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European Journal of Paediatric Neurology 44 (2023) 18–24

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Predicting respiratory failure and outcome in pediatric Guillain-Barré syndrome☆

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ARTICLE INFO

Keywords:
Guillain-Barré syndrome
Children
Prognostic models and
Respiratory failure

ABSTRACT

Background: Guillain-Barré syndrome (GBS) has a highly variable clinical course and outcome as indicated by the risk of developing respiratory failure and residual inability to walk. Prognostic models as Erasmus GBS Respiratory Insufficiency Score (EGRIS) developed in adult patients are inaccurate in children. Our aim was to determine the prognostic factors of respiratory failure and inability to walk in children with GBS and to develop a new clinical prognostic model for individual patients (EGRIS-Kids).

Methods: A multicenter retrospective cohort study was performed using the data of children (younger than 18 years) fulfilling the diagnostic criteria for GBS from the NINDS. This study was performed in two independent cohorts from centers in Germany, Switzerland, Austria (N = 265, collected 1989–2002) and The Netherlands (N = 156, collected 1987–2016). The predicted main outcomes were occurrence of respiratory failure during the disease course and inability to walk independent at one year after diagnosis.

Results: In the combined cohort of 421 children, 79 (19%) required mechanical ventilation and one patient died. The EGRIS-kids was developed including: age, cranial nerve involvement and GBS disability score at admission, resulting in a 9 point score predicting risks of respiratory failure ranging from 4 to 50% (AUC = 0.71). A lower GBS disability score at nadir was the strongest predictor of recovery to independent walking (at one month: OR 0.43 95%CI 0.25–0.74).

Conclusions: EGRIS-Kids and GBS disability score at admission accurately predict the risk of respiratory failure and inability to walk respectively in children with GBS, as tools to personalize the monitoring and treatment.

1. Introduction

The Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy that can affect persons of all ages. Most patients show a characteristic monophasic clinical course starting with a rapid clinical progression [1,2] during which about 15–25% of patients develop respiratory failure [3,4]. After reaching a plateau phase most patients start recovering but the rate and extent of recovery is highly variable [5,6]. The uncertainty of the clinical course in individual patients complicates the treatment and care, as indicated for example by the need for emergency intubation in children with GBS [7,8]. Accurate prediction models may early identify patients at risk of respiratory failure or of poor recovery which may help preventing emergencies or identify patients for future more intensive treatment.

For adult patients with GBS prognostic models have been developed that can predict the probability of respiratory failure and of residual inability to walk unaided [9,10]. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) predicts the probability of respiratory failure in the

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https://doi.org/10.1016/j.ejpn.2023.02.007
Received 9 October 2022; Received in revised form 20 January 2023; Accepted 28 February 2023
Available online 10 March 2023

first week, using three characteristics at hospital admission: time from onset of weakness until admission, extend of limb weakness indicated by the Medical Research Council (MRC) sum score and presence of facial and/or bulbar weakness [9]. The Erasmus GBS Outcome Score (EGOS) and modified EGOS predict the probability to walk unaided 6 months after diagnosis based on age, preceding diarrhea and the GBS disability/MRC sum score [10,11]. These prognostic models do not apply to pediatric GBS, as these scores were largely based on data from adult patients, and the clinical course of GBS in children differs from that in adult patients [12,13]. Previous studies have related the occurrence of respiratory failure in pediatric GBS to short time between infection and neurological onset, cranial nerve involvement, severe arm weakness, low MRC sum score, high GBS disability score, autonomic dysfunction and increased CSF protein [3,14,15]. Reported risk factors for a persistent disability in children are young age, high GBS disability score at presentation, intubation, cranial nerve involvement [16,17], quadriplegia [18], long plateau phase [19], rapid progression to maximal weakness [20,21] and absent compound muscle action potential (CMAP) [22]. Despite these studies there are at present no prognostic models for children with GBS that can be used for clinical practice.

The aim of the current study was to develop the first prognostic model to predict the risk of respiratory failure and residual inability to walk in children with GBS. First, serial data from two large and independent cohorts of children with GBS were used to identify characteristics associated with respiratory failure and limited clinical recovery. Second, we developed a prediction model for clinical practice to predict the chance of respiratory failure in individual children at the moment of hospital admission (EGRIS-Kids). Third, we aimed to predict the inability to walk unaided at various time points during follow-up.

