ANNALS of Clinical and Translational Neurology
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AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Validation and adjustment of modified Erasmus GBS outcome score in Bangladesh

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Received: 4 April 2022; Revised: 6 June 2022; Accepted: 20 June 2022

Annals of Clinical and Translational Neurology **2022; 9(8): 1264–1275**

doi: 10.1002/acn3.51627

Abstract

Objective: We have assessed and improved the performance of the modified Erasmus GBS Outcome Score (mEGOS) among patients with Guillain-Barré syndrome (GBS) from Bangladesh. **Methods**: Validation cohort consisted of patients with GBS from two prospective cohort studies in Bangladesh. Poor outcome was defined as being unable to walk independently at week 4 and week 26. We excluded patients able to walk independently, patients who died within the first week, or with missing GBS disability scores. Performance of mEGOS at entry and week 1 was determined based on the discriminative ability (ability to differentiate between patients able and unable to walk independently; measured using the area under the receiver operating characteristic curves [AUC]) and calibration (observed probability versus predicted probability of poor outcome). **Results**: A total of 506 patients aged ≥6-year-old were enrolled, with 471 and 366 patients included in mEGOS validation analysis at entry and week 1, respectively. The AUC values for predicting poor outcome (1) at week 4 were 0.69 (mEGOS entry) and 0.78 (mEGOS week 1) and (2) at week 26 were 0.67 (mEGOS entry) and 0.70 (mEGOS week 1). Mean predicted probabilities of poor outcome corresponded with observed outcomes except for the probability of poor outcome at week 4 which was overestimated by mEGOS week 1. This was resolved by updating the model intercept. **Interpretation**: The mEGOS shows valid outcome predictions among patients with GBS from Bangladesh. The model can aid the identification of patients at high risk of poor outcome and help to adequately allocate healthcare resources in low-resource settings.

Introduction

Guillain-Barré syndrome (GBS) is an acute, immune-mediated peripheral neuropathy with a variable clinical presentation, disease course, and outcome.[1–3] The clinical spectrum of GBS ranges from mild distal limb weakness to complete paralysis, respiratory failure, and death.[4] Even after receiving standard therapy for GBS (intravenous immunoglobulin [IVIg] or plasma exchange [PE]), 20% of patients remain unable to walk unaided at 6 months after disease onset and 2%–10% of patients die during the disease course.[1,2,5–7] Compared to patients in high-income countries, patients with GBS from Bangladesh are much younger, more often have the axonal variant of GBS, and present with more severe forms of the disease.[3] In addition, due to the low income per capita, the majority of patients in Bangladesh cannot afford treatment with IVIg or PE.[4] Facilities for supportive care such as ventilatory support are inadequate, and access to integrative rehabilitation services is limited.[3,4,8–10] Not surprisingly, the rates of poor outcome (30%–40%) and mortality (14%–17%) among patients with GBS are much higher in

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Bangladesh compared to patients in developed countries.[3,11] Therefore, it is required to identify patients with GBS who have a high risk of poor outcome at the earliest stage of the disease. This will enable physicians in low-resource settings to take the necessary precautions and to personalize disease management.

To date, several prognostic models have been developed for GBS.[12–14] Among them, the modified Erasmus GBS Outcome Score (mEGOS) is one of the most commonly used models in clinical practice in high-income countries. mEGOS was originally developed in 2011[14] based on a set of three clinical predictors: age, Medical Research Council (MRC) sum score, and preceding diarrhea. The mEGOS can be used at hospital admission and on day 7 of hospital admission (Table 1). The model can predict the risk of being unable to walk independently at 4 weeks, 3 months, and 6 months after the onset of weakness. However, this model was derived from a distinct group of severely affected patients from a Dutch population participating in different GBS clinical trials, which may restrict the general applicability of the mEGOS. Until now, the mEGOS has only been validated in a Dutch cohort and two Asian cohorts (Japan and Malaysia, separately).[14–16] In addition, the model was recently validated in a selected cohort of patients with GBS from high-income countries who were included in the International GBS Outcome Study (IGOS).[17] However, the performance of the mEGOS among patients with GBS from low- and middle-income countries (LMIC) is currently unknown. Several factors could differentially influence the prognosis and outcome of patients with GBS in these countries compared to high-income countries, including the higher proportions of younger patients, axonal subtypes, and untreated patients. In the current study, we aimed to validate the mEGOS model using one of the largest prospective cohorts from Bangladesh. We also assessed if the performance of the mEGOS model could be improved specifically for patients with GBS from Bangladesh.

Table 1. Modified Erasmus GBS Outcome Score (mEGOS).

Prognostic factor	Score at hospital admission	Score at week 1
Age at onset (year)		
≤40	0	0
41–60	1	1
>60	2	2
Preceding diarrhea		
Absent	0	0
Present	1	1
MRC sumscore		
51–60	0	0
41–50	2	3
31–40	4	6
00–30	6	9
mEGOS	0–9	0–12

The table presents the mEGOS scoring system, as originally developed in 2011 among Dutch patients with GBS.[14] The model is based on three clinical parameters and can be used at hospital admission (score ranging 0–9) and week 1 of hospital admission (score ranging 0–12) to predict the risk of being unable to walk independently at 4 weeks, 3 months, and 6 months after the onset of weakness.
MRC, Medical Research Council.

Methods

Validation dataset from Bangladesh

The validation cohort consisted of prospective data collected for 506 patients with GBS aged ≥6 years who were recruited within 2 weeks of the onset of weakness and met the National Institute of Neurological Disorders and Stroke (NINDS) criteria for GBS.[18] All patients were derived from two GBS studies conducted by icddr,b, in Bangladesh[9,19,20] (Fig. 1). The first study, a prospective observational cohort study, was conducted from February 2010 to June 2013 and included 313 patients with GBS.[9] The second study was the International GBS Outcome Study (IGOS), a prospective multicenter cohort study conducted in 21 countries worldwide[20]; 193 patients with GBS from Bangladesh were included in the IGOS between November 2013 and December 2016. The study protocols were reviewed and approved by the Ethical Committees at icddr,b. Written informed consent was obtained from all participants or their legal representatives. Baseline characteristics, including socio-demographic characteristics, history of preceding infection, and detailed clinical and neurological features (including GBS disability score and MRC sum score) were collected. After enrollment, patients underwent follow-up at standard time points (week 1, week 2, week 4, week 8, week 13, week 26, and week 52) according to predefined protocols. For the final analysis, we excluded patients who were able to walk independently (GBS disability score ≤2) at study entry or week 1; patients who died within the first week after study entry, and patients for whom data on GBS disability score was missing at entry or week 1.

