



Universiteit
Leiden
The Netherlands

Modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain-Barre syndrome

Luijten, L.W.G.; Doets, A.Y.; Arends, S.; Dimachkie, M.M.; Gorson, K.C.; Islam, B.; ... ; IGOS Consortium

Citation

Luijten, L. W. G., Doets, A. Y., Arends, S., Dimachkie, M. M., Gorson, K. C., Islam, B., ... Jacobs, B. C. (2022). Modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain-Barre syndrome. *Journal Of Neurology, Neurosurgery And Psychiatry*, 94(4), 300-308.
doi:10.1136/jnnp-2022-329937


Version: Publisher's Version

License: [Licensed under Article 25fa Copyright Act/Law \(Amendment Taverne\)](#)

Downloaded from: <https://hdl.handle.net/1887/3505448>

Note: To cite this publication please use the final published version (if applicable).

Modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain-Barré syndrome

Linda W G Luijten ^{1,2}, Alex Y Doets,¹ Samuel Arends,^{1,3} Mazen M Dimachkie ⁴, Kenneth C Gorson,⁵ Badrul Islam,⁶ Noah A Kolb,⁷ Susumu Kusunoki ⁸, Nowshin Papri,^{1,6} Waqar Waheed,⁷ Christa Walgaard,⁹ Yuko Yamagishi,⁸ Hester Lingsma,¹⁰ Bart C Jacobs ¹¹, The IGOS Consortium

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2022-329937>).

For numbered affiliations see end of article.

Correspondence to

Professor Bart C Jacobs, Neurology and Immunology, Ee2289, Erasmus Medical Center, Rotterdam, 3015 GD, The Netherlands; b.jacobs@erasmusmc.nl

LWGL and AYD contributed equally.

Received 6 July 2022
Accepted 26 October 2022
Published Online First 25 November 2022

ABSTRACT

Background This study aimed to determine the clinical and diagnostic factors associated with mechanical ventilation (MV) in Guillain-Barré syndrome (GBS) and to simplify the existing Erasmus GBS Respiratory Insufficiency Score (EGRIS) for predicting the risk of MV.

Methods Data from the first 1500 patients included in the prospective International GBS Outcome Study (IGOS) were used. Patients were included across five continents. Patients <6 years and patients from Bangladesh were excluded. Univariable logistic and multivariable Cox regression were used to determine which prespecified clinical and diagnostic characteristics were associated with MV and to predict the risk of MV at multiple time points during disease course.

Results 1133 (76%) patients met the study criteria. Independent predictors of MV were a shorter time from onset of weakness until admission, the presence of bulbar palsy and weakness of neck flexion and hip flexion. The modified EGRIS (mEGRIS) was based on these factors and accurately predicts the risk of MV with an area under the curve (AUC) of 0.84 (0.80–0.88). We internally validated the model within the full IGOS cohort and within separate regional subgroups, which showed AUC values of 0.83 (0.81–0.88) and 0.85 (0.72–0.98), respectively.

Conclusions The mEGRIS is a simple and accurate tool for predicting the risk of MV in GBS. Compared with the original model, the mEGRIS requires less information for predictions with equal accuracy, can be used to predict MV at multiple time points and is also applicable in less severely affected patients and GBS variants. Model performance was consistent across different regions.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a rapidly progressive, immune-mediated polyradiculoneuropathy.¹ During the acute phase of the disease 10%–30% of patients develop respiratory insufficiency requiring mechanical ventilation (MV).² Early recognition of patients at high risk of respiratory failure in GBS is crucial for triaging patients who need to be transferred to wards with stricter monitoring and for preventing pulmonary complications. In previous studies several features have been reported as predictors for the risk of MV,^{2,3} including facial

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Erasmus Guillain-Barré syndrome (GBS) Respiratory Insufficiency Score (EGRIS) predicts the risk of respiratory failure in the first week of hospital admission in patients with GBS. A recent validation study within the International GBS Outcome Study (IGOS) showed that the EGRIS can be applied to the full spectrum of GBS, including mild cases and variants, and to patients from different regions. The original model, however, requires testing of 12 separate muscle groups and only includes clinical factors, while several studies have shown that Nerve Conduction Study parameters and biomarkers may add to the prediction of respiratory failure in GBS.

WHAT THIS STUDY ADDS

⇒ This study provides an overview of the clinical and diagnostic factors associated with mechanical ventilation in GBS based on data collected in the IGOS-1500 cohort. Based on this analysis, we developed a simplified version of the EGRIS (mEGRIS), which can be used to predict the risk of respiratory failure in both the first week and other time points during follow-up with equal accuracy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The mEGRIS broadens the clinical applicability of the model in daily practice, as it only requires testing of three instead of 12 bilateral muscle groups without losing accuracy; can predict the risk of respiratory failure at any given time point during the first 2 months from disease onset; and also can be applied to GBS variants, mild forms and patients from different regions.

and bulbar palsy,^{4–6} autonomic dysfunction,⁴ severe muscle weakness at admission,^{4–7} rapid disease progression,^{5,7} respiratory parameters (eg, vital capacity)^{6,8} and the presence of a conduction block in the distal peroneal nerve.⁸

The Erasmus GBS Respiratory Insufficiency Score (EGRIS) has been developed to predict the



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Luijten LWG, Doets AY, Arends S, et al. *J Neurol Neurosurg Psychiatry* 2023;**94**:300–308.

need for MV in the first week of admission based on the presence of facial/bulbar weakness, time from onset of weakness until admission and the Medical Research Council (MRC) sum score at admission.⁵ This model was recently validated in the International GBS Outcome Study (IGOS),⁹ an ongoing prospective, observational, multicentre cohort study on the disease course and outcome of GBS, which showed that the EGRIS can be used in the full spectrum of GBS.¹⁰ Although the EGRIS can be applied early in the disease course, it requires testing of strength in 12 separate limb muscle groups. A simplified version of the EGRIS that only includes selected muscle groups from the MRC sum score, with equal accuracy, would broaden the clinical applicability. Furthermore, neck flexion strength is currently not included in the EGRIS, but may provide additional prognostic information as a recent study from the USA showed that severe weakness of neck flexors at time of admission was associated with a poor respiratory status.¹¹ In addition, the EGRIS only includes clinical factors, while certain electrophysiological characteristics and biomarkers also have been associated with MV in GBS,^{8 12} and may further improve the model in specific clinical settings.

IGOS collects detailed and standardised clinical and diagnostic data from a large cohort of GBS patients, providing the opportunity to search for novel predictors of MV. Our study aimed to: (I) provide an overview of the clinical and diagnostic determinants associated with MV in GBS and (II) develop a simplified version of the EGRIS for predicting the risk of MV at different time points (eg, <1 day, <3 days and <1 week from admission) during the disease course in order to facilitate its use in daily practice.

