Received: 1 May 2023 | Accepted: 21 September 2023

DOI: 10.1111/ene.16090

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Predictors of respiratory failure in Guillain–Barré syndrome: a 22 year cohort study from a single Italian centre

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Abstract

Background and purpose: The study aimed to identify predictors of respiratory failure leading to mechanical ventilation (MV) and tracheostomy in Guillain–Barré syndrome (GBS).

Methods: Two hundred and thirty adult cases admitted to the Neurology Unit of Modena, Italy, between January 2000 and December 2021 were studied. A cut-off of MV starting within 8 weeks from onset of weakness was used. Univariable, multivariable logistic and Cox regression analyses were used to determine which pre-specified clinical and diagnostic characteristics were capable of predicting MV and tracheostomy, due to weaning failure. The model was internally validated within the full cohort. The Erasmus GBS Respiratory Insufficiency Score was retrospectively applied.

Results: One hundred and seventy-six cases (76.5%) were classified as classical sensorimotor GBS and 54 (23.4%) as variants. Thirty-two patients (13.9%) needed MV: 84.3% required respiratory support within 7 days. Independent predictors of respiratory failure and MV were older age, facial, bulbar, neck flexor weakness, dysautonomia, axonal electrophysiological subtype, cardiovascular comorbidities and higher disability score at entry. There was no association with abnormal spinal fluid parameters nor with positive serology for recent infections. Twenty-two patients (68.7%) were ventilated for more than 7 days; 4.7% died within 8 weeks. The patients who required MV were treated more often with plasma exchange. Independent predictors of tracheostomy due to weaning trial failure were facial, bulbar, neck flexor weakness, autonomic dysfunction, associated cardiovascular morbidities and axonal electrophysiological subtype on nerve conduction study.

Conclusions: Our study indicates distinct predictors of MV and tracheostomy in GBS patients.

KEYWORDS
Guillain–Barré syndrome, internal calibration, mechanical ventilation, respiratory failure, tracheostomy

INTRODUCTION

Guillain–Barré syndrome (GBS) is a rapidly progressive, auto-immune polyradiculoneuropathy [1–7]. During the acute phase, patients may develop respiratory failure, eventually requiring mechanical ventilation (MV) [2, 4–14]. Early prediction of respiratory insufficiency is important to correctly triage the patients for appropriate level of care and to prevent complications related to delayed intubation [15–19]. Previous reports [17–35] identified as predictors of MV facial, bulbar, neck flexor weakness, autonomic dysfunction, low muscle strength at hospital admission, rapid progression, respiratory parameters and presence of conduction block in distal nerves. Furthermore, the Erasmus GBS Respiratory Insufficiency Score (EGRIS) was introduced to predict respiratory insufficiency in the acute stages of the disease. EGRIS was validated to define its performance in an international population [10, 18, 27, 32, 33].

The purpose of our study was to define predictors of MV in a population of GBS diagnosed at the Neurology Unit, University Hospitals of Modena, Italy. The secondary aim was to evaluate the need for tracheostomy, due to weaning failure, in the subgroup of patients undergoing endotracheal intubation.

PATIENTS AND METHODS

Patient neurological assessment and data collection

All consecutive adult GBS cases admitted between January 2000 and December 2021 were reviewed. The study design was approved by the Institutional Ethical Committee (no. N43/2022). Two hundred and thirty cases were included. Starting from 2012, 19 cases (8% of the whole GBS cohort from our centre) were included in the International GBS Outcome Study (IGOS) [4, 10]. Patients fulfilled the National Institute of Neurological Disorders and Stroke diagnostic criteria for GBS and variants [10, 18]. Excluded were cases aged <16 years, with insufficient demographic data, alternative diagnosis, missing values; 38% were studied in the first decade of the study frame and 62% in the second. Patients were enrolled within 2 weeks from onset of weakness. None was ventilated prior to study entry. Data were collected at the study entry and at standard time points [10], regarding demographic characteristics, antecedent events, comorbidities, clinical severity, cerebrospinal fluid (CSF) parameters, electrophysiological subtypes, preceding infections, comorbidities and treatments. Data were analysed by a multidisciplinary team, which included neurologists, pneumonologists, radiologists and cardiologists.

