In our study, MRI lesions remain an important predictor. However, the integration of additional predictors increased the discrimination ability of our model in comparison with considering brain lesions alone.

The presence of a previous nonspecific neurological symptom can also be another CDMS predictor. This refers to transient numbness that is reported by patients, although these do not meet the criteria of an MS attack (17,20). Morrow et al and Marques et al previously demonstrated that a nonspecific neurological symptom can be one of the

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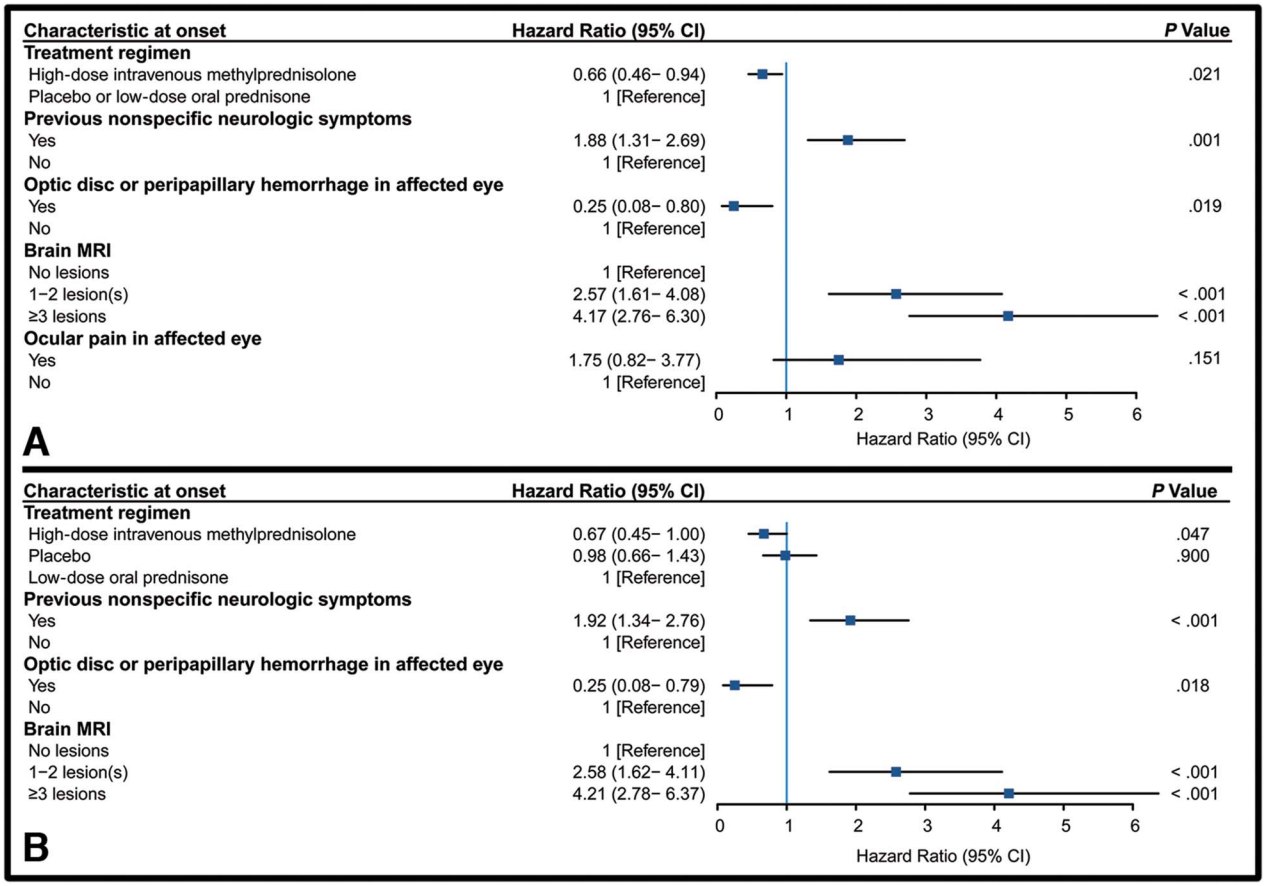

FIG. 3. The multivariable Cox proportional hazards regression model demonstrating the association of different variables with the development of clinically definite multiple sclerosis (CDMS) after optic neuritis. **A**. The proposed prognostic model and (**B**) a sensitivity analysis. Error bars indicate 95% CIs.

most powerful predictors for developing MS after optic neuritis (10,29). In agreement with these findings, we found that the presence of a nonspecific neurological symptom was the second-strongest single predictor associated with CDMS development in the ONTT cohort of patients. In addition, although the ocular pain association did not reach statistical significance, it was included in our prognostic model to improve the model's performance (24).