Statistical analysis

To validate mEGOS among patients with GBS from Bangladesh, we used the original regression formulas with mEGOS total score as a single predictor. Poor outcome was defined as being unable to walk independently (GBS disability score >2).[18] We evaluated the ability of mEGOS to predict a poor outcome in GBS at week 4, which is the most commonly used time point in treatment efficacy

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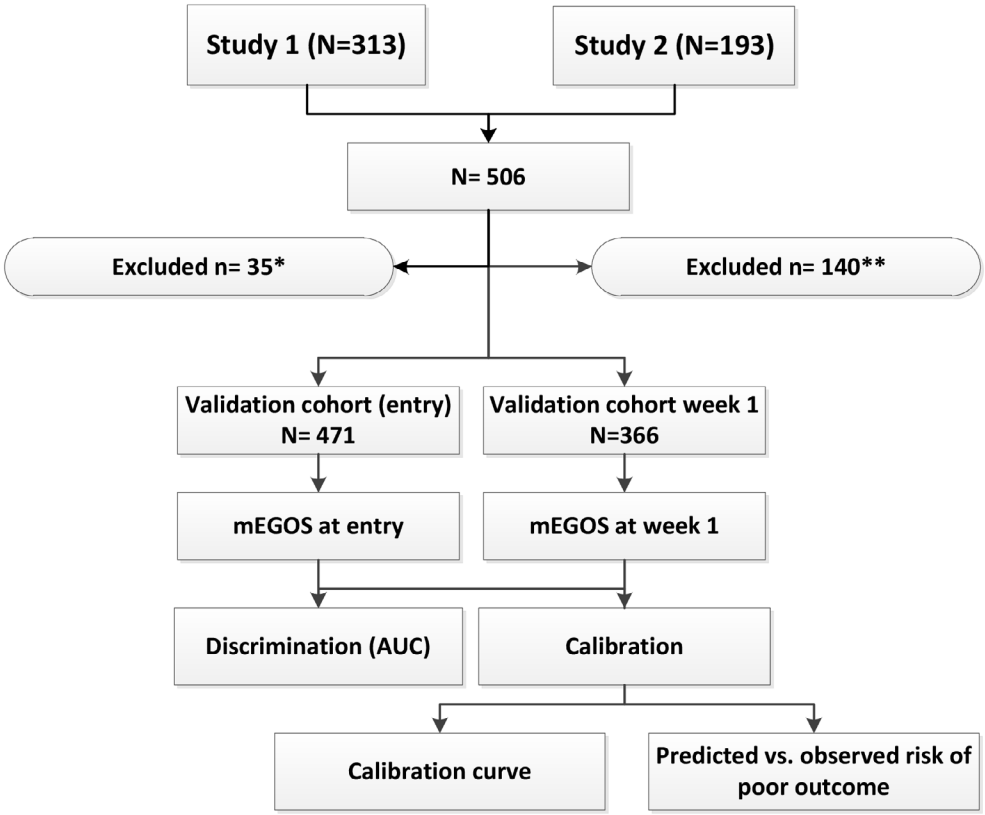

Figure 1. Study population of patients with GBS from Bangladesh was used to validate the mEGOS model. Study 1: Prospective observational cohort study, conducted between 2010 and 2013.[9] Study 2: International GBS Outcome Study; a prospective multicenter cohort study conducted between 2013 and 2016.[19] *Able to walk independently at study entry; $n = 35$. **Able to walk independently at week 1, $n = 40$; died, $n = 1$, missing data for GBS-DS at week 1, $n = 99$. AUC: area under the receiver operating characteristic curve; GBS-DS: GBS disability score; mEGOS: modified Erasmus GBS Outcome Score.

trials,[21,22] and at 6 months (week 26) to assess the ability of the model to predict long-term outcome.[23]

Missing values for mEGOS predictors and GBS disability scores at week 4 and week 26 were imputed using a multiple imputation method with ten imputed datasets.[24,25] We included information on age, sex, antecedent events, GBS variants, cranial nerve involvement, sensory deficits, pain, ataxia, autonomic dysfunction, treatment, and nerve conduction study findings in the imputation model. We also imputed the missing individual MRC scores and GBS disability scores using the available longitudinal data of the same variables at entry, week 1, week 2, week 4, week 8, week 13, week 26, and week 52.

Model performance was determined by discrimination (i.e., the ability of the model to differentiate between patients who are able and unable to walk independently) and calibration (i.e., the accuracy of the absolute risk estimates).[26,27] Discrimination was evaluated using the area under receiver operating characteristic curve (AUC), which ranges from 0.5 to 1.0. The AUC value indicates the probability that for any randomly selected pair of individuals, one with a good outcome and one with a poor outcome, the mEGOS score will be higher for the patient with the poor outcome. A value of 1 indicates the model has the perfect discriminative ability, while a value of 0.5 indicates that the model discriminates no better than chance. In addition, we refitted the model for the validation cohort, thereby re-estimating the values of the coefficients of individual predictors, to calculate the refitted AUC values. This allowed us to evaluate the highest possible discriminative ability of the model in the validation cohort.