The clinical variants of GBS were defined at week 4 [4, 10]. Patients who had reached nadir before entry or who were lost to follow-up within 4 weeks were excluded from analysis. Muscle strength was expressed using the Medical Research Council (MRC) scale in six extremity muscles, ranging from 60 (full strength) to 0 (complete paralysis) [2, 4]. Bulbar weakness was defined as involvement of speech or swallowing [27]; neck flexion strength was determined [30, 32]. Disability was measured with the GBS disability scale (GBS-DS) [29, 31]. Treating physicians registered treatment-related fluctuations (TRF), defined as deterioration in the MRC sum score ≥5 points and/or in GBS-DS >1 at two consecutive visits [2, 29]. Disease nadir was the lowest MRC sum score during the first 4 weeks of illness [2]. The presence of muscular, radicular, neuropathic pain was recorded.

The EGRIS scores, which range from 0 to 7, were determined. Indeed most of our patients were enrolled before the modified EGRIS was validated [10, 18, 32, 33]. Features of dysautonomia, which were ileus or gastric dysmotility, urinary retention, fever not attributable to infections, hypothermia <36°C, arterial blood pressure instability and heart rate fluctuations, were registered [35–37]. Mandatory for inclusion was the availability of at least one neurographic test, with confirmation by a second, the first at time of admission and the second obtained after 8–14 days [7]. Raw data from the first nerve conduction study (NCS) and local reference values were used to classify each study. The results were classified according to Hadden criteria as demyelinating (AIDP), motor axonal (AMAN), sensorimotor axonal neuropathy (AMSAN) [7, 12, 13, 38–41]. Laboratory tests included complete CSF analysis. Albumino-cytological dissociation (ACD) was defined as cell count <50 cells/μL with protein level >0.45 g/L [2, 4]. A protein level above the median value of 0.68 g/L was also determined.

Antecedent infectious events recorded within 4 weeks prior to onset were analysed. Patient sera were tested with diagnostic techniques for recent infections due to *Campylobacter jejuni* (CJ), *Mycoplasma pneumoniae* (MP), cytomegalovirus (CMV) and Epstein–Barr virus (EBV). CSF polymerase chain reaction for CMV, EBV, MP and *Borrelia burgdorferi* was performed and CJ was searched, when possible, in stool samples of AMAN cases. The presence of immunoglobulin (IgG/IgM) antibodies to gangliosides GM1, GM2 and GQ1b was tested using conventional enzyme-linked immunosorbent assay [2, 4, 7, 20]. From 2010, laboratory tests were implemented searching for other anti-ganglioside antibodies (GM2; GD1a, 1b; GD2, 3; GT1a, b; sulfatide) using immunoblot assays. The given treatments, plasma exchange (PE) and intravenous immunoglobulin (IVIG), either alone or combined, were noted. Mortality was registered at 8 weeks.

Cardiological assessment

Cardiological assessments at baseline included clinical evaluation, serial blood pressure measurements, electrocardiogram monitoring and transthoracic echocardiography, if necessary. Patients with resting blood pressure level above 140/90 mmHg were considered hypertensive. Parameters of cardiac dysautonomia were fluctuations on maximum systolic blood pressure >180 or >160 mmHg on antihypertensive medications, minimum diastolic blood pressure >90 mmHg, hypotension with systolic blood pressure <90 mmHg, tachycardia >120 beats per minute or tachycardia >100 beats per

minute with beta-blocker use, or bradycardia <50 beats per minute for over 2 h [35–37].

Radiological data collection

Radiological findings were evaluated by an expert radiologist. Chest X-ray was performed in all patients at entry and repeated in double projection or at the bedside. The non-contrast chest computed tomography scans were reviewed. The scans were reconstructed as axial images. In the case of suspected pulmonary embolism, intravascular iodine contrast was injected. Pneumonia was defined by findings of radiological consolidation, in association with clinical features suggestive of infections.