Furthermore, the ONTT evaluated the impact of corticosteroids therapy on delaying the development of CDMS. Previous reports suggested that the impact of high-dose IVMP treatment on patients with CDMS was transient and its beneficial effect was likely to be lost after 2 years (17,30). By contrast, our analysis found that high-dose IVMP was associated with a reduced CDMS risk over the 15-year interval studies. This discrepancy could mainly be attributed to 2 reasons. First, the cross-sectional analysis that was used in 1 previous study lacked the required sensitivity to uncover the association between high-dose IVMP treatment and CDMS development (30). Second, the baseline imbalance in the treatment groups was not properly adjusted regarding the predisposition for CDMS (e.g., brain lesions) in the previous studies (20,30).

Recently, 2 prognostic models based on several CSF biomarkers, such as IL-10, neurofilament light chain, and OCB, were developed to predict the development of CDMS after optic neuritis (31). The area under the curves of the 2 prognostic were relatively high (0.86 and 0.89, respectively). However, these models were developed based on small sample sizes (40 cases and 16 events) with small ratios of events per variable. This can lead to instability and unreliability of the models with overoptimistic model performance expectations (32). Furthermore, these models relied on variables that required an invasive lumbar puncture procedure to obtain the CSF. On average, up to 57% of patients will have difficulty enduring such invasive sampling techniques (16). Our prognostic model showed a relatively high C-index (0.72) and did not rely on invasive testing techniques or included sophisticated measurements of CSF variables. Therefore, the variables of our model are much easier to obtain and are convenient for clinicians to use.

The discovery of novel biomarkers has enabled the categorization of optic neuritis into several subtypes (33). Optic neuritis associated with serum aquaporin-4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG) antibodies has distinct characteristics compared with patients who are

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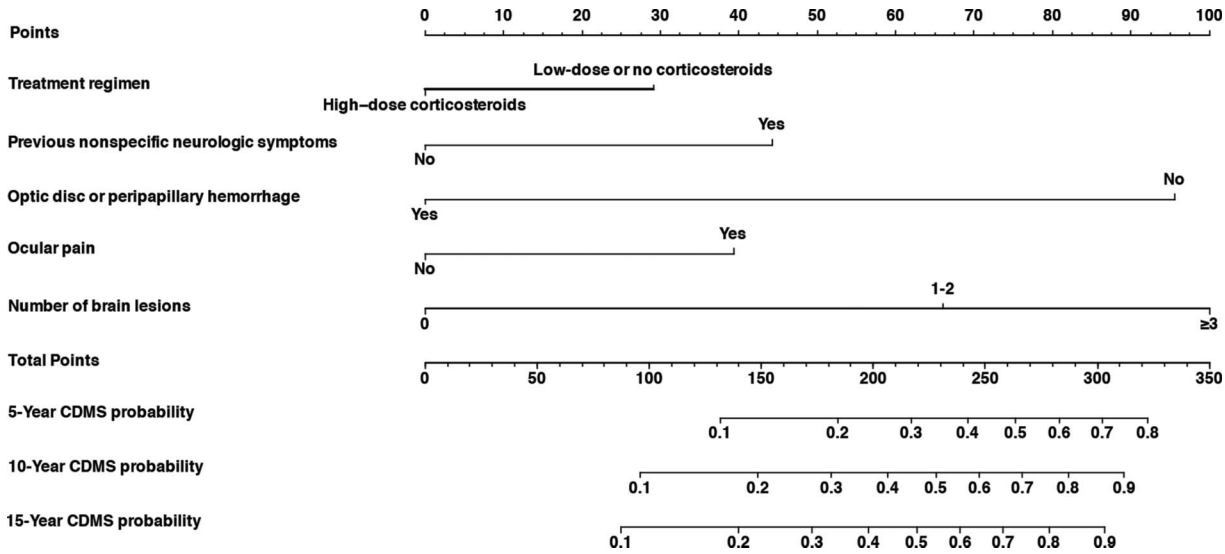