Calibration was assessed by comparing the mean predicted and observed risks of a poor outcome in the validation cohort and was graphically presented by plotting the observed versus predicted outcomes in a calibration plot. Calibration plots were based on data from the first imputation set. To select the appropriate method for updating the model, we used the closed testing procedure described by Vergouwe et al.[28] In the closed testing

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procedure, different updating methods, varying in extent (i.e., minimum: either keep the original model or systematically increase or decrease all predicted probabilities by the same number; maximum: full model revision with re-estimation of all coefficients) are compared to determine which updating method provides the most appropriate model for the validation sample. The closed testing procedure was performed using the first imputation set.

To assess the performance of mEGOS in different categories of patients, separate subgroup analyses were performed among patients who did not receive any immunotherapy; younger patients (age ≤40 years), patients with a pure motor variant of GBS, and patients with an axonal subtype of GBS. The subgroup analyses were performed using the first imputation set and included discrimination (AUC) and calibration (predicted vs. observed proportion of poor outcome).

A separate analysis was performed with complete case data, and the results of this analysis were compared with the results from the main analysis using imputed data. We also assessed and compared the predictive ability of individual factors included in mEGOS between the development and validation cohorts. Data analysis was performed using SPSS Statistics version 20 and R Studio version 4.0.2 (R packages: Hmisc, rms, devtools, CalibrationCurves).

Results

From a total of 506 patients with GBS from Bangladesh, we excluded the patients who were able to walk independently at study entry (n = 35) or week 1 (n = 40), patients who died within the first week (n = 1), and patients with missing data for GBS disability score at week 1 (n = 99). Thus, the cohorts from Bangladesh for validation of mEGOS at entry and week 1 contained 471 and 366 patients with GBS, respectively (Fig. 1).

In total, 6% of the data points (224/4048) were imputed for the predictive factors of mEGOS (age, antecedent diarrhea, and MRC sum score at entry and week 1) and the outcome variables (GBS disability score at week 4 and week 26).

Characteristics of the development and validation cohorts

Compared to the original Dutch mEGOS development cohort,[14] the patients with GBS in the current validation cohort from Bangladesh were younger (median age 28 years vs. 52 years), had a higher frequency of preceding diarrhea (51% vs. 23%), had more severe muscle weakness at study entry and week 1 based on MRC sum score, more frequently had cranial nerve involvement (62% vs. 39%), and less frequently had sensory deficits (19% vs. 66%; Table 2). The median duration from onset of weakness to study entry was longer in the validation cohort (8 days) than in the development cohort (5 days). Most patients (86%) in the validation cohort did not receive any immunotherapy for GBS, whereas all patients in the development cohort received either IVIg or PE. The proportion of patients with a poor outcome was higher in the validation cohort than in the development cohort at all follow-up time points.

Discrimination

The discriminative ability of mEGOS among the patients with GBS from Bangladesh is described in Table 3. For mEGOS at entry, the AUC values were 0.69 (95% CI: 0.63–0.74) and 0.67 (95% CI: 0.62–0.72) for predicting a poor outcome at week 4 and week 26, respectively. Thus, in 100 random pairwise comparisons of one patient with a good outcome and one patient with a poor outcome, the model gave a higher mEGOS score for the patient with a poor outcome in 69% of cases at week 4 and 67% of cases at week 26. For mEGOS at week 1, the AUC values for predicting a poor outcome were 0.78 (95% CI: 0.71–0.85) at week 4 and 0.70 (95% CI: 0.64–0.75) at week 26. The AUC values of mEGOS were lower at all time points in the validation cohort from Bangladesh than in the development cohort.

We refitted the model including the individual predictors (age, preceding diarrhea, and MRC sum score at entry or week 1) in the validation cohort. The refitted AUC values for mEGOS entry and mEGOS week 1 were almost similar to the AUC values obtained during validation of the model using the mEGOS total score as a single predictor (Table 3). This indicates that the discriminative ability of the model for the GBS population in Bangladesh cannot be further improved using the existing sets of predictor variables. We compared the predictive ability of the individual predictors included in the model in the development and validation cohorts to predict a poor outcome at week 4. All predictors from the original model had lower effects (measured by odds ratio [OR]) in the validation cohort compared to the development cohort; this was most prominent for the MRC sum score where considerable differences in OR between development and validation cohort were observed (Table 4). Surprisingly, some categories of predictors showed an opposite association with a poor outcome in the validation cohort compared to the development cohort. This means that in these categories, the predictors were associated with an increased risk of a poor outcome (OR >1) in the development cohort, but a lower risk of a poor outcome (OR <1) in the validation cohort. For example,

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Table 2. Characteristics of the patients in the validation cohorts and development cohort.