2. Patients and method

2.1. Study design, settings and patients

This study was based on a cohort of 421 children with GBS from four Western European countries: Switzerland, Austria, Germany and the Netherlands. The cohort from the German speaking countries, referred to as 'German cohort', includes 265 children (median age 6 years, range 16 years) and was based on the combination of a retrospective multicenter cohort study, in which 69 hospitals participated between 1989 and 1994 (N = 175) and a prospective multicenter treatment trial, collecting data from 63 hospitals between 1999 and 2002 (N = 90). The Dutch cohort includes 156 children (median age 7 years, range 17 years) and was based on the combination of a retrospective single center cohort study conducted between 1987 and 2013 (N = 68), the Dutch patients participating in the prospective multicenter International GBS Outcome Study (IGOS) (N = 14) and a retrospective cohort study in 9 Dutch hospitals, between 2004 and 2016 (N = 74). The clinical characteristics of the German cohort and majority of the Dutch cohort were published but not previously used to develop a prognostic model for GBS [6,13,23,24].

The National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria from 1990 were used as guideline for the diagnosis [1]. Children were defined as patients under 18 years old. Data regarding previously reported clinical predictors for outcome in GBS were collected, including clinical information regarding preceding infection, presenting neurological symptoms, neurological deficits at admission and nadir, treatment regimen, results of cerebrospinal fluid (CSF) and nerve conduction study (NCS). Autonomic dysfunction was defined as any evidence of hyper- or hypotension, cardiac arrhythmias, bladder or bowel dysfunction. Severity of the disease at nadir was defined by the highest GBS disability score. The GBS disability score ranges from 0 to 6: 0 (normal), 1 (minor symptoms capable of running), 2 (able to walk 10 m or more without assistance but unable to run), 3 (able to walk 10 m across an open space with help), 4 (bedridden or chair bound), 5 (requiring assisted ventilation for at least part of the day), 6 (dead) [25]. Poor outcome was defined as the inability to walk unaided (GBS disability score of 2 or lower) at 1, 2, 3, 6 and 12 months after start of symptoms). A raised protein found in CSF was defined as a level above 0.40 g/l independent of the age of the child, based on a previously published study [6].

The medical ethics committee of the Erasmus MC and of the university of Freiburg approved the study.

2.2. Statistical analyses

Continuous data were presented as means and standard deviations if normally distributed, and as medians and interquartile ranges (IQR) when not normally distributed. Categorical data were presented as proportions. Continuous data of the two cohorts were compared with *t*-test if normally distributed and with Mann-Whitney *U* test if not normally distributed. Proportions were compared using the Chi-square or Fisher exact test. A two-sided p-value <0.05 was considered significant.

Univariable and multivariable regression analysis were performed on the combined cohort. Missing data used in the regression analyses were imputed using a multiple imputation method. Predictors with a p-value <0.20 in the univariable analysis were further analyzed in a multivariable logistic regression model. The stepwise backward method was used and variables with a p-value >0.20 were removed from the model. A false negative result could lead to severe complications, therefore we decided to accept the 0.20 as cut-off value at both the univariable and multivariable regression analyses. In parallel to the EGRIS for adult patients, the EGRIS-Kids model for children was constructed based on the regression coefficients of the multivariable