FIG. 4. A nomogram for predicting the probability of clinically definite multiple sclerosis (CDMS) development after optic neuritis. To estimate the probability of CDMS development, we estimated the number of points on the Points axis to determine the score associated with the treatment regimen for a given patient with optic neuritis. Then, we repeated the same process with previous nonspecific neurologic symptoms, optic disc or peripapillary hemorrhage, ocular pain, and the number of brain lesions. We then calculated the total number of points and determined the sum on the Total points axis. Finally, a vertical line was drawn down to the 5-, 10-, and 15-year CDMS probability axes, and we analyzed the corresponding probabilities. An online user-friendly calculator of CDMS probability is available at https://drduyi.shinyapps.io/cdms/.

optic neuritis seronegative for both these antibodies (34–36). Chen et al recently showed that none (0/177) of the ONTT patients were seropositive for AQP4 antibodies, and only 1.7% (3/177) were seropositive for MOG antibodies (37). Therefore, our prognostic model should also be used for CDMS prognosis in patients seronegative for both AQP4 and MOG antibodies.

Although DMTs can delay the development from optic neuritis to MS (13), the problems faced by individual patients are obviously more complicated, including financial costs and potential side-effects. One study showed that not being sick enough is one of reasons that make patients choose not to take the DMTs (38). However, DMTs might benefit the most when optic neuritis does not develop to

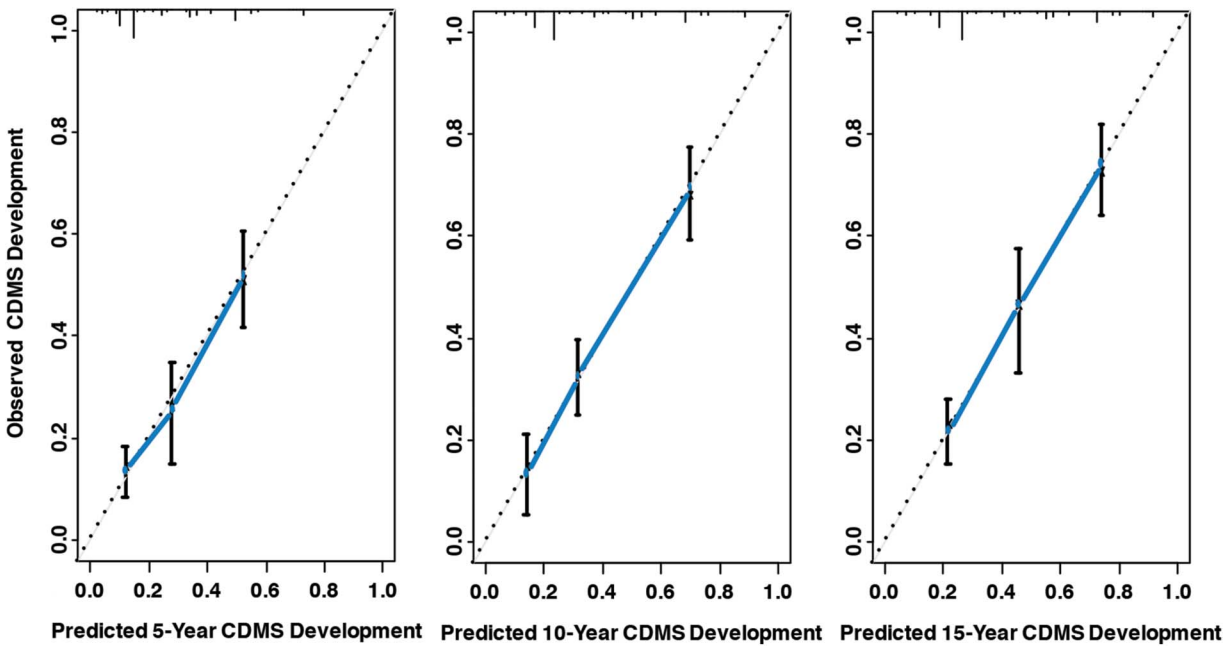

FIG. 5. Calibration curves for the proposed prognostic model. The dotted line represents the ideal fit; circles represent model-predicted probabilities; crosses represent the bootstrap-corrected estimates; error bars indicate 95% CIs.