METHODS

Study design

Data were used from the first 1500 patients with GBS who were prospectively enrolled in IGOS. Patients fulfilled the National Institute of Neurological Disorders and Stroke diagnostic criteria for GBS (or its clinical variants), and were included between May 2012 and May 2017, <2 weeks from the onset of weakness, regardless of the disease severity or treatment.^{13 14} Patients with alternative diagnoses, protocol violations or insufficient data were excluded. In addition, we excluded patients <6 years, because they have a different disease course than adults and therefore may have other risk factors for MV, and because some neurological tests (eg, the MRC scores) are challenging in preschool children.¹⁵ Patients from Bangladesh were also excluded, because of the limited resources to provide MV and treatment, which could underestimate the effect of the studied predictors.¹⁶

In the first part of the study, we identified factors associated with MV. In the second part, to develop a simplified score to predict the risk of MV at different time points, we excluded patients in whom MV was started prior to study entry and patients who developed weakness after admission as ‘time between onset weakness and admission’, a predictor in current models, could not be determined in these patients. Patients in whom MV was started >2 months after the onset of GBS were not included in the primary outcome, because respiratory insufficiency in these patients is more likely to be caused by (pulmonary) complications rather than respiratory weakness caused by GBS.

Data collection

Clinical data and biomaterials were prospectively collected at standard time points according to the original IGOS study

protocol, which is elaborately described in previous publications.^{9 17} In study part I, we assessed several characteristics, including demographics, antecedent events, comorbidities, clinical features and severity of GBS at study entry, cerebrospinal fluid (CSF) parameters, forced vital capacity (FVC), electrophysiological subtype, positive serology for recent preceding infections and treatment with intravenous Ig or plasma exchange. Muscle strength was expressed using MRC scores.¹⁸ Both individual muscle MRCs and combined scores were assessed, including the MRC sum score (sum of MRCs of bilateral shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and foot extensors) as well as separate sum scores of proximal arm and leg, distal arm and leg, only arm and only leg muscles. Bulbar weakness was assessed clinically and defined as problems with speech or swallowing caused by lower cranial nerve involvement. Disease severity was indicated by the GBS disability scale (GBS-DS).¹⁹ The presence of autonomic dysfunction was determined by the local clinician and defined as disturbances in cardiac, gastroenteric, bladder, pupillary and sudomotor functions. For patients whose Nerve Conduction Study (NCS) data were available, the Hadden criteria were used to determine the electrophysiological subtype.²⁰ In addition, we investigated the presence of a conduction block of the peroneal nerve between the fibular head and ankle. We used two separate definitions for a conduction block: (1) a $\geq 30\%$ ²¹ and (2) $\geq 50\%$ ⁸ decrease (proximal vs distal) in the compound muscle action potential amplitude in early NCS, performed in the first week after onset of weakness. For 635 patients, blood samples were available and tested for preceding infections with *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus and hepatitis E virus, and interpreted as positive or negative for a recent infection. A detailed description of the test methods and interpretation is described in a previous publication.²²

In study part II, we only considered variables that were previously reported in literature as independent predictors of MV in GBS,²⁻⁸ and for which data were available in the IGOS database. In addition, the variables had to be suitable for the early prediction of MV.

Statistical analysis

Numeric variables were described as median (IQR) and categorical variables as count (percentage). Comparative statistics were performed using a Mann-Whitney U test for numerical and a χ^2 test or Fisher’s exact test for categorical variables.

In study part I, univariable logistic regression was performed to calculate ORs and corresponding 95% CIs for the association between the specified characteristics and MV. For the prediction of MV in study part II we used multivariable Cox regression, which also takes into account the time to start of MV. Patients not requiring MV were censored at the time point of 2 months or, if they were lost to follow-up or deceased before reaching the 2 months time point, at the assessment date of the last visit before they were lost or at the date of death, respectively. For each predictor the proportional hazard and linearity, assumptions were graphically inspected and no major violations were found. Variables were only included as predictor if <15% of values were missing.

In the final model, we included all predictors with a $p < 0.15$. Using this higher p value avoids overfitting of the model to the IGOS dataset, and provides a model that is more generalisable.²³ The effect of the predictors was expressed using a HR. Based on the coefficients of the model, a scoring system was developed, in

which each coefficient was multiplied by a factor five to obtain rounded numbers that maintained the balance between the coefficients. The score plot shows the predicted probabilities of MV, which we provided for MV within 1 day, 3 days and 1 week from admission, and is based on the point estimates of the score and CIs of the coefficients.

Because the variables FVC and early conduction block of the peroneal nerve had too many missing values, these could not be included in our prediction model. Instead, we conducted an association analysis by using multivariable logistic regression, with adjustment for our newly developed prediction score to assess their (independent) relation with MV.

Model performance was assessed by the area under the receiver operating characteristic curve (AUC), which indicates the ability of the model to correctly distinguish a patient who required MV and who did not, where an AUC of 0.5 equals flipping a coin and a value of 1 indicates perfect discriminative ability. An AUC between 0.5 and 0.7 is usually considered as suboptimal, 0.7–0.8 as good and >0.8 as excellent.²⁴ Bootstrapping was used to internally validate the model, and a geographical fourfold cross-validation was used for internal–external validation.^{25 26} Hereto, the dataset was divided into four different regions: Asia, Europe, North America and other (Argentina, Australia, Africa). Then, the model was trained on a subset that consisted of three regions and validated in the region left out. This procedure was repeated four times, so that each region was used for both training and validation. For each region, a separate AUC value and calibration curve is provided in which the observed probabilities of MV within 1 week were compared with the predicted probabilities based on the model.

Statistical analyses were performed with R studio (V4.0.2). Two-sided p values <0.05 were considered statistical significant. Variables with <15% missing values were imputed using multiple imputation.

RESULTS

Study population

From the IGOS-1500 cohort, patients with alternative diagnoses (n=85), protocol violations (n=34), insufficient data (n=11), included in Bangladesh (n=203) and age <6 years (n=34) were excluded (figure 1). In the remaining cohort (n=1133), the median age was 54 years (IQR 39–66, range 6–91) and 671 (59%) patients were male. Patients were enrolled within a median of 1 day (IQR 0–4, range –2–13) from hospital admission. In 185/1133 (16%) patients, MV was needed and 149/182 (82%) patients required MV <1 week from admission. The median time from onset of weakness until start of MV was 4 days (IQR 3–8, range 0–44, n=178). Median total duration of MV (including 11 patients with a 2nd and two with a 3rd MV episode) was 20 days (IQR 10–54, range 1–525, n=170).

Clinical and diagnostic factors associated with mV

In univariable analysis, factors strongly associated with MV were older age, a shorter time from onset of weakness until admission, facial and bulbar palsy, more severe neck flexor weakness, both a lower MRC sum score and lower individual muscle MRC scores, areflexia, autonomic dysfunction, a lower FVC, a higher GBS-DS and treatment (table 1).