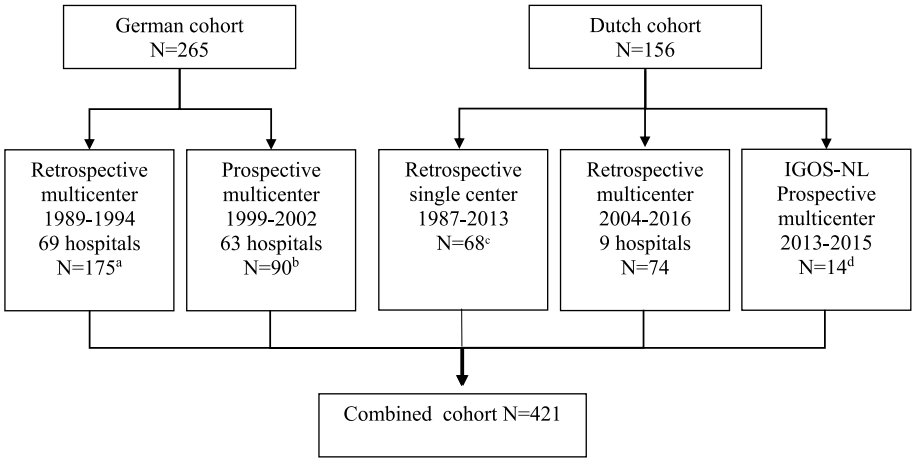

Fig. 1. Patient inclusion of the combined cohort
The study design and part of the cohorts were described previously:
[a:] Korinthenberg R, Schessl J, Kirschner J. Clinical presentation and course of childhood Guillain-Barre syndrome: a prospective multicentre study. *Neuropediatrics.* 2007; 38(1):10–17.[6]
[b:] Korinthenberg R, Monting JS. Natural history and treatment effects in Guillain-Barre syndrome: a multicentre study. *Arch Dis Child.* 1996; 74(4):281-287.[13]
[c:] Roodbol J, de Wit MY, van den Berg B et al. Diagnosis of Guillain-Barre syndrome in children and validation of the Brighton criteria. *J Neurol.*201.[23]
[d:] Roodbol J, de Wit MC, Walgaard C, de Hoog M, Catsman-Berrevoets CE, Jacobs BC. Recognizing Guillain-Barre syndrome in preschool children. *Neurology.*2011; 76(9):807-810.[24].

analysis in the combined cohort and items which we assumed to be clinically practical. Area under de receiver operating curve (AUC) was used to quantify the model performance. We performed internal validation with bootstrap resampling to correct for optimism of the model performance. Because the selection of variables was partly done based on clinical knowledge, we were not able to include the full variable selection process in the internal validation procedure.

We used SPSS 25 and R statistical software (version 3.4.4) to perform statistical analyses.

3. Results

The combined study cohort consisted of 421 children (265 children from three German speaking countries and 156 children from The Netherlands) with a median age of 6 years (IQR 3–11 years) including 229 boys and 192 girls (Fig. 1). A clinical description of the cohorts is provided in Table 1.

3.1. Clinical outcome

In the combined cohort, 12 (3%) patients were excluded from the analysis with respiratory failure as endpoint, because the patients were already intubated at hospital admission (N = 10) or the timing of the intubation was unknown (N = 2). In total, 79 (19%) of the remaining 409 children developed respiratory failure and required mechanical ventilation. The proportion of ventilated patients was 24% (37/154) in

Table 1
Clinical characteristics of the study cohorts of children with GBS.

	Dutch cohort (N = 156)	German cohort (N = 265)	p-value[a]	Combined cohort (N = 421)
Demographic features				
Male: female (% Male)	82:74 (53)	147:118 (56)	ns	229:192 (54)
Median age (IQR, full range)	7 (3–13, 0–17)	6 (3–10, 1–17)	**0.041**	6 (3–11, 0–17)
Age distribution			**0.029**	
< 6 years (%)	67 (43)	126 (48)		193 (46)
6–10 years (%)	35 (22)	78 (29)		113 (27)
> 10 years (%)	54 (35)	61 (23)		115 (27)
Preceding infection				
No antecedent event (%)	19/143 (13)	52/265 (20)	ns	71/408 (17)
Respiratory tract infection (%)	66/146 (45)	98/256 (38)	ns	164/402 (41)
Diarrhea (%)	47/145 (32)	35/256 (14)	**<0.001**	82/401 (20)
Vaccination (%)	11/130 (9)	12/256 (5)	ns	23/386 (6)
Clinical symptoms admission				
GBS disability score				
0, 1 and 2 (%)	44/137 (32)	146/258 (57)	**<0.001**	190/395 (48)
3 (%)	42/137 (31)	44/258 (17)		86/395 (22)
4 (%)	48/137 (35)	61/258 (24)		109/395 (28)
5 (%)	3/137 (2)	7/258 (3)		10/395 (3)
Weakness arms (%)	90/131 (69)	64/258 (25)	**<0.001**	154/389 (40)
Cranial nerve involvement (%)	51/141 (36)	104/263 (40)	ns	155/404 (38)
Autonomic dysfunction (%)	13/122 (11)	67/261 (26)	**0.001**	80/383 (21)
Clinical symptoms nadir				
GBS disability score				
0, 1, 2 (%)	17/151 (12)	72/264 (27)	**0.001**	89/415 (21)
3 (%)	27/151 (18)	38/264 (14)		65/415 (16)
4 (%)	70/151 (46)	112/264 (42)		185/415 (44)
5 (%)	32/151 (24)	42/264 (16)		78/415 (19)
6 (%)	1/151 (1)	0		1/415 (0.2)
Weakness arms (%)	126/144 (88)	123/261 (47)	**<0.001**	249/405 (62)
Cranial nerve involvement (%)	77/140 (55)	102/258 (40)	**0.003**	179/398 (45)
Autonomic dysfunction (%)	64/136 (47)	76/119 (64)	**0.007**	140/255 (55)
Nerve conduction studies[b]			nc	
Normal (%)	8/86 (9)	20/169 (12)		28/255 (11)
Demyelinating (%)	51/86 (60)	101/169 (60)		152/255 (60)
Axonal (%)	8/86 (9)	27/169 (16)		35/255 (14)
Demyelinating and axonal (%)	2/86 (2)	16/169 (10)		18/255 (7)
Equivocal[c] (%)	16/86 (19)	0		16/255 (6)
Unresponsive (%)	1/86 (1)	5/169 (3)		6/255 (2)
Treatment			nc	
Intravenous immunoglobulins (%)	101/131 (77)	127/178 (71)		228/309 (74)
Plasma exchange (%)	3/131 (2)	5/178 (3)		8/309 (3)
Other[d] (%)	27/131 (21)	46/178 (26)		73/309 (24)
Median onset-treatment in days[e] (IQR, full range)	7 (4–10, 2–78)	12 (8–21, 1–62)	**<0.001**[f]	8 (5–15, 1–78)