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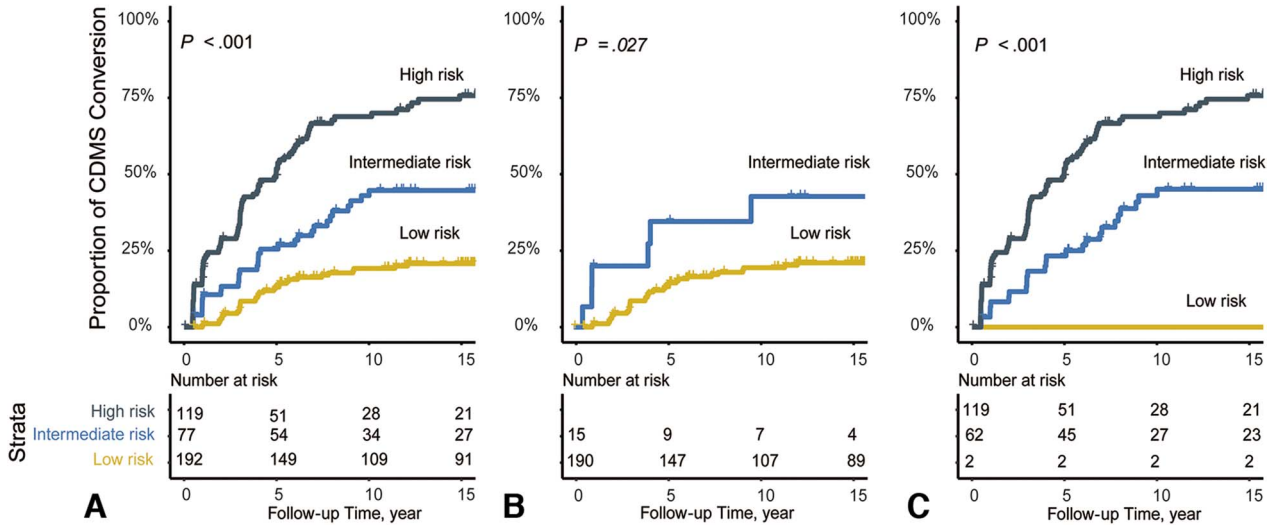
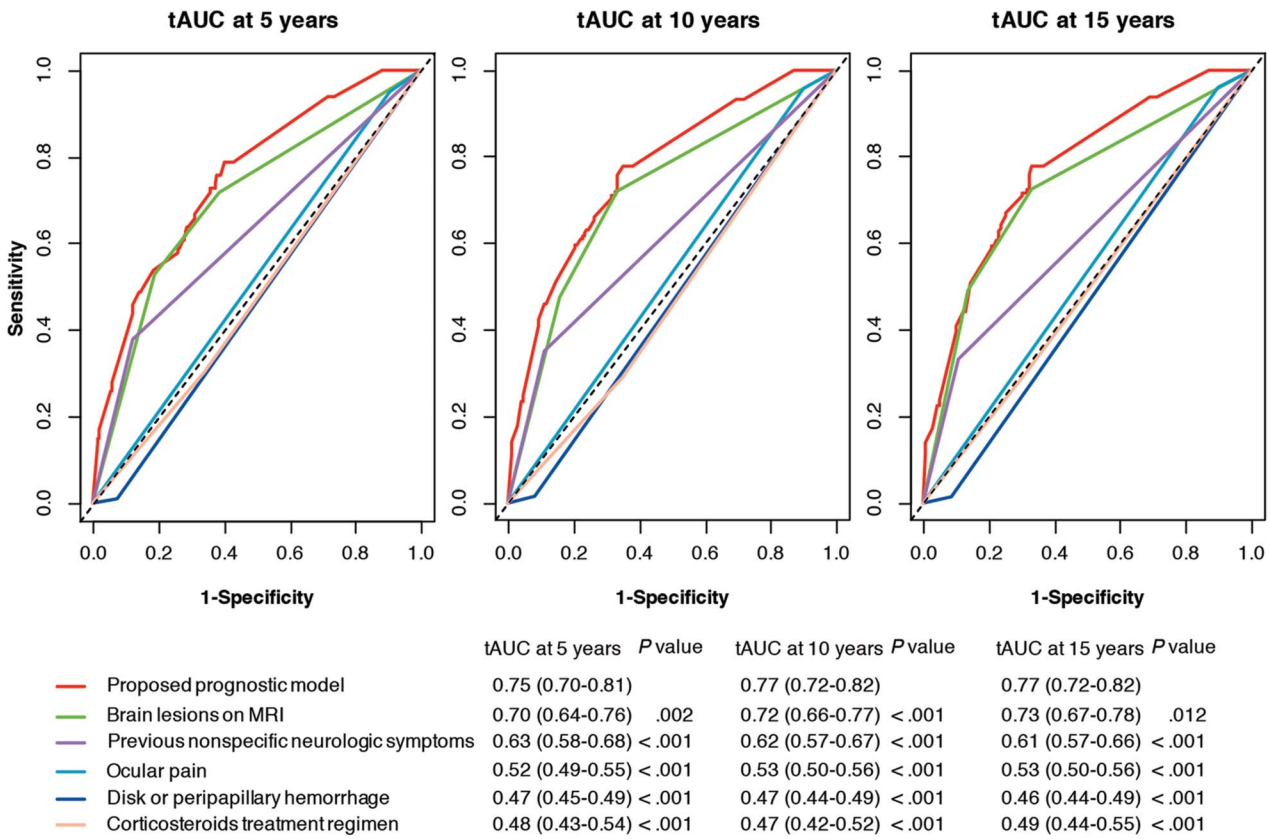