Primary and secondary outcome definition

The primary outcome was the need for endotracheal intubation for MV. A cut-off of MV starting within 8 weeks from onset of weakness was used, because if a lower cut-off (4 or 6 weeks) was used patients with respiratory failure due to TRF or prolonged progressive phase could potentially be missed [10, 27, 32]. With respect to the censoring method for patients with MV, the time until MV start was used, whilst patients not requiring MV were censored at 2 months, or at the date of lost to follow-up or death [10, 27]. As per institutional protocol, endotracheal intubation and MV were initiated when the physiological and/or clinical parameters vital capacity <20 mL/kg or negative inspiratory force <−20 cmH_2O were identified and/or persistence of the following clinical signs: unsustainable work of breathing, refractory hypoxaemia, hypercapnia or acidaemia. Bulbar muscle dysfunction with inadequate airway protection, ineffective cough, retention of bronchial secretions and altered consciousness were factors which generally contraindicated a non-invasive ventilation (NIV) trial and required elective endotracheal intubation [15, 35–37]. The secondary outcome was the need for tracheostomy due to weaning failure. In patients who underwent endotracheal intubation a weaning trial was considered when physiological parameters showed clear evidence of improved respiratory muscle strength: maximal inspiratory pressure (MIP) >−20 cmH_2O, maximal expiratory pressure (MEP) >40 cmH_2O, forced vital capacity (FVC) >10 mL/kg. Extubation was attempted when patients showed no clinical signs of respiratory fatigue during a spontaneous breathing trial with pressure support ventilation (PSV), in conjunction with other physiological parameter improvement: FVC of at least 15 mL/kg, MIP ≥−20 cmH_2O, normal exchanges on arterial blood gas analysis. In patients who failed several weaning trials and/or showed no improvement of physiological respiratory muscle parameters after 15 days of MV, tracheostomy was performed with the percutaneous dilatational technique [15]. In patients who underwent intubation, the duration of MV in days was dichotomized for statistical purposes as less than or more than 7, to distinguish patients successfully extubated from those who required prolonged intubation.

Statistical analysis

Statistical analysis was performed using Stata 14.2 (Stata Corporation). Patient characteristics were analysed using descriptive statistics. For continuous variables, data were presented as median with minimum–maximum range or as mean with standard deviation (SD). For comparison between groups, the Mann–Whitney test was used for continuous variables and the Mantel–Haenszel chi-squared exact test for ordered categorical variables. The odds ratio (OR) for association between the clinical variables and MV was calculated. The Kaplan–Meier statistic estimated the progression in respect of the primary outcome; the curves were compared with the log-rank test. Hazard ratio and 95% confidence interval were used to estimate the 'hazard' of each end-point, based on clinical attributes at baseline. Two-sided p values <0.05 were considered significant. The margin statistic was used to compute marginal prediction, based on previously fitted linear model regression.

Our model performance was assessed by determining the discrimination (i.e., the ability of the model to distinguish between patients who needed and did not need MV), which is quantified by the area (AUC) under the receiver operating characteristic curve [10, 32]. The receiver operating characteristic curve (ROC) provides the sensitivity (i.e., true positive rate) of a model at different probability thresholds plotted against 1 − specificity (i.e., false positive rate). The k-fold cross-validation for the two main outcomes was calculated. Internal validation of the model was done by bootstrapping [10]. Predictor missing values were imputed and estimated if below 15%, using the multiple imputation chained equation method [42].

RESULTS

Characteristics of the cohort

The study algorithm is shown in Figure 1. Tables 1 and 2 show the demographic and clinical characteristics in relation to the need for MV. Among 230 patients, 62.1% were males and 37.9% were females. The median age at onset was 59.6 years (range 16–92, interquartile range [IQR] 30). The mean MRC sum score at entry was 41.2 in MV subjects and 53.9 in those non-ventilated. In all, 176 cases (76.5%) were classified as classical sensorimotor GBS; 54 (23.4%) were variants. Miller–Fisher syndrome or Miller–Fisher syndrome overlapping GBS was diagnosed in 22; facial diplegia and paraesthesias in 12, paraparetic in 14, cervico-brachial in two, bilateral hypoglossal, small hand weakness, Bickerstaff encephalopathy and sensory GBS in one each. Sixty-seven patients (29.1%) had three or more chronic diseases, which were cardiac (46.3%), autoimmune (13.4%), solid

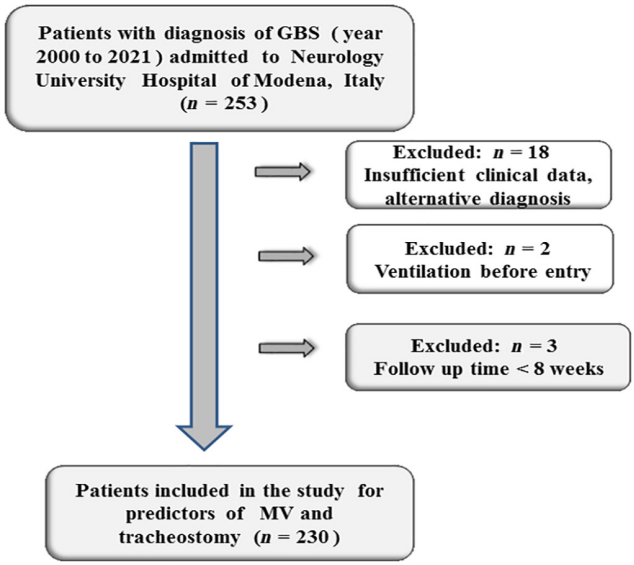

FIGURE 1 Algorithm of the study design. GBS, Guillain–Barré syndrome; MV, mechanical ventilation.