The 'German cohort' includes patients from the German speaking countries Germany, Austria and Switzerland.
ns is not-significant (p-value ≥0.05).
nc is not calculated.

[a] P-value shows the differences between the German and Dutch cohort.

[b] No NCS was performed in 51 patients of the entire cohort.

[c] Equivocal: Nerve conduction study (NCS) is abnormal but does not fulfill any of the criteria for specific GBS subtype.

[d] Other treatment protocols were (N = 73 patients): 17 patients received corticosteroids alone (all patients from the German cohort). 4 patients corticosteroids and plasma exchange (all patients from German cohort). 28 patients with intravenous immunoglobulins (IVIg) and methylprednisolone (15 from German cohort and 13 from Dutch cohort). 14 patients participated in a trial treated with IVIg with or without methylprednisolone (all patients from Dutch cohort). 9 patients IVIg and plasma exchange (all patients from German cohort). 1 patient with IVIg and plasma exchange and corticosteroids (from German cohort).

[e] In the German group in 171 patients and 38 patients in the Dutch cohort the information about onset until start of treatment was missing.

[f] The difference in treatment was based on the number of patient who did not receive treatment between the two groups. 26% of the entire cohort did not receive treatment (33% German cohort and 14% Dutch cohort).

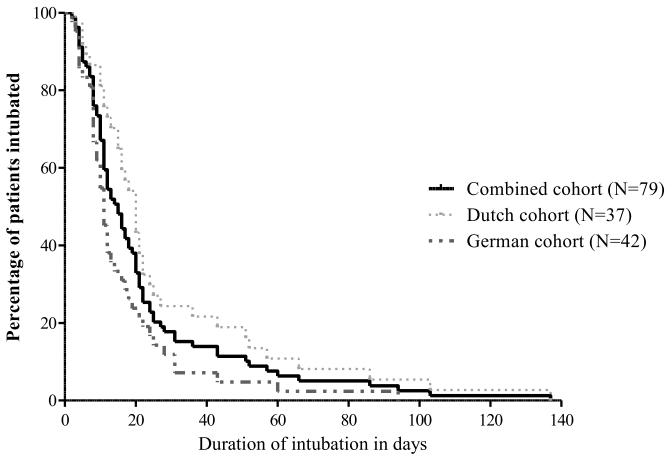

Fig. 2. Duration of intubation in ventilated children with GBS in Dutch, German and combined cohort.
Kaplan-Meier curves of the duration of mechanical ventilation
The table under the curve shows the number of children still intubated on the several time points (20, 40, 60, 80, 100, 120 and 140 days).

the Dutch cohort, which was higher than in the German cohort (16%, 42/265) ($p = 0.039$). In the combined group the median duration of ventilation was 15 days (IQR 9–24, full range 2–137). The median intubation period was 20 days (IQR 12–32 and full range 3–134) in the Dutch cohort and 11 days (IQR 8–20, range 2–92) in the German cohort ($p = 0.005$). A Kaplan-Meier analysis comparing the intubation period of the two cohorts and the whole group is shown in Fig. 2. Of the combined cohort 26% of patients were untreated. The proportion of patients who did not receive treatment was higher in the German cohort (14% vs 33%, $p < 0.001$). A nerve conduction study was performed in the majority (83%) of patients from the combined cohort (86% in the German cohort and 78% in the Dutch cohort). The median time between onset of symptoms and nerve conduction study was 10 days (IQR 5–17, full range 1–230). This was comparable in the two cohorts.