MRC sum scores of both bilateral proximal muscles (shoulder abduction and hip flexion) and distal muscles (wrist extension and ankle dorsiflexion) were associated with MV (OR 0.77, 95%CI 0.74 to 0.80 vs OR 0.81, 95%CI 0.79 to 0.84). Also sum scores of bilateral muscle groups in the arms (shoulder

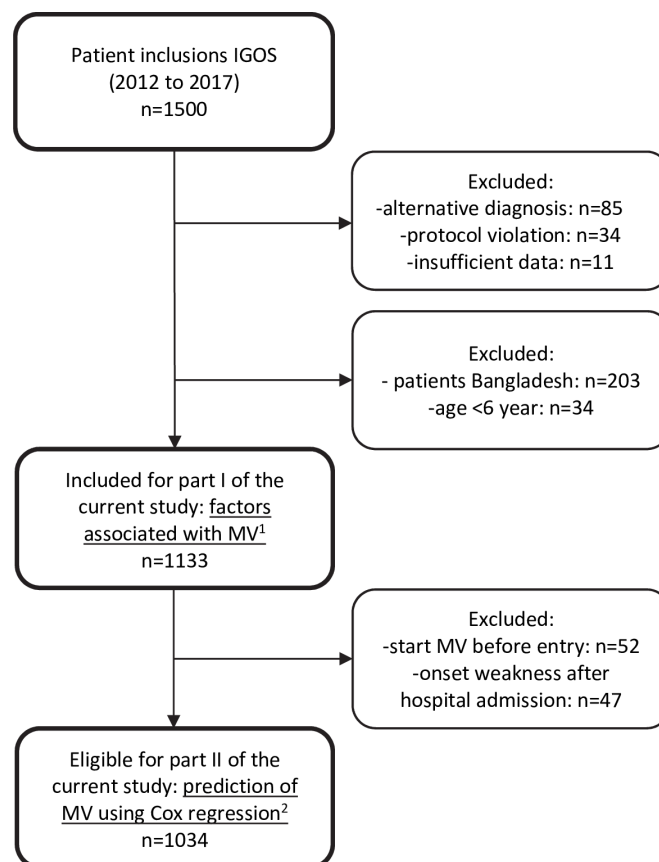


Figure 1 Study population. ¹Part I consisted of univariable logistic regression analysis of clinical and diagnostic factors in association with MV. ²In part II, a prediction model was developed for the risk of MV using multivariable Cox regression analysis. GBS, Guillain-Barré syndrome; IGOS, International GBS Outcome Study; MV, mechanical ventilation.

abduction, elbow flexion and wrist extension) and legs (hip flexion, knee extension and ankle dorsiflexion) were associated with MV (OR 0.84, 95%CI 0.83 to 0.87 vs OR 0.87, 95%CI 0.85 to 0.88). Subcategories of autonomic dysfunction that were associated with MV included cardiac, bladder and pupillary dysfunction, whereas gastrointestinal dysfunction and sudomotor changes were not. FVC (n=414) was significantly lower in patients with facial or bulbar weakness compared with those with normal facial and bulbar function: 2.4 L (IQR 1.7–3.2) and 3 L (IQR 2.2–3.7), respectively. After adjusting for facial/bulbar weakness using multivariable logistic regression, a lower FVC was still associated with MV (adjusted OR 0.46, 95%CI 0.33 to 0.63, p=0.008). Patients who required MV were significantly more often treated with either intravenous Ig or plasma exchange and had a shorter time from onset weakness until start of treatment (table 1).

Diagnostic investigations including CSF, NCS and preceding infections in relation to MV are shown in table 2.

Apart from a slightly elevated cell count in CSF, which was associated with a lower frequency of MV, there was no association between MV and CSF parameters, nor between MV and positive serology for recent preceding infections. NCS data were available for 796/1133 (70%) patients, of whom 358 patients underwent an early NCS (<1 week of onset weakness). A demyelinating subtype according to the Hadden criteria and a conduction block in the distal peroneal nerve were both associated with a higher risk of MV (table 2).

Table 1 Clinical features in association with MV

	MV (n=185)	No MV (n=948)	OR (95% CI)	P value
Demographics				
Age (years)	59 (44–70)*	53 (38–65)	1.02 (1.01 to 1.03)	<0.001*
Male sex	101 (55%)	570 (60%)	0.80 (0.58 to 1.10)	0.16
Region				
Asia	21 (11%)	88 (9%)	1.25 (0.74 to 2.04)	0.38
Europe/North-America	153 (83%)	789 (83%)	0.96 (0.64 to 1.48)	0.86
Other†	11 (6%)	71 (7%)	0.78 (0.38 to 1.44)	0.46
Disease onset in summer‡	40/184 (22%)	199/943 (21%)	1.04 (0.70 to 1.51)	0.85
Antecedent event				
Respiratory tract symptoms	73 (39%)	437/944 (46%)	0.76 (0.55 to 1.04)	0.09
Gastrointestinal symptoms	47 (25%)	246/944 (26%)	0.97 (0.67 to 1.38)	0.85
Neurological features at study entry				
Cranial nerve involvement				
Oculomotor	41/182 (23%)*	152/943 (16%)	1.51 (1.02 to 2.22)	0.037*
Facial	101/182 (55%)*	253/943 (27%)	3.40 (2.46 to 4.72)	<0.001*
Bulbar	96/182 (53%)*	144/943 (15%)	6.19 (4.41 to 8.73)	<0.001*
Weakness (MRC score)				
Sum score (0–60)§	30 (16–44)* n=183	50 (44–56) n=938	0.92 (0.90 to 0.93)	<0.001*
Neck flexion (0–5)	3 (2–4)* n=176	5 (4–5) n=924	0.33 (0.28 to 0.39)	<0.001*
Shoulder abduction (0–10)	4 (2–8)* n=184	8 (8–10) n=940	0.64 (0.60 to 0.68)	<0.001*
Elbow flexion (0–10)	6 (4–8)*	9 (8–10) n=944	0.64 (0.59 to 0.68)	<0.001*
Wrist extension (0–10)	6 (3–8)*	8 (8–10) n=941	0.69 (0.64 to 0.73)	<0.001*
Hip flexion (0–10)	4 (1–6)* n=184	8 (6–10) n=944	0.64 (0.60 to 0.68)	<0.001*
Knee extension (0–10)	5 (2–8)* n=184	9 (8–10) n=943	0.70 (0.66 to 0.74)	<0.001*
Foot extension (0–10)	4 (2–8)* n=184	8 (6–10) n=944	0.74 (0.71 to 0.78)	<0.001*
Days from onset weakness—admission	1 (0–2)* n=184	3 (1–5) n=942	0.91 (0.87 to 0.94)	<0.001*
Sensory deficits				
Pain	82/183 (45%)	496/941 (53%)	0.73 (0.53 to 1.00)	0.05
Areflexia	137/181 (76%)*	439/942 (47%)	3.57 (2.50 to 5.18)	<0.001*
Ataxia	22/40 (55%)	315/672 (47%)	1.39 (0.73 to 2.66)	0.32
Autonomic dysfunction¶	84/184 (46%)	195/941 (21%)	3.21 (2.31 to 4.47)	<0.001*
GBS disability score				
1	0/183 (0%)	48/939 (5%)	—	—
2	8/183 (4%)	258/939 (28%)	0.12 (0.05 to 0.23)	<0.001
3	6/183 (3%)	234/939 (25%)	0.10 (0.04 to 0.21)	<0.001
4	95/183 (52%)	398/939 (42%)	1.47 (1.07 to 2.02)	0.018*
Clinical GBS variant				
Sensorimotor	134/176 (76%)*	581/898 (65%)	1.74 (1.21 to 2.55)	0.004*
Pure motor	20/176 (11%)	137/898 (15%)	0.71 (0.42 to 1.15)	0.18
Miller Fisher syndrome	1/176 (0.6%)*	82/898 (9%)	0.07 (0.01 to 0.26)	0.004*
Miller Fisher overlap syndrome	13/176 (7%)	54/898 (6%)	1.25 (0.64 to 2.27)	0.49
Other**	8/176 (5%)	44/898 (5%)	0.92 (0.40 to 1.90)	0.84
Respiratory features at study entry				
Respiratory comorbidity	19/183 (10%)	84/943 (9%)	1.18 (0.68 to 1.96)	0.53
Forced vital capacity at entry (litre)	2.0 (1.2–2.8)* n=55	2.8 (2.1–3.5) n=359	0.42 (0.30 to 0.58)	<0.001*
Treatment				
Intravenous Ig or plasma exchange	183 (99%)	848 (89%)	10.79 (3.38 to 65.81)	<0.001*
Days from onset weakness—treatment	3 (2–5) n=182	5 (3–7) n=852	0.83 (0.78 to 0.88)	<0.001*