	Validation cohort from Bangladesh			Development cohort[14]
	Total cohort (*N* = 506)	Patients unable to walk at study entry[a] (*n* = 471)	Patients unable to walk at week1[b] (*n* = 366)	Total cohort (*n* = 394)
Age (years)	28 (18-42)[c]	28 (18-42)[c]	28 (17-43)[c]	52 (33–66)
≤40	373 (74%)	347 (74%)	264 (72%)	138 (35%)
41–60	120 (24%)	111 (24%)	94 (26%)	114 (29%)
>60	13 (2%)	13 (2%)	8 (2%)	142 (36%)
Sex (male)	337 (67%)	308 (65%)	232 (63%)	215 (55%)
Preceding diarrhea	250/493 (51%)	234/459 (51%)	182/358 (51%)	89/392 (23%)
Weakness to admission (days)	(*N* = 193)	(*N* = 177)	(*N* = 163)	NA
	4 (2-7)[c]	4 (2-7)[c]	4 (2-7)[c]	
Weakness to study entry (days)	8 (5-11)[c]	8 (5-11)[c]	8 (5-11)[c]	5 (3–8)
Total MRC sum score at study entry	22 (4-36)[c]	20 (4-32)[c]	18 (4-30)[c]	43 (33–48)
51–60	19 (4%)	7 (1%)	6 (1%)	47/393 (12%)
41–50	55 (11%)	37 (8%)	22 (6%)	180 (46%)
31–40	88 (17%)	83 (18%)	54 (15%)	82/393 (21%)
00–30	344 (68%)	344 (73%)	284 (78%)	84/393 (21%)
Cranial nerve involvement at study entry	311 (62%)	294 (62%)	227 (62%)	152 (39%)
Autonomic dysfunction at study entry	89/497 (18%)	88/462 (19%)	61/360 (17%)	NA
Total MRC sum score at week 1	(*N* = 430)	(*N* = 405)	(*N* = 348)	(*N* = 385)
	28 (8-40)[c]	26 (8-38)[c]	23 (6-36)[c]	43 (30–50)
51–60	18 (4%)	9 (2%)	5 (1%)	95 (25%)
41–50	78 (18%)	66 (17%)	45 (13%)	116 (30%)
31–40	86 (20%)	82(20%)	59 (17%)	75 (20%)
00–30	248 (58%)	248 (61%)	239 (69%)	99 (26%)
GBS clinical variant	(N = 493)	(N = 457)	(N = 358)	
Sensorimotor	80 (16%)	80 (18%)	64 (18%)	NA
Pure motor	406 (82%)	375 (82%)	292 (82%)	NA
Miller Fisher syndrome/ataxic form	5 (2%)	2 (0%)	2 (0%)	0 (0%)
Mechanical ventilation	108 (21%)	108 (23%)	85 (23%)	118 (30%)
Treatment				
Intravenous immunoglobulin	39 (8%)	39 (8%)	32 (9%)	IVIg/PE
Plasma exchange	21 (4%)	21 (5%)	19 (5%)	394 (100%)
Small volume plasma exchange	10 (2%)	10 (2%)	10 (3%)	0
Supportive care only	436 (86%)	401 (85%)	305 (83%)	0
Disease onset to start treatment (days)	(N = 63)	(N = 63)	(N = 57)	NA
	6 (4–9)[c]	6 (4–9)[c]	6 (4–9)[c]	
GBS disability score >2[d] at week 4	321/489 (66%)	320/457 (70%)	277/359 (77%)	217/394 (55%)
GBS disability score >2[d] at 3 months	211/484 (44%)	211/452 (47%)	177/351 (50%)	111/389 (29%)
GBS disability score >2[d] at 6 months	141/480 (29%)	141/448 (32%)	109/346 (32%)	74/388 (19%)
Nerve conduction study	(*N* = 364)	(*N* = 337)	(*N* = 271)	NA
Axonal	178 (49%)	162 (48%)	129 (48%)	
AIDP	117 (32%)	111 (33%)	89 (33%)	
I nexcitable	14 (4%)	14 (4%)	14 (5%)	
Equivocal	49 (14%)	44 (13%)	35 (13%)	
Normal	6 (1%)	6 (2%)	4 (2%)	

The characteristics of the development cohort have been published previously,[14] and are shown for comparison purposes only.
MRC, Medical Research Council sum score; AIDP, Acute Inflammatory Demyelinating Polyradiculopathy.
[a]Included in mEGOS entry analysis.
[b]Included in mEGOS week 1 analysis.
[c]Median with interquartile range (IQR).
[d]Proportion of patients unable to walk independently.

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Table 3. Discriminative ability of the mEGOS in the validation and development cohorts.

		mEGOS entry	mEGOS week 1
Validation cohort			
Week 4	AUC	0.69 (CI: 0.63–0.74)	0.78 (CI: 0.71–0.85)
	AUC (refitted)	0.69 (CI: 0.63–0.74)	0.79 (CI: 0.71–0.86)
Week 26	AUC	0.67 (CI: 0.62–0.72)	0.70 (CI: 0.64–0.75)
	AUC (refitted)	0.68 (CI: 0.62–0.72)	0.70 (CI: 0.64–0.76)
Development cohort			
Week 4	AUC	0.73	0.87
Week 26	AUC	0.77	0.84

The table presents the discriminative ability of mEGOS in the validation cohort and compares the findings with the previously published development cohort (for comparison only).[14] AUC is a measure of the discriminative ability of the model and ranges from 0.5 (no better than chance) to 1.0 (perfect discrimination). The refitted AUC is calculated by re-estimating the values of the coefficients of the predictors that indicate the highest discriminative ability of the model.
AUC, area under the receiver operating characteristic curve; mEGOS, modified Erasmus GBS Outcome Score; CI, 95% confidence interval.

Table 4. Effects of the individual predictors of the original mEGOS model for prediction of outcome at week 4 in the development and validation cohorts.

Predictors	mEGOS at entry vs. outcome at week 4		mEGOS at week 1 vs. outcome at week 4	
	Validation cohort OR (95% CI)	Development cohort OR (95% CI)	Validation cohort OR (95% CI)	Development cohort OR (95% CI)
Age, years				
≤40	1	1	1	1
41–60	1.11 (0.67–1.86)	1.9 (1.1–3.3)	0.81 (0.43–1.52)[a]	2.1 (1.0–4.2)
>60	3.0 (0.52–17.35)	2.3 (1.3–3.8)	1.60 (0.19.08)	2.8 (1.4–5.4)
MRC ss				
60–51	1	1	1	1
50–41	0.19 (0.04–1.06)[a]	2.8 (1.3–6.2)	0.59 (0.08–4.06)[a]	3.8 (1.7–8.4)
40–31	0.88 (0.18–4.22)[a]	6.1 (2.5–14)	2.23 (0.34–14.63)	10 (4.2–26)
≤30	2.77 (0.6–12.72)	9.6 (3.8–24)	12.73 (1.95–83.16)	58 (18–188)
Diarrhea	1.12 (0.72–1.73)	1.7 (1.0–2.9)	1.14 (0.61–2.13)	2.1 (1.0–4.4)

The table presents the results for the previously published development cohort for comparison purposes only.[14]
mEGOS, modified Erasmus GBS Outcome Score; MRC ss, Medical Research Council sum score; OR, odds ratio, 95% CI, 95% confidence interval.
[a]Predictor showing an opposite association in the validation cohort as compared to the development cohort (OR <1 in the validation cohort, versus OR >1 in the development cohort). The characteristics of these subgroups are described in Table 5.

in the mEGOS entry cohort, patients with more severe muscle weakness (MRC sum scores of 41–50 and 31–40) had a lower risk of a poor outcome than the patients with less severe muscle weakness (MRC sum score of 51–60). Similarly, for the mEGOS week 1 cohort, patients aged 41–60 years and patients with MRC sum scores of 41–50 had lower risks of a poor outcome compared to the patients aged ≤40 years and patients with MRC sum scores of 51–60, respectively. Compared to the overall cohort from Bangladesh, these groups of patients who had a lower OR than the reference categories less frequently required mechanical ventilation and had higher proportions of sensorimotor involvement and the AIDP variant of GBS—except for the subgroup of patients with MRC sum scores of 31–40, who more frequently had the axonal variant (Table 5).