FIG. 6. Kaplan–Meier survival curves for risk groups stratified by the prognostic model. **A**. Overall number of cases. **B**. Cases without brain lesions on MRI. **C**. Cases with 1 or more brain lesions on MRI. *P* values were calculated by the log-rank test.

MS before disability (13). We believe that our prognostic model can help physicians and patients share decision-making as to whether to start using DMT because the proposed nomogram and online calculator can easily show the risk of developing MS for specific individuals.

Limitations

The ONTT had rather strict inclusion criteria such as restricting the analyzed age groups to between 18 and 46 years old, and most study participants were of Caucasian ethnicity. These factors may limit the generalizability of the



	tAUC at 5 years	*P* value	tAUC at 10 years	*P* value	tAUC at 15 years	*P* value
Proposed prognostic model	0.75 (0.70-0.81)		0.77 (0.72-0.82)		0.77 (0.72-0.82)	
Brain lesions on MRI	0.70 (0.64-0.76)	.002	0.72 (0.66-0.77)	<.001	0.73 (0.67-0.78)	.012
Previous nonspecific neurologic symptoms	0.63 (0.58-0.68)	<.001	0.62 (0.57-0.67)	<.001	0.61 (0.57-0.66)	<.001
Ocular pain	0.52 (0.49-0.55)	<.001	0.53 (0.50-0.56)	<.001	0.53 (0.50-0.56)	<.001
Disk or peripapillary hemorrhage	0.47 (0.45-0.49)	<.001	0.47 (0.44-0.49)	<.001	0.46 (0.44-0.49)	<.001
Corticosteroids treatment regimen	0.48 (0.43-0.54)	<.001	0.47 (0.42-0.52)	<.001	0.49 (0.44-0.55)	<.001

FIG. 7. Time-dependent area under the curves (tAUC) comparing the prognostic accuracy of the proposed model and the single predictors. A tAUC value of 0.5 indicates a random predictions and 1.0 a perfect concordance. *P* values show the tAUC for the prognostic model vs the tAUC for the single predictors. Numbers in parentheses indicate 95% CIs for tAUC.

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results obtained here. Therefore, a future multicenter study with a more diverse patient cohort and external validation will be required to examine the broader application of our prognostic model. In addition, the ONTT used Poser's criteria to diagnose MS, which required a second attack to be established, and it used outdated MRI technology to detect brain lesions. Thus, some of the ONTT subjects could have met the MS diagnostic criteria if more contemporary criteria were used (39). Despite these shortcomings, the ONTT still holds the merits of having a relatively large sample size and long-term follow-up.

CONCLUSIONS

Using the multicenter ONTT data set, we identified baseline features associated with the development of CDMS and established a prognostic model to predict the development of CDMS in patients after optic neuritis. The model showed better discrimination ability compared with the standard practice that relies solely on using brain lesions on MRI. We propose that this model can be useful for making treatment and counseling decisions based on individualized patient needs. We demonstrated that high-dose corticosteroids treatment was associated with a reduced risk of CDMS development over a longer period. Nevertheless, future investigations will be required to validate our model and confirm its findings.

STATEMENT OF AUTHORSHIP
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