or haematological tumours (11.9%), renal disorders. At the study entry, GBS-DS was 1 in 57 (24.7%), 2 in 111 (48.2%), 3 in 47 (20.4%) and 4 in 15; a high GBS-DS was significantly associated with MV ($p < 0.001$) (Table 1). The EGRIS scores by Mann–Whitney test were significantly different in ventilated patients from scores in the non-ventilated patients ($p < 0.001$).

On NCS, there were no patients with normal or equivocal results after serially repeated NCS. AIDP was diagnosed in 184 patients (80%), AMAN/AMSAN in the remaining 20%. Seventeen AIDP (9.2%) patients needed MV. The AIDP subtype was associated with lower risk of endotracheal intubation (OR 0.21, $p < 0.001$) (Table 2).

In 142 patients (61.7%), an infectious event occurring within the previous 4 weeks was identified: 55.6% had upper respiratory tract symptoms, 40% a gastroenteritis and the remaining patients genito-urinary infections. Amongst the AIDP cases, gastroenteritis was confirmed in 23% and 34% had upper respiratory tract infection.

Cerebrospinal fluid was obtained in 200 subjects (87.8%) at a median time of 7 days from neurological onset (Table 2). Protein content ranged from 19 to 479 mg/μL (median 68, IQR 66), with the level above the median value in 49.5%. Albumino cytologic dissociation (ACD) was found in 150 cases (98.6%) and in 79.3% of those who needed MV. CSF cell number ranged from 0 to 100/mm^3. Anti-ganglioside antibodies, either GM1 IgG or IgM, were detected in 34 cases (14.7%); 19 had AIDP. Other antibodies to gangliosides were detected in 54 patients (23.7%) and 7 needed MV.

Amongst 191 chest computed tomography scans, pneumonia was confirmed in 20 cases (10.4%) and 60% needed MV. Treatment with PE (5–6 exchanges over 2 weeks) and IVIG (0.4 g/kg/day for 3–5 days) was given. IVIG was administered to 216 (93.9%) and PE to 30 patients (13%); in 212 (92.17%), IVIG represented the first-line treatment. Amongst the ventilated subjects 18 underwent PE (56.2%), whereas only 6% received PE among the non-ventilated. Intravenous methylprednisolone was given to 17 subjects (7.3%); 14 patients (5%) did not receive pharmacological treatments. Fifty-six per cent of subjects received gabapentinoids because of limb pain; 40% of ventilated patients experienced severe muscle aching at nadir. Table 3 depicts the outcome at 8 weeks of patients with or without need for MV. Deceased and tracheostomized subjects and cases with TRF or with prolonged intensive care unit (ICU) stay showed significantly higher risk of MV, as well as patients with GBS-DS equal to 5.

Prediction of MV

Thirty-two patients (13.9%) required MV, 84.3% within 7 days after admission. The median time from symptom onset to admission was 6 days (IQR 8). Time from symptom onset, either above or below the median had no significant effect on MV need. Factors strongly associated with MV in univariable analysis were older age, facial, bulbar, neck flexor weakness, autonomic dysfunction, higher GBS-DS at entry, associated cardiovascular disorders, and axonal features on NCS (Tables 1 and 2). There was no association between MV and CSF parameters, nor with positive serology for recent infections (Table 2). Amongst the ventilated patients, a CJ enteritis was confirmed in five (15.6%); all had axonal features on NCS. On multivariable logistic regression model, strong predictors of MV were older age (OR 4.8, $p = 0.003$), bulbar (OR 6.9, $p < 0.001$), neck flexor weakness (OR 12.7, $p < 0.001$), dysautonomia (OR 6.6, $p < 0.001$), coincident cardiovascular disorders (OR 4.5, $p < 0.001$) and axonal subtype on NCS (OR 6.6, $p = 0.007$). Out of 32 ventilated subjects, 68.7% had ICU stay longer than 7 days; predictors of longer intubation were older age, neck flexor and bulbar weakness and dysautonomia. Figure 2a,b confirms the excellent discriminative ability of the model for the independent variables included as predictors.