This table provides an overview of the unadjusted ORs for the association of clinical factors with MV. Numerical variables are expressed as median (IQR) and categorical variables as number (percentage). Comparative statistics are performed between the MV and no MV group.

*Significant values p<0.05.

†Including South Africa, Argentina and Australia.

‡Defined as the meteorological summer of 1 June–31 August for the Northern Hemisphere and 1 December–28 February for the Southern Hemisphere.

§Sum of the MRC scores of bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot extension.

¶Disturbances in cardiac, gastroenteric, bladder, sudomotor and pupillary functions.

**Including pharyngeal-cervical-brachial weakness, pure sensory and ataxic.

GBS, Guillain-Barré syndrome; MRC, medical research council; MV, mechanical ventilation.

Table 2 Diagnostic features in association with MV

	MV (n=185)	No MV (n=948)	OR (95% CI)	P value
Cerebrospinal fluid examination				
Leucocytes count (cells/ μ L)				
<5	135/162 (83%)	670/857 (78%)	1.40 (0.91 to 2.21)	0.14
5–10	9/162 (6%)*	115/857 (13%)	0.40 (0.18 to 0.72)	0.007*
11–50	14/162 (9%)	63/857 (7%)	1.19 (0.63 to 2.12)	0.57
>50	4/162 (2%)	9/857 (1%)	2.39 (0.64 to 7.42)	0.15
Protein level (g/L)	0.6 (0.4–1.1) n=167	0.6 (0.4–1.1) n=863	1.02 (0.86 to 1.17)	0.73
Nerve Conduction Study (NCS)				
Electrophysiological subtype				
Demyelinating	85/131 (65%)*	363/665 (55%)	1.54 (1.05 to 2.28)	0.031*
Axonal	11/131 (8%)	39/665 (6%)	1.47 (0.70 to 2.86)	0.28
Normal	0/131 (0%)*	49/665 (7%)	–	–
Equivocal/inexcitable	35/131 (26%)	214/665 (32%)	0.77 (0.50 to 1.16)	0.22
Early NCS parameters (<1 week)†				
Conduction block peroneal nerve \geq 50%	26/64 (41%)	53/294 (18%)	3.11 (1.73 to 5.55)	<0.001*
Conduction block peroneal nerve \geq 30%	37/64 (58%)	104/294 (35%)	2.50 (1.45 to 4.38)	0.001*
Positive infection serology‡				
<i>Campylobacter jejuni</i>	24/117 (21%)	150/518 (29%)	0.63 (0.35 to 1.02)	0.07
<i>Mycoplasma pneumonia</i>	11/117 (9%)	50/518 (10%)	0.97 (0.47 to 1.86)	0.93
Epstein-Barr virus	1/117 (1%)	5/518 (1%)	0.88 (0.05 to 5.55)	0.91
Cytomegalovirus	8/117 (7%)	22/518 (4%)	1.65 (0.68 to 3.68)	0.24
Hepatitis E virus	3/117 (3%)	12/518 (2%)	1.11 (0.24 to 3.56)	0.87

This table provides an overview of the unadjusted ORs for the association of diagnostic factors with MV. Numerical variables are expressed as median (IQR) and categorical variables as number (percentage). Comparative statistics are performed between the MV and no MV group.

*Significant values $p < 0.05$.

†For patients whose raw NCS data were available and underwent NCS <1 week from onset of weakness. Both a decrease of $\geq 50\%$ and $\geq 30\%$ in compound muscle action potential amplitude between the fibular head and ankle of the distal peroneal nerve were assessed.

‡Infection serology was only tested for the first 1000 patients included in IGOS.

IGOS, International GBS Outcome Study.

Prediction of MV

After excluding patients in whom MV was started prior to study entry ($n=52$) and who developed muscle weakness after admission ($n=47$), 1034 patients were eligible for multivariable prediction analysis (figure 1). From these patients, 126 (12%) needed MV, within a time range of 0 to 33 days from hospital admission (figure 2). The majority of patients required MV within the first week (98/126, 78%). The following predictors were assessed in multivariable analysis: age, facial and bulbar palsy, time from onset weakness until admission, autonomic dysfunction and MRC scores of neck flexion, bilateral hip flexion and bilateral elbow flexion. In online supplemental table 1, a more detailed overview of the selection procedure is provided. The included predictors in the final and simplified model are indicated in table 3.

Bulbar palsy, a shorter time from onset of weakness to admission, and lower MRC scores of neck flexion and bilateral hip flexion significantly increased the hazard of MV. This model showed excellent discriminative ability (AUC 0.84, 95% CI 0.80 to 0.88). Internal validation by bootstrapping showed an AUC of 0.83 (95% CI 0.81 to 0.88). Geographical fourfold cross-validation showed a mean AUC of 0.85 (95% CI 0.72 to 0.98) with no significant miscalibration and no extreme variability across settings (online supplemental figure 1).