Calibration

In the validation cohort, the mean predicted probabilities of a poor outcome at week 4 and week 26 based on the original mEGOS model at entry and week 1 corresponded to the observed outcomes (Fig. 2). However, a slight overestimation of a poor outcome at week 4 based on the original mEGOS model at week 1 was observed (81% predicted probability vs. 77% observed probability).

The calibration plots showed more prominent discrepancies between the predicted and observed risks for the

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Table 5. Subgroup analysis of patients with MRC scores of 41–50 and 31–40 in the validation cohort.

	Validation cohort (Entry)			Validation cohort (Week 1)		
	Patients with MRC ss 41–50 (n = 37)	Patients with MRC ss 31–40 (n = 83)	mEGOS entry cohort (n = 471)	Patients with MRC ss 41–50 (n = 45)	Patients aged 41–60 (n = 94)	mEGOS week 1 cohort (n = 366)
Age, years						
Median with IQR	30 (21–50)	29 (19–40)	28 (18–42)	34 (18–50)	50 (45–55)	28 (17–43)
Age range	9–65	7–60	6–75	7–65	41–60	6–75
Sex (male)	23 (62%)	60 (72%)	308 (65%)	32 (71%)	56 (60%)	232 (63%)
Preceding diarrhea	18 (49%)	37 (45%)	234 (51%)	22 (49%)	48 (51%)	182/358 (51%)
Patients with MV at entry	2 (5%)	3 (4%)	86 (18%)	3 (7%)	13 (14%)	67 (18%)
Patients with MV at week 1	1 (4%)	3 (5%)	79 (21%)	3 (7%)	17 (18%)	80 (23%)
GBS clinical variant						
Sensorimotor	9 (24%)	16 (19%)	80 (18%)	11 (24%)	33 (36%)	64/358 (18%)
Pure motor	28 (76%)	66 (80%)	375 (82%)	34 (76%)	57 (63%)	292/358 (82%)
Nerve conduction study	N = 30	N = 61	N = 337	N = 39	N = 71	
Axonal	12 (40%)	34 (56%)	162/337 (48%)	16 (41%)	23 (32%)	129/271 (48%)
AIDP	12 (40%)	19 (31%)	111/337 (33%)	14 (36%)	38 (54%)	89/271 (33%)
Treatment						
Supportive only	33 (89%)	76 (91%)	401 (85%)	36 (80%)	77 (82%)	305/366 (83%)
IVIg/PE	4 (11%)	6 (8%)	60 (13%)	6 (13%)	13 (13%)	51/366 (14%)

MRC ss, Medical Research Council sum score; MV, mechanical ventilation; IQR, interquartile range; AIDP, acute inflammatory demyelinating polyradiculopathy; IVIg, intravenous immunoglobulin; PE, plasma exchange.

subgroup of patients with a low predicted probability (<0.3) of a poor outcome at week 4 (Fig. 3). The observed outcomes for this subgroup of patients were worse than predicted; in other words, mEGOS model underestimated the risk of a poor outcome for this subgroup. We performed subgroup analysis to describe the characteristics of patients with a low predicted probability of a poor outcome (<0.3) at week 4 based on mEGOS at entry (n = 5; mEGOS entry score ranging from 0–1) and mEGOS week 1 (n = 18; mEGOS week 1 score ranging from 0–3). In this subgroup, the mean predicted probabilities (± standard deviation [SD]) of a poor outcome at week 4 based on mEGOS at entry and week 1 were 20% ± 4% (vs. observed probability of 40%) and 23% ± 8% (vs. observed probability of 39%), respectively. The majority of these patients were ≤ 40-year-old, had a preceding upper respiratory tract infection, and had the AIDP variant of GBS. Compared to the overall cohort, the patients with a low predicted probability of a poor outcome less frequently had cranial nerve involvement and a higher proportion were untreated compared to the overall validation cohort (data not shown).

Application of the closed testing procedure showed that the most appropriate model for the Bangladesh GBS population was the "Original Model" at all time points, except for predicting week 4 outcome based on mEGOS at week 1 (the time point at which the original model overestimated a poor outcome). To predict the outcome at week 4 based on mEGOS at week 1, the model was further improved by systematically decreasing the predicted probabilities (updating the model intercept), which subsequently improved the performance of the model.

Subgroup analysis

Compared to the overall Bangladesh cohort, the AUC values (discrimination) for all time points were found almost similar in different subgroups for example, patients who did not receive immunotherapy, patients aged ≤40 years, patients with the pure motor variant and axonal subtype of GBS (Table S1).