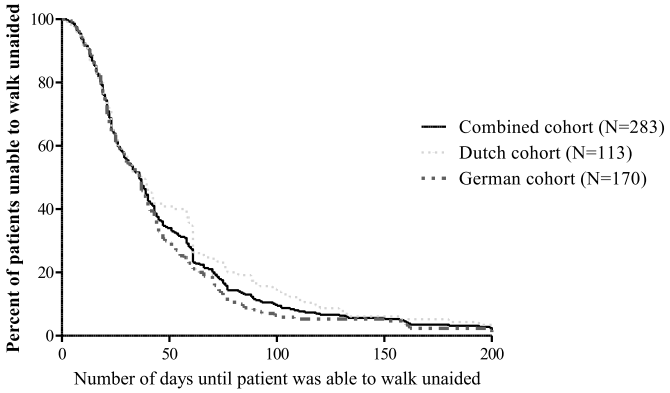

Fig. 3. Time to independent walking in children with GBS in the Dutch, German and combined cohort.
Kaplan-Meier curves of the time to regain the capacity to walk independently in children with GBS unable to walk at nadir. In the combined cohort, 283 (67.2%) of 421 children were unable to walk and eligible for the analysis. Excluded were children with milder forms of GBS (able to walk independently at nadir, N = 89), missing GBS disability score at nadir (N = 6), missing time between developing and recovering from the inability to walk (N = 43) were excluded from the analysis. The graph is based on the patients who regained the capacity to walk within 200 days. In 7 patients not presented in the graph the time to independent walking was respectively 210, 210, 220, 250, 302, 365 and 423 days.
The table under the curve shows the number of children still unable to walk on the several time points (50, 100, 150 and 200 days).

The progression of the disease as indicated by the time between onset of symptoms and hospital admission or nadir was similar in both cohorts. The median time between start of symptoms and admission in the combined cohort was five days (IQR 3–9, full range -15-47). Five patients were already admitted for a different diagnosis when the first symptoms of GBS started. The median time between onset of symptoms and nadir in the combined cohort was eight days (IQR 5–13, full range 0–40).

The proportion of children unable to walk at nadir was 79% in the whole group and higher in the Dutch cohort (89%) compared to the German cohort (73%) ($p < 0.001$). The time until the children were able to walk unaided was comparable between the two groups, with a median of 36 days (IQR 20–61, full range 2–423). A Kaplan-Meier analysis of the time the patients of the combined cohort required to walk independently is shown in Fig. 3.

3.2. Risk factors and prediction of respiratory failure

Univariable and multivariable analysis of factors associated with the development of respiratory failure are shown in Table 2. In multivariable analysis, respiratory failure was associated with increasing age, shorter time between onset of neurological symptoms and hospital admission, the presence of cranial nerve involvement, the presence of autonomic dysfunction, a higher GBS disability score at admission and a higher CSF protein level. No relation was found between the type of NCS abnormalities and the risk of respiratory failure.

The EGRIS-Kids model was based on three prognostic factors (age, GBS disability score and cranial nerve involvement) because of their high predictive value in multivariable analysis and feasibility in clinical practice. Not selected for practical reasons were CSF protein level (not all patients will routinely have an lumbar puncture and level depends on timing of the puncture), autonomic dysfunction (complex definition in emergency setting) and time between onset and admission (frequently unknown in children). The EGRIS-Kids ranges from 1 to 9 with a corresponding risk of respiratory failure of 4%–50% and an AUC of 0.73 (Table 3). After internal validation the corrected AUC was 0.71 (Fig. 4).

3.3. Risk factors and prediction of inability to walk

In the combined cohort, 326 (79%) of children were unable to walk at nadir and in 6 children this information was missing. In the analysis on the predictors of inability to walk at 4 weeks, 35 (11%) children were excluded because of insufficient information on the disability. The univariable and multivariable analysis of predictors of the inability to walk independently at 1 month is presented in Supplemental Table 1. The multivariable analysis showed that children were more often unable to walk unaided at one month with a higher GBS disability score at nadir and a higher level of CSF protein. The GBS disability score at nadir was the predominant predicting factor associated with outcome at most time points. Therefore we decided to use the GBS disability score at admission and nadir to predict the probability to walk unaided at several time points (Table 4A and B).

4. Discussion

In the current study we have identified the clinical and diagnostic factors associated with respiratory failure and inability to walk in childhood GBS. The most predictive set of factors was selected to develop a simple prognostic model for clinical practice based on information available as early in the disease course as possible. The EGRIS-Kids is a 9-point score based on the patient age, presence of cranial nerve involvement and GBS disability score at hospital admission, that accurately predicts the risk of respiratory failure in individual children ranging from 4 to 50%. In addition, we identified factors predicting the inability to walk, as an outcome measure frequently used in treatment trials in GBS. Several predictors were found but the predominant factor

Table 2
Prognostic factors at admission in relation to respiratory failure in the combined cohort of children with GBS.