The modified EGRIS (mEGRIS) ranges from 0 to 32 (table 4). The predicted probabilities for a patient to be mechanically ventilated within 1 day (yellow), 3 days (blue) and 1 week (light blue) from admission for each score are indicated in figure 3. For example, a patient with bulbar weakness (5 points), admitted to the hospital 1 day after onset weakness (6 points), with neck

flexion weakness MRC 4 (2 points) and bilateral symmetrical hip flexion weakness MRC 3/5 (4 points), has a total score of 17, corresponding to a predicted risk of 17% to be mechanically ventilated <1 day, 26% <3 days and 35% <1 week.

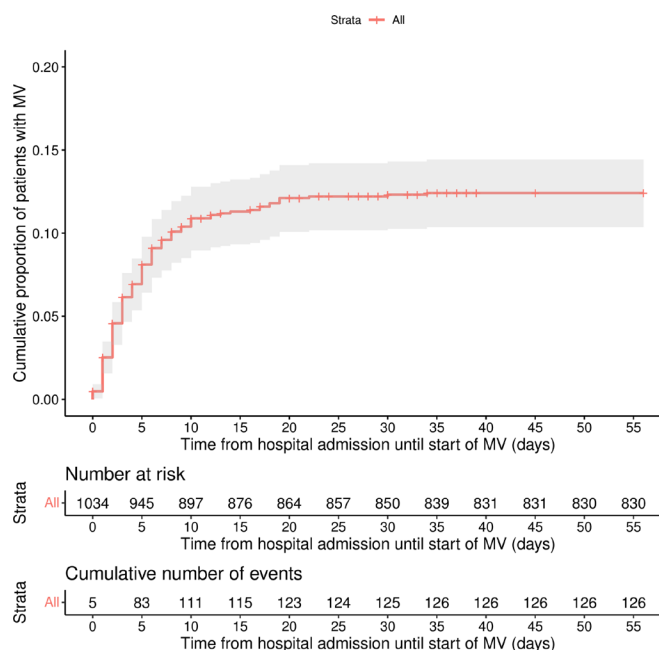


Figure 2 Cumulative incidence function for the time to start of mechanical ventilation (MV).

Table 3 Multivariable Cox regression for prediction of the risk of MV

Predictor	Coefficient (SE)	HR (95% CI)	P value
Bulbar weakness	1.07 (0.18)	2.92 (2.04 to 4.19)	<0.001*
Time from weakness—admission (per day)	−0.19 (0.05)	0.83 (0.76 to 0.91)	<0.001*
Neck flexion strength (per MRC score)	−0.43 (0.09)	0.65 (0.56 to 0.78)	<0.001*
Bilateral hip flexion strength (per MRC score)	−0.20 (0.04)	0.82 (0.76 to 0.88)	<0.001*

The coefficients of the final model were corrected for overfitting by multiplying with a heuristic shrinkage factor (a penalty for the complexity of the model) calculated with the formula: $s = (\text{model } \chi^2\text{-df}) / \text{model } \chi^2$.
Reference: Steyerberg EW. Clinical prediction models—a practical approach to development, validation and updating: Springer 2009.
*Significant values $p < 0.05$.
MRC, Medical Research Council; MV, mechanical ventilation.

Additional analysis

In multivariable logistic regression analysis with correction for the mEGRIS, a lower FVC was no longer associated to MV (adjusted OR 1.37, 95%CI 0.76 to 2.49, $p=0.30$). A $\geq 50\%$ conduction block of the peroneal nerve remained significantly associated (adjusted OR 3.67, 95%CI 1.66 to 8.21, $p=0.001$) with MV, whereas a $\geq 30\%$ conduction block was not (adjusted OR 1.96, 95%CI 0.95 to 4.11, $p=0.07$).

Table 4 The modified EGRIS score

Predictor	Category	Score
Bulbar weakness	Yes	5
	No	0
Time from weakness—admission (days)	0	7
	1	6
	2	5
	3	4
	4	3
	5	2
	6	1
	≥ 7	0
Neck flexion MRC score (0–5)	0	10
	1	8
	2	6
	3	4
	4	2
	5	0
Bilateral hip flexion MRC score (0–10)	0	10
	1	9
	2	8
	3	7
	4	6
	5	5
	6	4
	7	3
	8	2
	9	1
	10	0
Total		0–32

EGRIS, Erasmus GBS Respiratory Insufficiency Score.

DISCUSSION

In this study, we developed a simplified and broadly applicable model for predicting the risk of MV in GBS based on a large dataset from the IGOS study, including all clinical variants and patients from various regions. The mEGRIS is based on four clinical features available at admission: time from weakness onset until admission, bulbar palsy, neck flexion weakness and bilateral hip flexion weakness. Advantages compared with the original model are that the mEGRIS: (1) requires testing of only three muscle groups, while model accuracy is similar,⁵ (2) accurately predicts the risk of MV at multiple time points (eg, <1 day, <3 days, <1 week) and (3) is also applicable in GBS variants and mildly affected patients. Adding more clinical predictors, previously identified in the literature as risk factors for respiratory failure, did not improve the predictive ability of the model.

We found a strong independent association of MV with bulbar weakness, rapid disease progression and severe limb muscle weakness at admission, consistent with previous publications.^{2,4–7} In addition, our study demonstrated that weakness of individual limb muscle groups was strongly associated as well, especially weakness of neck flexion. A previous case series, describing ultrasonographic changes in GBS, showed more profound involvement of cervical spinal roots compared with peripheral nerves in patients requiring MV.²⁷ This may suggest that GBS patients with involvement of the cervical spinal roots are more prone to develop respiratory failure.

In line with prior studies,^{6,8} we found an association between a lower FVC at admission and MV, which persisted after adjusting for facial/bulbar weakness. However, FVC is less attractive to use as a predictor because it is not always available in clinic and may not be accurate in patients with facial/bulbar weakness. After adjusting for the mEGRIS, a lower FVC was no longer significant, which means that FVC is less contributory than other clinical variables for the prediction of MV.

NCS is often used to support the clinical diagnosis of GBS. Although early NCS is not routinely performed, this may have prognostic value, as our study indicated a strong association of MV with an early $\geq 50\%$ conduction block of the distal peroneal nerve, even after correcting for the mEGRIS. The prognostic value of this variable also has been previously demonstrated by Durand *et al.*⁸ They proposed a model based on conduction block of the distal peroneal motor nerve and FVC.⁸ Although the predictive value of this model is good (AUC 0.79),⁸ it is less applicable in settings where no NCS is available.

A previous study reported a high rate of respiratory insufficiency in CMV-related GBS.²⁸ Our study did not find an association between positive infection serology for *C. jejuni*, *M. pneumoniae*, Epstein-Barr virus, cytomegalovirus or hepatitis E virus and MV. Since only a small subgroup of patients tested positive for these recent preceding infections, we suppose that the added value of this predictor for clinical practice is small.