Regarding calibration, the differences between predicted probability and observed probability were minor for all

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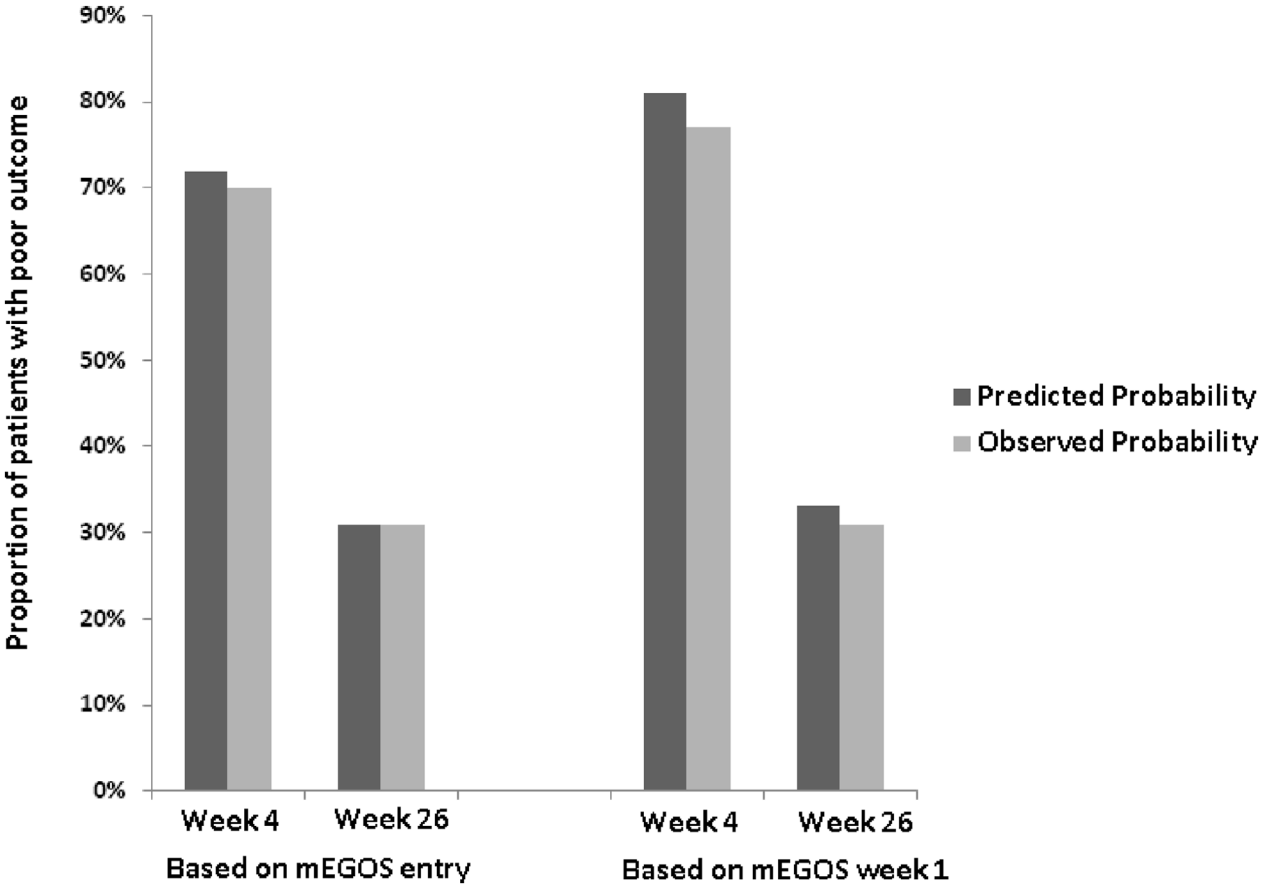

Figure 2. Mean observed vs. predicted risks of a poor outcome as per the original mEGOS model in the validation cohort. This figure represents the predicted probability of a poor outcome (GBS disability score >2) based on the original mEGOS at entry and week 1, which corresponded well with the observed frequency of a poor outcome in the validation cohort of patients from Bangladesh. For mEGOS at week 1, the model overestimated the probability of a poor outcome at week 4; after updating the model intercept, the predicted probability and observed frequency of a poor outcome became equal (77% vs. 77%). mEGOS: modified Erasmus GBS Outcome Score.

subgroups of patients and were almost similar to the overall cohort.

Complete case analysis

External validation of mEGOS was performed among the subgroup of patients in the validation cohort with complete data (n = 430 for entry and n = 319 for week 1) and showed similar results to the analysis based on the imputed dataset (data not shown).

Discussion

This study validated the ability of the mEGOS model to predict the short- and long-term outcomes of patients with GBS from Bangladesh, and then improved the performance of mEGOS for local use through recalibration. We showed that, at entry, mEGOS can correctly differentiate between patients with good versus poor outcomes (discrimination) at week 4 in 69% of cases and at week 26 in 67% of cases. Similarly, when the model was used at week 1, the discriminative ability of the model for predicting a poor outcome was 78% and 70% at week 4 and week 26, respectively. In terms of calibration, the predicted probabilities for a poor outcome corresponded with the observed probabilities, except for an overestimation of the risk of a poor outcome at week 4 based on mEGOS at week 1. We adjusted the model for this time point by systematically decreasing the predicted probabilities by updating the model intercept, which substantially improved the model accuracy.

To date, mEGOS has been validated in the GBS population from the Netherlands, Japan, and Malaysia.[14–16] The model has been recently validated in patients participating in the IGOS where 809 patients were included in the analysis mostly from Europe/North America (n = 677).[17] Patients from Bangladesh were excluded from the analysis of the IGOS cohort because the