The AUC (0.86; SD ±0.13) in Figure S1b further attests the accuracy of the full model, which included as predictors age over median value and dysautonomia. The model performance remained excellent (AUC 0.87, ±SD 0.12) in a separate analysis, which included among the predictors the classical sensorimotor GBS, the predominant variant in our cohort.

Figure 3a shows the prediction of MV in relation to EGRIS scores at entry. Figure S1a shows the EGRIS score distribution in ventilated and non-ventilated subjects.

Table 4 shows the results obtained in the Cox regression analyses, Figure 3b shows the Kaplan–Meier curves for patients treated with PE, and in Figure 3c,d the estimates for patients exhibiting neck and bulbar weakness.

Prediction of extubation failure, that is, tracheostomy

Table S1 shows the results amongst the tracheostomized subjects: seven males and five females. Nine subjects (75%) had

TABLE 1 Clinical features in association with mechanical ventilation (MV) in 230 GBS patients.

	MV ($n=32$)	No MV ($n=198$)	OR	p value
Demographics				
Age (years above median age)	25/32 (78.1%)	94/198 (47.4%)	**3.95**	**0.0013**
Male sex (ref male)	18/32 (56.2%)	125/198 (63%)	0.75	0.45
Antecedent event				
Respiratory tract symptoms	11/32 (34.3%)	68/198 (34.3%)	1.00	0.99
Gastro-intestinal symptoms	7/32 (21.8%)	50/198 (25.2%)	0.82	0.68
Genito-urinary and others	2/32 (6.25%)	13/198 (6.5%)	0.95	0.94
Neurological features at admission				
Cranial nerve involvement				
Oculomotor	7/32 (21.8%)	20/198 (10%)	2.3	0. 07
Facial	21/32 (65.6%)	54/198 (27.2%)	**5.09**	**<0.001**
Bulbar	16/32 (50%)	17/198 (8.5%)	**10.6**	**<0.001**
Neck weakness	11/32 (34.3%)	6/198 (3.0%)	**16.7**	**<0.001**
Muscle weakness				
MRC sum score at entry[a] (0–60) (mean, ±SD)	41.2 (8–60, SD ±14.0)	53.9 (32–60, SD ± 5.5)		**<0.001**
Sensory deficits	24/32 (75%)	157/198 (79%)	1.0	0.92
Pain	13/32 (40.6%)	100/198 (50%)	0.67	0.30
Total areflexia	32/32 (100%)	176/198 (88.8%)	1.02	0.048
Ataxia	7/32 (21.8%)	39/198 (19.6%)	1,14	0.77
Autonomic dysfunction	23/32 (71.8%)	44/198 (22.2%)	**8.3**	**<0.001**
GBS-DS at entry				
1	2/32 (6.25%)	55/198 (27.8%)	**0.17**	**<0.001**
2	10/32 (31.2%)	101/198 (51.0%)	**0.43**	**0.03**
3	10/32 (31.2%)	37/198 (18.6%)	1.97	0.10
4	10/32 (31.2%)	5/198 (2.5%)	**17**	**<0.001**
Clinical GBS phenotypes				
Classical sensorimotor ($n=176$)	28/32 (87.5%)	148/198 (74.7%)	1.32	0.62
GBS variants ($n=54$)	4/32 (12.5%)	50/198 (25%)	0.42	0.11
Comorbidities more than 3 (respiratory, neoplastic, metabolic, autoimmune, renal disorders)	17/32 (53.1%)	50/198 (25%)	**10**	**<0.001**
Associated cardiovascular disorders[b]	20/30 (62.5%)	55/189 (29.1%)	**4.9**	**<0.001**
Treatment of GBS				
IVIG	32/32 (100%)	184/198 (92.9%)	0.62	0.12
PE	18/32 (56.2%)	12/198 (6.0%)	**19.9**	**<0.001**

Note: Overview of unadjusted odds ratios for the association of clinical factors with mechanical ventilation. Numerical variables are expressed as mean (± standard deviation). Comparative statistics are made between ventilated and not ventilated patients. Significant values are in bold.

Abbreviations: GBS, Guillain–Barré syndrome; GBS-DS, GBS disability scale; IVIG, intravenous immunoglobulins; MRC, Medical Research Council; MV, mechanical ventilation; OR, odds ratio; PE, plasma exchange.

[a]Mann–Whitney test.

[b]This parameter refers to the number of patients with cardiovascular disorders.