The proportion of patients requiring MV (16%) was lower compared with prior studies, which were mainly based on trial cohorts (patients with GBS-DS >2 only), while IGOS also included patients with mild forms of GBS and GBS variants. Since the mEGRIS was developed based on this more representative cohort, it has a broader applicability and can also be used in mildly affected patients and GBS variants. Although, the need for MV in MFS patients is exceptional, it is not fully ruled out when these patients develop severe bulbar palsy or transit

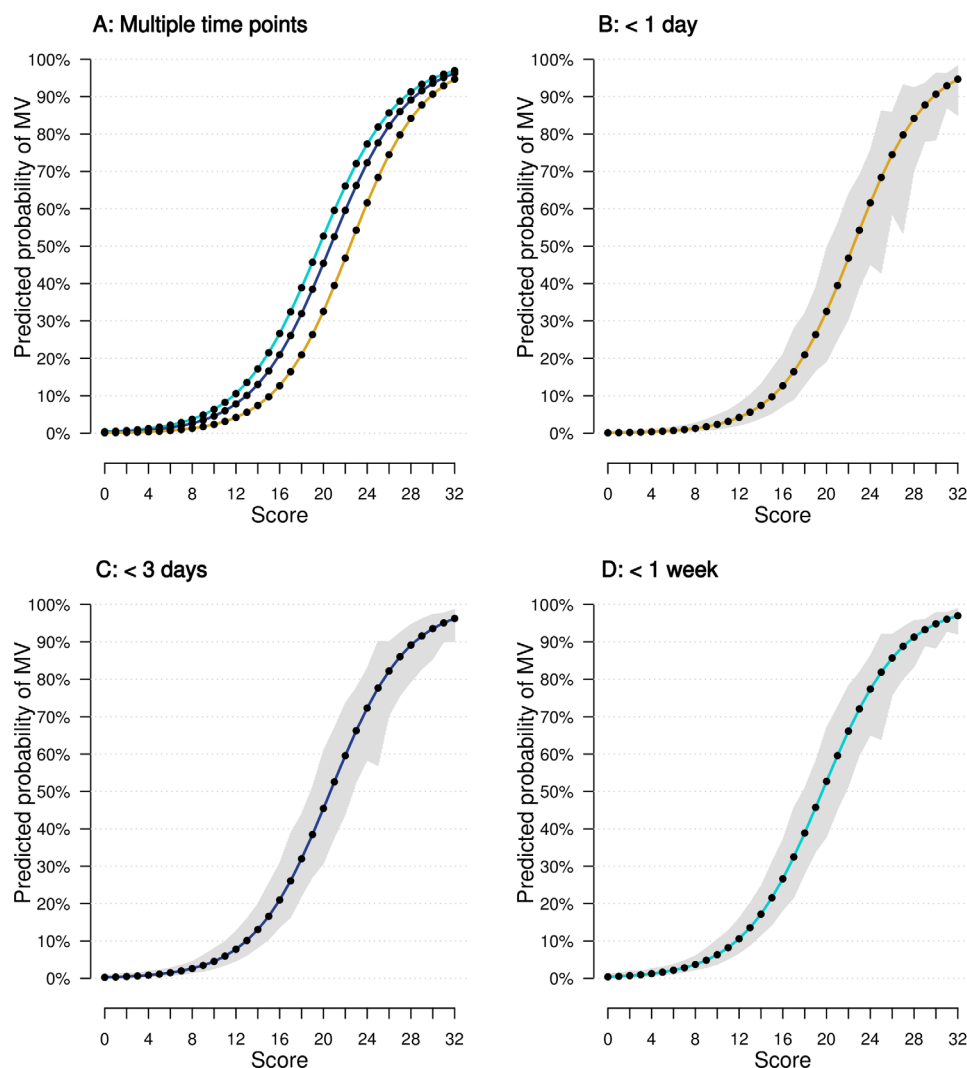


Figure 3 Predicted probabilities for MV within 1 day, 3 days and 1 week per mEGRIS score. A shows the predicted probabilities of MV within 1 day (yellow), 3 days (blue) and 1 week (light blue) from hospital admission for each mEGRIS score. The mEGRIS score can be calculated based on the scoring system (table 4). The corresponding 95% CIs for each time point are shown in (B) (<1 day), (C) (<3 days) and (D) (<1 week). For example, a patient with an mEGRIS score of 17 has a predicted probability to be mechanically ventilated of 17% (20%–28%) within 1 day, 26% (17%–29%) within 3 days and 32% (22%–45%) within 1 week. mEGRIS, modified Erasmus GBS Respiratory Insufficiency Score; MV, mechanical ventilation.

to MFS-GBS overlap (limb weakness),²⁹ which are both represented in the mEGRIS.

The mEGRIS is based on only four clinical characteristics available at admission, and is easily applicable in daily practice, especially in the emergency setting or in hospitals without specialised neurological care. No additional diagnostic tests are necessary. The score ranges from 0 to 32 and corresponds with a predicted risk of respiratory failure between 0 and 100%. The model is able to accurately predict the risk of MV in individual GBS patients and provides consistent predictions across different settings, as is shown by the internally–externally fourfold cross-validation procedure. However, we cannot draw conclusions regarding model performance in some specific regions (Australia, South Africa and South America) as patients numbers were small.²⁶ Model predictions remained good in subgroups enrolled in IGOS ≤ 1 day and > 1 day after hospital admission. In daily practice, the mEGRIS can be used as a simple bedside tool that assists in triaging patients who need to be transferred to wards with stricter monitoring. The score can be calculated via the scoring system in table 4 and corresponding probability plots provided in figure 3, and in

future also via de QxMD app or online (<https://gbstools.erasmusmc.nl>). The mEGRIS and the recalibrated version of the original EGRIS for Europe and North America have equal performance and are both recommended, but for practical purposes we prefer the use of the mEGRIS.

Our study has several limitations. First, our model was not externally validated. However, recent literature showed that internal–external validation by geographical cross-validation can be alternatively used and has the advantage of validating the model across different settings.^{25 26} Second, we were unable to include NCS and biological factors in our model, because in only a limited number of patients an early NCS was conducted (consistent with clinical practice), and assessment of novel biological factors in IGOS patients is still ongoing. Future research is needed to establish the potential predictive value of these determinants in addition to clinical predictors, although such models might be less applicable in settings where no NCS or biological testing is available. Furthermore, it would be interesting to define cut-offs for mEGRIS that could enhance the clinical impact and guide the decision to admit a patient to a hospital ward, monitored telemetry bed

or intensive care unit, based on the calculated risk for MV. This can be assessed by decision curve analysis, which will define the net benefit of the model while incorporating factors specific to the hospital and the country, such as resource availability and cost-effectiveness issues. Lastly, separate models need to be developed for children <6 years and patients from Bangladesh.