Prognostic factors	N = 409	MV (N = 69)	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value
Age			1.54 (1.13–2.10)	**0.006**	1.56 (1.11–2.17)[c]	**0.010**
<6 years (%)	190	22 (12)				
6–10 years (%)	109	21 (19)				
>10 years (%)	110	26 (24)				
Preceding diarrhea			1.39 (0.73–2.65)	ns		–
Yes (%)	79/392 (20)	16/79 (20)				
No (%)	313/392 (80)	47/313 (15)				
Preceding URTI[a]			0.96 (0.56–1.66)	ns		–
Yes (%)	160/394 (41)	25/160 (16)				
No (%)	234/394 (59)	39/234 (17)				
Time onset symptoms- admission in days	393		0.91 (0.86–0.97)	**0.002**	0.92 (0.87–0.98)[d]	**0.007**
GBS disability score	385		1.35 (1.03–1.77)	**0.029**	1.40 (1.06–1.86)[b]	**0.018**
Cranial nerve involvement			4.14 (2.37–7.24)	**<0.001**	3.32 (1.82–6.04)	**<0.001**
Yes (%)	146/393 (37)	42/146 (29)				
No (%)	247/393 (63)	21/247 (9)				
Autonomic dysfunction			2.52 (1.26–5.06)	**0.011**	1.76 (0.80–3.87)	**0.154**
Yes (%)	75/373 (20)	22/75 (29)				
No (%)	298/373 (80)	41/298 (14)				
Weakness arms			1.44 (0.82–2.52)	ns		–
Yes (%)	144/378 (38)	27/144 (19)				
No (%)	234/378 (62)	30/234 (13)				
Protein in CSF	391		1.20 (0.98–1.47)	**0.078**	1.23 (0.98–1.56)	**0.075**

Univariable and multivariable regression analysis with outcome measure mechanical ventilation (MV) is based on 409 (97.1%) of 421 children from the combined cohort. Excluded were patients from whom information regarding mechanical ventilation was missing (N = 2) and patients who were already intubated at hospital admission (N = 10).
P-values used in the univariable analysis of >0.2 were excluded from the multivariable analysis and referred to in the table as not significant (ns).
[a] URTI = upper respiratory tract infection.
[b] With an increase of one point of the GBS disability score at admission the odds of respiratory failure is 1.40 times higher.
[c] With an higher age category the odds of respiratory failure is 1.56 times higher.
[d] With an increase of one day between the onset of symptoms and admission the odds of respiratory failure is 0.92 times lower.

Table 3
EGRIS-Kids for predicting respiratory failure in children with GBS.

Predictors at hospital admission	Categories	Score
Age (years)	≤5	0
	6–10	1
	11–17	2
Cranial nerve involvement	Absent	0
	Present	3
GBS disability score	1	1
	2	2
	3	3
	4	4
EGRIS-Kids		1–9

EGRIS-Kids = Erasmus GBS Respiratory Insufficiency Score for children.

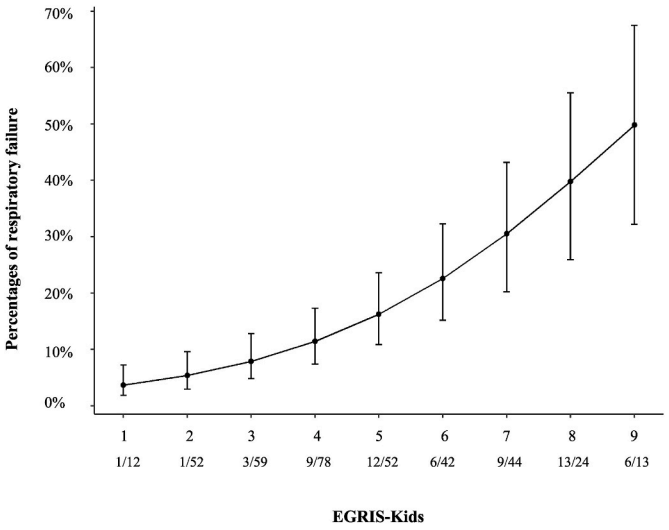

Fig. 4. Proportion of Respiratory Failure Based on EGRIS-Kids
Predicted percentages of patients with respiratory failure per EGRIS-Kids on the Y-axis. Total score on the EGRIS-Kids and the number of patients who actually required mechanical ventilation per EGRIS-Kids on the X-axis. The line dots represent the predicted percentages and the whiskers the 95% confidence intervals per EGRIS-Kids.
Included were 376 children with GBS from the combined cohort. Excluded were patients in whom information on mechanical ventilation was missing (N = 2), information regarding cranial nerve dysfunction or GBS disability score at admission was missing (N = 33), and 10 patients were already intubated at hospital admission.
Area under de receiver operating curve (AUC) was used to quantify the model performance and after internal validation the AUC was 0.71.