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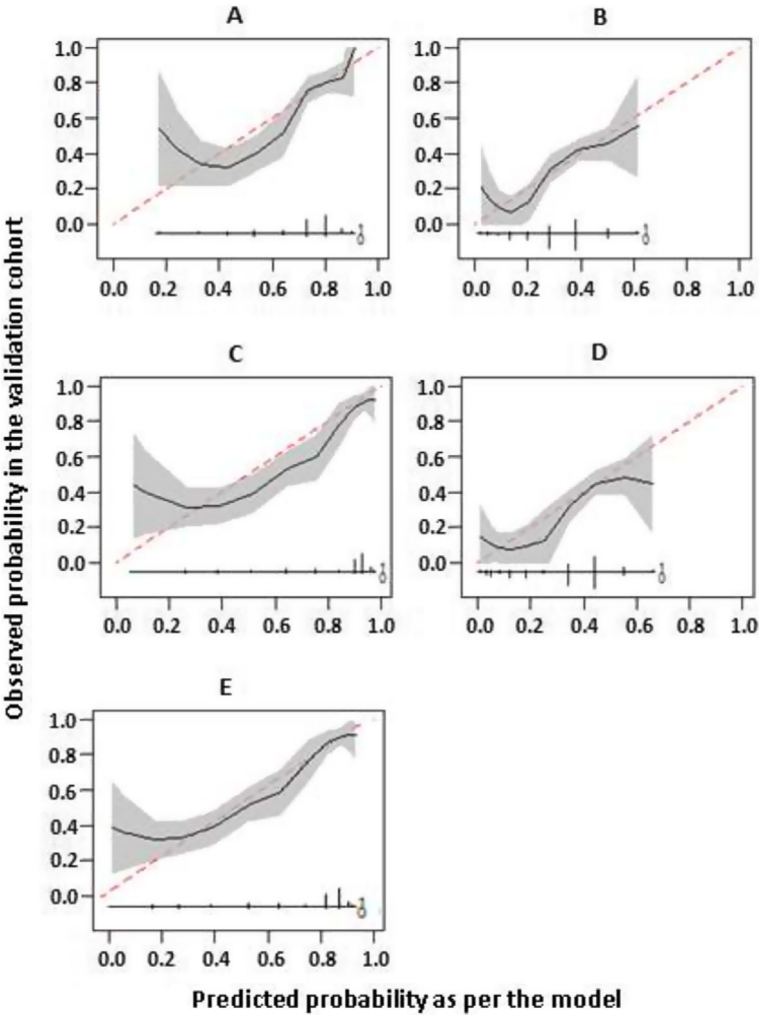

Figure 3. Calibration curves for the validation cohort as per the original and recalibrated models. The calibration curves were generated by plotting the observed probability (*y*-axis) versus the predicted outcome (*x*-axis) for (A) mEGOS (original) at entry and outcome at week 4; (B) mEGOS (original) at entry and outcome at week 26; (C) mEGOS (original) at week 1 and outcome at week 4; (D) mEGOS (original) at week 1 and outcome at week 26, and (E) mEGOS (recalibrated) at week 1 and outcome at week 4. The red dotted lines represent perfect calibration when the predicted risk is equal to the observed frequencies; the gray-shaded areas around the calibration curves are 95% confidence intervals. Miscalibration is mostly observed (calibration plot away from the perfect calibration line) among the patients with a predicted probability of a poor outcome <0.3 at week 4 for both mEGOS entry and week 1. Model recalibration was only performed for predicting a poor outcome at week 4 based on mEGOS week 1 (E). No recalibration was performed for other time points, as the "Closed test procedure" recommended keeping the original model for these time points.

majority of patients in Bangladesh received no immunotherapy, which could influence the clinical course and outcome. The discriminative ability (AUC) of mEGOS entry and week 1 to predict outcome at week 4 and week 26 have been found better in the IGOS cohort as compared to the Bangladesh cohort.

In general, an AUC value between 0.5 and 0.7 is considered sub-optimal performance; 0.70–0.80 is good performance, and >0.8 indicates excellent performance.[29] Validation of the model to predict a poor outcome at week 4 and week 26 among the Bangladeshi cohort revealed that mEGOS at entry had sub-optimal performance, whereas the model showed good performance when used at week 1. The discriminative ability of mEGOS (AUC) was lower at all time points in the Bangladesh cohort than in the development cohort from the Netherlands.[14] This can be partially explained by the higher homogeneity of the Bangladeshi cohort compared to the Dutch cohort. More than two-thirds of the patients in the Bangladeshi cohort were males aged ≤40-year-old who presented with severe muscle weakness (as measured by the MRC sum score), a pure motor variant of GBS, and did not receive any immunotherapy. Due to the homogenous presentation of patients with GBS in Bangladesh, it is expected that the predicted risk of a poor outcome will be more or less similar for the majority of patients; therefore, it is more difficult for the model to discriminate between patients with a good and a poor outcome.[26] The homogeneity of the Bangladeshi cohort may have also influenced the predictive ability (OR) of individual predictors in the model; the OR of individual predictors was lower in the validation cohort than in the development cohort.[26] In Bangladesh, the higher proportion of pure motor and axonal neuropathy, lack of immunotherapy, and limited access to rehabilitation programs may have adversely affected the clinical outcomes of the validation cohort. In the current study, 70% and 32% of patients with GBS from Bangladesh had a poor

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outcome at week 4 and week 26, respectively; the rates of poor outcome were much lower in the development cohort (55% and 19%, respectively). Previous studies also reported higher proportions of patients from Bangladesh had poor outcomes.[4,9,10]

Surprisingly, some categories of predictors showed an opposite association with poor outcome in the validation cohort compared to the development cohort. For example, for mEGOS entry and week1, categories of patients with more severe muscle weakness showed a lower risk of a poor outcome than the patients with less severe muscle weakness (MRC sum score of 51–60). In contrast, MRC sum score < 40 was reported as an important predictor of poor outcome of GBS in the original model and also in previous studies including the international validation study of mEGOS in IGOS.[7,17] The contradictory findings in the current study might be due to the low sample size in the reference category (patients with MRC sum score of 60–51). For instance, in Bangladesh cohort, only 4% of the patients (n = 19) had an MRC sum score of 60–51 which might be too low for the comparison.

Refitting of the model with the existing sets of predictors did not improve the discriminative ability of mEGOS among the validation cohort. This indicates that novel predictive factors not included in the original model need to be added, such as biomarkers, in order to further improve the performance of mEGOS, especially its discriminative ability, for patients with GBS from Bangladesh. Examples of biomarkers that have been associated with poor outcomes in GBS are serum anti-ganglioside antibodies, for example, antibodies against the gangliosides GM1 and GD1a, albumin and IgG, neurofilament light chain, glial fibrillary protein, and cerebrospinal fluid proteins.[7,15,30] In addition, electrophysiological findings, including the degree of conduction block, inexcitable nerves, and low distal compound muscle action potential (CMAP) have also been associated with a poor prognosis in GBS.[7] All of these factors could potentially be used to further update and improve the performance of the model in specific regions.