In conclusion, the mEGRIS is a simple and broadly applicable clinical score that can predict the risk of MV for individual GBS patients at different time points during disease course. Future studies are needed to establish the net benefit of this score in clinical practice and whether early NCS and biological factors can further improve the model predictions.

Author affiliations

- ¹Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
- ²Neurology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands
- ³Neurology, Haga Hospital, Den Haag, The Netherlands
- ⁴Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA
- ⁵Neurology, St. Elizabeth's Medical Center, Boston, Massachusetts, USA
- ⁶Laboratory of Gut-Brain Signaling, Laboratory Sciences and Services Division (LSSD), International Centre for Diarrhoeal Disease Research Bangladesh, Dhaka, Bangladesh
- ⁷Neurology, University of Vermont Medical Center, Burlington, Vermont, USA
- ⁸Neurology, Kindai University Faculty of Medicine Graduate School of Medical Sciences, Osakasayama, Osaka, Japan
- ⁹Neurology, IJsselland Hospital, Capelle aan den IJssel, The Netherlands
- ¹⁰Public Health, Erasmus Medical Center, Rotterdam, The Netherlands
- ¹¹Neurology and Immunology, Erasmus Medical Center, Rotterdam, The Netherlands

Acknowledgements We thank all patients who participated in this study. We thank Laura de Koning for her efforts in management and maintenance of the IGOS database. We thank Marieke van Woerkom for her efforts in coordinating the IGOS study.

Collaborators Richard A.C. Hughes, David R. Cornblath, Hans-Peter Hartung, Pieter A. van Doorn, Hugh J. Willison, Bianca van den Berg, Christine Verboon, Joyce Roodbol, Sonja E. Leonhard, Robin C.M. Thomma, Laura C. de Koning, Melissa Mandarakas, Marieke van Woerkom, Stephen W. Reddel, Zahirul Islam, Quazi Deen Mohammad, Peter van den Bergh, Tom E. Feasby, Yuzhong Wang, Thomas Harbo, Yann Péréon, Helmar C. Lehmann, Efthimios Dardiotis, Eduardo Nobile-Orazio, Nortina Shahrazila, Kathleen Bateman, Luis Querol, Paolo Ripellino, Sung-Tsang Hsieh, Govindsinh Chavada, Amy Davidson, James M. Addington, Senda Ajroudr-Driss, Lucas Alessandro, Henning Andersen, Giovanni Antonini, Shahram Attarian, Umesh A. Badrising, Fabio A. Barroso, Isabelita R. Bella, Luana Benedetti, Tullio E. Bertorini, Ratna Bhavaraju-Sanka, Mariangela Bianco, Thomas H. Brannagan, Chiara Briani, Jan Bürmann, Mark Busby, Stephen Butterworth, Carlos Casasnovas, Guido Cavaletti, Chi-Chao Chao, Shan Chen, Kristl G. Claeys, Maria Eugenia Conti, Jeremy S. Cosgrove, Marinos C. Dalakas, Charlotte Dornonville de la Cour, Andoni Echaniz-Laguna, Filip Eftimov, Catharina G. Faber, Raffaella Fazio, Janev Fehmi, Chris Fokke, Toshiaki Fujioka, Ernesto A. Fulgenzi, Giuliana Galassi, T. Garcia-Sobrinho, Marcel P.J. Garssen, Cees J. Gijssbers, James M. Gilchrist, H. Jacobus Gilhuis, Jonathan M. Goldstein, Namita A. Goyal, Volkan Granit, Stefano G. Grisanti, Gerardo Gutiérrez-Gutiérrez, Lauri Gutmann, Robert D.M. Hadden, Jakob V. Holbech, James K.L. Holt, Min Htut, Korné Jellema, Ivonne Jericó Pascual, María C. Jimeno-Montero, Kenichi Kaida, Summer Karafiath, Hans D. Katzberg, Henk Kerkhoff, Mohammad ali M. Khoshnoodi, Lynette Kiers, Ruud P. Kleyweg, Norito Kokubun, Hans Kramers, Krista Kuitwaard, Satoshi Kuwabara, Justin Y. Kwan, Shafeeq S. Ladha, Lisbeth Landschoff Lassen, Victoria Lawson, Edward Lee Pan, Luciana León Cejas, Cintia Lorena Marchesoni, Michael P. T. Lunn, Amelle Magot, Hadi Manji, Gerola A. Marfia, Celedonio Márquez-Infante, Lorena Martín Aguilar, Eugenia Martínez-Hernández, Georgia Mataluni, Marcelo G. Mattiazzi, Chris J. McDermott, Gregg D. Meekins, James A.L. Miller, Maria Soledad Monges, Germán Moris de la Tassa, Julieta Mozzoni, Caterina Nascimbene, Richard J. Nowak, Michael Osei-Bonsu, Julio Pardo, Robert M. Pascuzzi, Valeria Prada, Michael T. Pulley, Simon Rinaldi, Rhys C. Roberts, Iñigo Rojas-Marcos, Stacy A. Rudnicki, George M. Sachs, Johnny P.A. Samijn, Lucio Santoro, Angelo Schenone, Lenka Schwindling, Maria J. Sedano Tous, Kazim A. Sheikh, Nicholas J. Silvestri, Soren H. Sindrup, Claudia L. Sommer, Beth Stein, Amro M. Stino, Cheng-Yin Tan, Hatice Tankisi, Paul T. Twydel, Philip Van Damme, Anneke J. van der Kooij, Taco C. van der Ree, Gert W. van Dijk, Rinske van Koningsveld, Jay D. Varrato, Valentina Vélez-Santamaría, Frederique H. Vermeij, Jan J.G.M. Verschuuren, Leo H. Visser, Michal V. Vytopil, Paul W. Wirtz, Guorong Zhang, Lan Zhou, Sasha Zivkovic.

Contributors LWGL and AYD contributed to the design of the study and had a major role in collection of data, analysis, interpretation of the data and drafting

of the manuscript. BCJ contributed to the design of the study, interpretation of the data and drafting of the manuscript and is responsible for the overall content as guarantor. HL contributed to the design of the study, interpretation of the data and drafting of the manuscript. MMD, KCG, BI, NAK, SK, NP, WW, CW, YY and SA contributed to the design of the study and had a major role in the collection of data, interpretation of the data and drafting the manuscript. The IGOS consortium members had a major role in the collection of data and critically revised the manuscript for intellectual content.

Funding IGOS is financially supported by the GBS-CIDP Foundation International, Gain, Erasmus MC University Medical Center Rotterdam, Glasgow University, CSL Behring, Grifols, Annexon, Hansa Biopharma and Roche.