was the GBS disability score at nadir. Other factors did not improve the accuracy of the prediction. Based on this finding tables were provided to estimate the chances of being able to walk at various time points during the first year after diagnosis.

The study cohort is representative for the general West-European population of children with GBS, as reflected by the slight over-representation of males, frequencies and types of preceding infections, median time to admission after onset of neurological symptoms, range of GBS disability scores at admission and nadir and presence of cranial nerve involvement [26,27]. Most patients received the regular standard treatment with either immunoglobulins or plasma exchange, especially more severly affected patients, in accordance with current guidelines [2,28]. Autonomic dysfunction was frequent in both cohorts, as reported previously in studies on paediatric GBS, although strict criteria for autonomic dysfunction were not used [29–31]. Preschool children were overrepresented in both cohorts, but similar age distributions in GBS cohort studies have been reported previously [32,33]. Patients from the Dutch cohort in general were more severly affected than the patients from the German cohort, as reflected by the distributions of the GBS disability scores. The differences in age and clinical severity is probably related to referral bias and the types of centers participating. Most

Table 4A
GBS disability score at admission in relation to recovery of walking.

GBS disability score at admission (N = 395)	N	Proportion able to walk unaided (GBS disability score 2)				
		1 month (N = 367)	2 months (N = 366)	3 months (N = 369)	6 months (N = 370)	12 months (N = 368)
1	55	37/48 (77%)	42/48 (88%)	46/48 (96%)	50/50 (100%)	50/50 (100%)
2	135	94/128 (73%)	114/128 (89%)	125/129 (97%)	127/129 (98%)	128/129 (99%)
3	86	37/78 (47%)	59/78 (76%)	70/78 (90%)	75/77 (97%)	77/77 (100%)
4	109	40/104 (39%)	74/103 (72%)	88/105 (84%)	99/105 (94%)	102/103 (99%)
5	10	1/9 (11%)	4/9 (44%)	5/9 (56%)	7/9 (78%)	9/9 (100%)

The table shows the relation between the GBS disability score at admission and ability to walk unaided at several time points based on an analysis in 395 children with GBS.

Table 4B
GBS disability score at nadir in relation to recovery of walking.

GBS disability score at nadir (N = 325)	N	Proportion able to walk unaided (GBS disability score 2)				
		1 month (N = 290)	2 months (N = 289)	3 months (N = 251)	6 months (N = 294)	12 months (N = 292)
3	65	43/59 (73%)	56/59 (95%)	59/60 (98%)	61/61 (100%)	61/61 (100%)
4	182	73/162 (45%)	127/161 (79%)	149/122 (92%)	160/163 (98%)	162/162 (100%)
5	78	12/69 (17%)	33/69 (48%)	49/69 (71%)	62/70 (89%)	68/69 (99%)

The outcome ability to walk unaided at several time points is presented here for patients with a GBS disability score of 3,4 or 5. The GBS disability score at nadir was known in 325 children. Patients with a GBS disability score of 1 (N = 16), GBS disability score 2 (N = 73), GBS disability score 6 (N = 1) and patients in which the GBS disability score was missing at nadir (N = 6) were excluded.

patients in the Dutch cohort were included by tertiary academic hospitals with ICU facilities, while in the German cohort many secondary care centers participated. The combination of these two cohorts enabled us to select the predictors that performed best in either cohort to improve the generalizability of the models.

Mechanical ventilation was required in 19% of the children in this study, a similar proportion as usually reported in adult patients with GBS [9]. Some predictive factors for respiratory failure were the same in children as in adults, including the rate of progression (indicated by the time from neurological onset to admission), GBS disability score and presence of cranial nerve involvement. The EGRIS for adult patients is based on the MRC sum score at admission, but the GBS disability score at admission was also strongly associated with respiratory failure. An accurate MRC sum score however is more challenging in children, especially of young age, and usually this information is not available in clinical practice, and we therefore selected the GBS disability score. In contrast to adult patients, the risk of respiratory failure increases with age in childhood GBS. We found no relation between respiratory failure and an increased CSF protein level and demyelinating or axonal subtypes in NCS. These diagnostic features are also influenced by the timing of the examination and/or may be too late for an early prediction model. High flow nasal oxygen (HFNO) or other forms of non-invasive ventilation (NIV) may be alternatives for intubation, but were mostly unavailable during the study period. A limitation of HFNO/NIV in children with GBS is that they frequently have an inability to cough effectively and often need sedation due to pain, anxiety or prolonged need for ventilatory support with intact consciousness.