In situations where the discriminatory power of a prediction model may be affected by the population distribution, as observed for the homogeneity of the current study population, model calibration becomes a more important measure of performance than discrimination.[27] As per the original mEGOS, the overall mean predicted risks of a poor outcome in the Bangladeshi GBS cohort corresponded with the observed frequencies. However, based on mEGOS at week 1, the predicted risk of poor outcome at week 4 was 81%, which was a slight overestimation compared to the observed probability of 77%. This difference was resolved after recalibration of the model, as the predicted probabilities and observed probabilities were equal after recalibration (77%). As the difference in the predicted probabilities between the original and recalibrated model is very narrow (4%), we recommend the original mEGOS model should be used at both time points (mEGOS entry and week 1) to predict the outcomes at week 4 and week 26 for patients with GBS from Bangladesh.

Based on the calibration plot, the model underestimated the risk of a poor outcome at week 4 for the patients with mEGOS entry scores of 0–1 and/or mEGOS week 1 scores ranging from 0 to 3 (predicted probability <0.3 as per the model). This discrepancy can be partially explained by the low sample size of this subgroup (n = 5 and n = 18 for mEGOS entry and week 1, respectively). In addition, a higher proportion of patients in this subgroup were untreated compared to the overall Bangladesh cohort (100% and 92% for mEGOS entry and week 1, respectively, vs. 85% for the overall validation cohort).

There are several limitations to this study. Firstly, around 6% of the data points for predictive factors and outcome variables were missing; these data were imputed using a multiple imputation method. We generated 10 imputation sets to minimize the uncertainty induced by imputation and took the average values for interpretation. We also used longitudinal data for imputation of missing GBS disability scores and MRC sum scores. Secondly, we excluded patients <6-year-old; therefore, the applicability of the model among younger pediatric patients could not be confirmed. But, it is worth mentioning that the current study validated and performed region-specific adjustment of mEGOS to predict the outcome at an early stage of the disease for patients with GBS from Bangladesh. The clinical management of GBS and health infrastructure of Bangladesh is representative of most other low- and middle-income countries around the world; therefore, this study also indicates the applicability of mEGOS in other resource-poor settings. In addition, this study also showed that mEGOS is applicable in different subgroups of GBS patients, for example, among the patients who do not receive any immunotherapy, patients age ≤40 years, patients with pure motor variant and axonal subtype of GBS.

In conclusion, we recommend that mEGOS can be used as an easy-to-administer and useful tool to predict both the short-term and long-term outcomes of patients with GBS from Bangladesh. The greatest advantage of this model is that it requires easily accessible clinical parameters in the acute phase of the disease, without the need for data from serological or other investigations. In addition, the mEGOS model may be of special importance in low- and middle-income countries, where the majority of patients cannot afford standard treatment for GBS and ICU facilities and rehabilitation services are very limited.[4]

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The mEGOS model can identify patients who are at risk of being unable to walk within the first 6 months after disease onset, and therefore may enable physicians to take the necessary measures to ensure this group of patients receives standard immunotherapy and other supportive cares. Unfortunately, there is no low-cost treatment for GBS at present, other than IVIg or PE. Thus, the mEGOS model may be useful in the future for conditional clinical trials and stratification of patients who are at risk of a poor outcome for the development of new, low-cost effective treatment interventions. Currently, a number of efficacy trials at different phases for new investigational products are ongoing in patients with GBS in Bangladesh,[31] and mEGOS or similar models could also be used to assess the treatment efficacy in these trials. Future studies need to be conducted to evaluate the ability of other clinical, electrophysiological, and biological factors to further improve the model predictions. Moreover, new predictive models need to be developed for other outcome measures, such as activity limitations and quality of life, to enable integrated management of GBS.

Acknowledgements

This research activity was funded by icddr,b and GBS-CIDP Foundation International. icddr,b is grateful to its core donors including the Governments of Bangladesh, Canada, Sweden, and the United Kingdom for providing core/unrestricted support for its operations and research. Q.D.M. received consulting honoraria from Annexon Biosciences for activities unrelated to this manuscript. Z.I. received restricted grant (number 1K43TW011447-01) support from Fogarty International Center and the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), and Annexon Biosciences for activities unrelated to the subject matter of this manuscript. B.C.J. received unrestricted support for research from GBS-CIDP Foundation International, Prinses Beatrix Spierfonds, EU Horizon 2020, Annexon Biosciences, CSL-Behring, Griffols, and Hansa Biopharma for activities unrelated to the subject matter of this manuscript. H.P.E. received unrestrictive support from EU Horizon 2020, the Bill and Melinda Gates Foundation and Fondation Mérieux for activities unrelated to the current manuscript. We are indebted to the neurologists who referred their patients to us. We thank the patients who participated in the study and provided their valuable data.

Conflicts of Interest

The authors have no competing interests to declare.

Author Contributions

All authors contributed substantially to initial discussions of the content of this article and to review or editing of the manuscript before submission. N.P. and A.Y.D. contributed to the study design and conceptualization of the study, analysis and interpretation of the data, and drafting the manuscript. H.F.L. contributed to interpretation of the data and provided intellectual input regarding statistical analysis; Z.I. and B.C.J. participated in study design, conceptualization, data interpretation, and drafting a significant portion of the manuscript. Q.D.M. and H.P.E. contributed to revising the manuscript for intellectual content.

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Supporting Information

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

Table S1. Discrimination and calibration of the model in different subgroups of GBS patients from Bangladesh. This table presents the discrimination (measured by AUC) and calibration (predicted probability vs. observed probability) of mEGOS in the different subgroups of patients from Bangladesh including patients who did not receive any immunotherapy; younger patients (age ≤40 years), patients with a pure motor variant of GBS, and patients with an axonal subtype of GBS.

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