Competing interests BCJ received grants from Grifols, CSL-Behring, Annexon, Prinses Beatrix Spierfonds, Baxalta, Hansa Biopharma, Roche, Horizon 2000 and GBS-CIDP Foundation International and is on the Global Medical Advisory Board of the GBS CIDP Foundation International. BCJ received consultancy fees from Roche for activities outside the current study. KCG provides consulting services for Annexon, Argenc, Janssen, Pfizer, Roche and UCB Pharma, and participates on data safety monitoring boards or advisory boards from Annexon, Argenc, Janssen, Immunopharma and Roche. MMD received grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, UCB Biopharma/RaPharma, Viromed/Healixmith & TMA; MMD received consultancy fees from Amgen, Argenc, Catalyst, Cello, Covance/LabCorp, CSL-Behring, EcoR1, Janssen, Kezar, Medlink, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma and UpToDate; MMD received payment or honoraria for lectures/presentations from AAN, AANEM, Medlink, SANAM2022, CATALYST, SPARK, OCTOPHARMA, CSL-Behring; MMD participated in the data safety monitoring boards of Covance/LabCorp DMC and advisory boards of Sanofi, Argenc, Takeda and Janssen. SK received grants and honoraria for speech from Teijin, Nihon Pharm and the Japan Blood Products Organization. YY received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Teijin and CSL Behring.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Erasmus MC University Medical Center, MEC-2011-477. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data of included patients in IGOS will be used for future studies and may be made available on reasonable request after consulting the IGOS Steering Committee.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Linda W G Luijten <http://orcid.org/0000-0002-0199-4516>
Mazen M Dimachkie <http://orcid.org/0000-0002-7148-989X>
Susumu Kusunoki <http://orcid.org/0000-0002-1584-8704>
Bart C Jacobs <http://orcid.org/0000-0002-8985-2458>

REFERENCES

- 1 Leonhard SE, Mandarakas MR, Gondim FAA, *et al.* Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol* 2019;15:671–83.
- 2 Green C, Baker T, Subramaniam A. Predictors of respiratory failure in patients with Guillain-Barré syndrome: a systematic review and meta-analysis. *Med J Aust* 2018;208:181–8.
- 3 Rajabally YA, Uncini A. Outcome and its predictors in Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry* 2012;83:711–8.
- 4 Islam Z, Papri N, Ara G, *et al.* Risk factors for respiratory failure in Guillain-Barré syndrome in Bangladesh: a prospective study. *Ann Clin Transl Neurol* 2019;6:324–32.
- 5 Walgaard C, Lingsma HF, Ruts L, *et al.* Prediction of respiratory insufficiency in Guillain-Barré syndrome. *Ann Neurol* 2010;67:781–7.
- 6 Kannan Kanikannan MA, Durga P, Venigalla NK, *et al.* Simple bedside predictors of mechanical ventilation in patients with Guillain-Barre syndrome. *J Crit Care* 2014;29:219–23.

- 7 Sharshar T, Chevret S, Bourdain F, *et al.* Early predictors of mechanical ventilation in Guillain-Barré syndrome. *Crit Care Med* 2003;31:278–83.
- 8 Durand M-C, Porcher R, Orlikowski D, *et al.* Clinical and electrophysiological predictors of respiratory failure in Guillain-Barré syndrome: a prospective study. *Lancet Neurol* 2006;5:1021–8.
- 9 Jacobs BC, van den Berg B, Verboon C, *et al.* International Guillain-Barré syndrome outcome study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome. *J Peripher Nerv Syst* 2017;22:68–76.
- 10 Doets AY, Walgaard C, Lingsma HF, *et al.* International validation of the Erasmus Guillain-Barré syndrome respiratory insufficiency score. *Ann Neurol* 2022;91:521–31.
- 11 Arnold LM, Hehir MK, Tandan R, *et al.* Neck flexion strength as a predictor of need for intubation in Guillain-Barre syndrome. *J Clin Neuromuscul Dis* 2022;23:119–23.
- 12 Fokkink W-JR, Walgaard C, Kuitwaard K, *et al.* Association of albumin levels with outcome in intravenous Immunoglobulin-Treated Guillain-Barré syndrome. *JAMA Neurol* 2017;74:189–96.
- 13 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol* 1990;27 Suppl:S21–4.
- 14 Sejvar JJ, Kohl KS, Gidudu J, *et al.* Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599–612.
- 15 Roodbol J, de Wit MCY, Walgaard C, *et al.* Recognizing Guillain-Barre syndrome in preschool children. *Neurology* 2011;76:807–10.
- 16 Papri N, Islam Z, Leonhard SE, *et al.* Guillain-Barré syndrome in low-income and middle-income countries: challenges and prospects. *Nat Rev Neurol* 2021;17:285–96.
- 17 Doets AY, Verboon C, van den Berg B, *et al.* Regional variation of Guillain-Barré syndrome. *Brain* 2018;141:2866–77.
- 18 Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991;14:1103–9.
- 19 Hughes RA, Newsom-Davis JM, Perkin GD, *et al.* Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978;2:750–3.
- 20 Hadden RD, Cornblath DR, Hughes RA, *et al.* Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. plasma Exchange/Sandoglobulin Guillain-Barré syndrome trial group. *Ann Neurol* 1998;44:780–8.
- 21 Van den Bergh PYK, van Doorn PA, Hadden RDM, *et al.* European Academy of Neurology/Peripheral nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task Force-Second revision. *Eur J Neurol* 2021;28:3556–83.
- 22 Leonhard SE, van der Eijk AA, Andersen H, *et al.* An international perspective on preceding infections in Guillain-Barré syndrome: the IGOS-1000 cohort. *Neurology* 2022;99:e1299–313.
- 23 Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. *J Clin Epidemiol* 1999;52:935–42.
- 24 Drailos RLB. Measuring performance: AUC (AUROC), 2019. Available: <https://glassboxmedicine.com/2019/02/23/measuring-performance-auc-auroc/> [Accessed 18 Nov 2021].
- 25 Takada T, Nijman S, Denaxas S, *et al.* Internal-external cross-validation helped to evaluate the generalizability of prediction models in large clustered datasets. *J Clin Epidemiol* 2021;137:83–91.
- 26 Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016;69:245–7.
- 27 Gallardo E, Sedano MJ, Orizaola P, *et al.* Spinal nerve involvement in early Guillain-Barré syndrome: a clinico-electrophysiological, ultrasonographic and pathological study. *Clin Neurophysiol* 2015;126:810–9.
- 28 Visser LH, van der Meché FG, Meulstee J, *et al.* Cytomegalovirus infection and Guillain-Barré syndrome: the clinical, electrophysiologic, and prognostic features. Dutch Guillain-Barré Study Group. *Neurology* 1996;47:668–73.
- 29 Hu Q, Li H, Tian J, *et al.* Bulbar paralysis associated with Miller-Fisher syndrome and its overlaps in Chinese patients. *Neuro Sci* 2018;39:305–11.