Regaining the ability to walk independently and reaching of a GBS disability score of 2 is a valuable milestone for patients and frequently used outcome measure in treatment trials in GBS. In adult patients with GBS, 75–80% will be able to walk unaided after a follow-up of 6–12 months [11]. In our study we found that already 88% of children reached this endpoint within 3 months and 96% within 6 months. This finding of a much better recovery of GBS in children compared to adults is in accordance with most previous studies [13,26,34]. The higher recovery rate in children with GBS also limited the possibilities to develop a prognostic model for reaching independent walking at 6 months or longer. Reaching this endpoint at 1, 2 and 3 months was predominantly predicted by the GBS disability score at nadir in both cohorts. Also in the EGOS for adult patients, the GBS disability score (at 2 weeks) is the predominant predictor of the ability to walk unaided during longer follow-up [10]. In contrast to adult patients, age is not a predictive factor for this endpoint in childhood GBS, probably because in children age is not limiting the regenerative capacity of damaged peripheral nerves. Despite the good long-term outcome in children with GBS with respect to walking, previous studies showed that these children may suffer from residual pain, deficits in sensation and fine motor skills, and severe fatigue which may limit their daily activities [35]. Prospective studies with validated outcome measures are required to determine which factors may influence these deficits and complaints.

Our study has several limitations. First, despite the large cohort of children included for such a rare disorder, the number of patients in each of the two cohorts was insufficient for a proper independent validation study. We therefore had to combine the two cohorts to develop the prognostic model, which needs further validation in an independent cohort. Second, the study population consisted of West-European patients and frequently had a demyelinating subtype of GBS. Considering the global variation of GBS, validation studies are required in other regions, especially in patients with axonal subtypes of GBS [21,35,36]. Third, the accuracy of the EGRIS-Kids indicated by an AUC of 0.71 is less than the EGRIS in adult patients (AUC 0.82). Further improvement may come from prognostic biomarkers which were not included in the current study. Such validations and model improvements may come from the International GBS Outcome Study (IGOS), in which also children are included and data and biosamples are collected prospectively [37].

We would like to give further background for the use of these models in clinical practice. Importantly, based on the EGRIS-Kids respiratory failure cannot be excluded in individual children with GBS. Patients with the lowest scores still have a small risk of requiring mechanical ventilation and also these patients require frequent monitoring of in the acute progressive phase of disease [28]. Patients with a higher score and increased risk of respiratory failure may be transferred to an ICU. Predicting the chances to recover to walk independently is important to inform patients and their relatives and plan rehabilitation. In the future, these models may help for the identification of patients with poor prognosis who may profit from additional early treatments.

Declaration of competing interest

Drs. J. Roodbol has no disclosures to report.

Prof. Dr. R Korinthenberg has no actual conflicts of interest to report.

Drs E. Venema has no disclosures to report.

Dr. M.C.Y. de Wit received honoraria paid to her institution by Novartis for serving on a steering committee and presenting at a conference, and has received research funding from the Epilepsiefonds (Dutch Epilepsy Foundation), Hersenstichting and Sophia Foundation.

Dr. H. F. Lingsma has no disclosures to report.

Dr. C.E. Catsman-Berrevoets has no disclosures to report.

Dr. B.C. Jacobs has received funding for travel from Baxter International Inc, and has received research funding from the Netherlands Organization for Health Research and Development, Erasmus MC, Prinses Beatrix Spierfonds, Stichting Spieren voor Spieren, CSL-Behring, Grifols, Annexon, Hansa Biopharma and the GBS-CIDP Foundation

International.

Acknowledgements

This study was supported by a research grant from the Dutch Prinses Beatrix Spierfonds and Spieren voor Spieren (W.OR 12-04 to, J.R., M.C. Y.d W, B.C.J.).

This study was possible with data provided by the Working Group GBS in Children in Germany, Austria and Switzerland and the Dutch Pediatric GBS Study Group. And all contributors to the retro- and prospective studies [6,13].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2023.02.007.

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