AMAN and three AIDP. Figure 2c shows the discriminative ability of predictors and the best cut-off for sensitivity and specificity of neck weakness for tracheostomy need (Figure 2d). Figure S1c shows the adjusted prediction of MV based on GBS-DS at entry and Figure S1d the prediction of tracheostomy in relation to GBS-DS at entry.

DISCUSSION

Our study retrospectively analysed over 22 years the clinical parameters that could serve as prognostic markers of respiratory failure, endotracheal intubation and tracheostomy in 230 GBS patients followed at our Neurology Unit. Early assessment of

TABLE 2 Diagnostic features in association with mechanical ventilation (MV) in 230 GBS patients.

	MV ($n=32$)	No MV ($n=198$)	OR	p value
Cerebrospinal fluid examination				
Protein level (g/L) above median value ($n=99$)	14/29 (48.2%)	85/171 (49.7%)	0.94	0.88
Days before CSF (median 7, IQR 8)	13/29 (44.8%)	76/171 (44.4%)	1.02	0.96
Albumino-cytological dissociation ($n=150$)	23/29 (79.3%)	127/148 (85.8%)	0.63	0.67
Nerve conduction study				
Main electrophysiological subtype				
AMAN/AMSAN ($n=46$)	15/32 (46.8%)	31/198 (15.6%)	**4.75**	**<0.001**
AIDP ($n=184$)	17/32 (53.1%)	167/198 (84.3%)	**0.21**	**<0.001**
Antibody profiles				
Anti-ganglioside (GM1) positive abs	4/32 (12.5%)	30/198 (15.1%)	0.75	0.61
Other anti-ganglioside (GD1b, GD3, GT1a, GT1b, GQ1b) positive abs	7/32 (21.8%)	47/198 (23.7%)	0.89	0.82

Note: Overview of unadjusted odds ratios for association of diagnostic features with mechanical ventilation. Continuous data are expressed as median. Comparative statistics were made between ventilated and non-ventilated subjects. Significant values are expressed in bold.

Abbreviations: abs, antibody; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; CSF, cerebrospinal fluid; IQR, interquartile range; MV, mechanical ventilation; OR, odds ratio.

TABLE 3 Outcome at 8 weeks.

	All 230 patients *N* (%)	32 MV patients *N* (%)	198 non-MV patients *N* (%)	OR	p value
GBS-DS score					
0–1	130 (56.6%)	7 (21.9%)	121 (61.1%)	**0.17**	**<0.001**
2–3	35 (15.2%)	8 (25.0%)	29 (14.7%)	1.94	0.13
4	51 (22.1%)	5 (15.6%)	46 (23.2%)	0.61	0.33
5	3 (1.3%)	3 (9.4%)	0 (0.0%)	**20.0**	**0.04**
Patients deceased	11 (4.8%)	9 (28.1%)	2 (1.0%)	**38.3**	**<0.001**
Treatment-related fluctuations	28 (12.1%)	9 (28.1%)	19 (9.6%)	**3.6**	**0.02**
Mechanical ventilation	32 (14.0%)				
Prolonged ICU stay (≥7 days)	22 (9.6%)	22 (68.8%)	0 (0.0%)	**433**	**<0.001**
Tracheostomy	12 (5.2%)	12 (37.5%)	0 (0.0%)	**236**	**<0.001**

Note: Overview of the outcome at 8 weeks after study entry, with unadjusted odds ratios. Comparative statistic was made between ventilated and non-ventilated subjects. The values in parentheses refer to the percentages of patients. Significant p values are expressed in bold.

Abbreviations: GBS-DS, Guillain–Barré syndrome disability scale; ICU, intensive care unit; MV, mechanical ventilation; *N*, number; OR, odds ratio.

respiratory failure is crucial in GBS to prevent mortality and to decide the appropriate patient care. In previous studies, several features have been reported as predictors for the risk of MV, including advanced age, short interval from symptom onset to admission, rapid disease progression, lower cranial nerve weakness, low MRC sum score at nadir, high GBS-DS scores at entry, dysautonomia, conduction block and/or axonal features on NCS [4, 5, 10, 15, 17–19, 22–27, 32, 33, 43, 44].

Epidemiology of GBS patients requiring MV

The incidence of MV in our cohort was low (13.4%), in agreement with the Granieri et al. study [44] but higher than described by Giannaneschi et al. (8.3%) [7]. Doets et al. [10] reported that 10% of IGOS patients required MV within the first week and 12% during overall follow-up. In Bangladeshi cases, the proportion requiring ventilation was 16% within the first week and 18% overall, whereas 45% of the

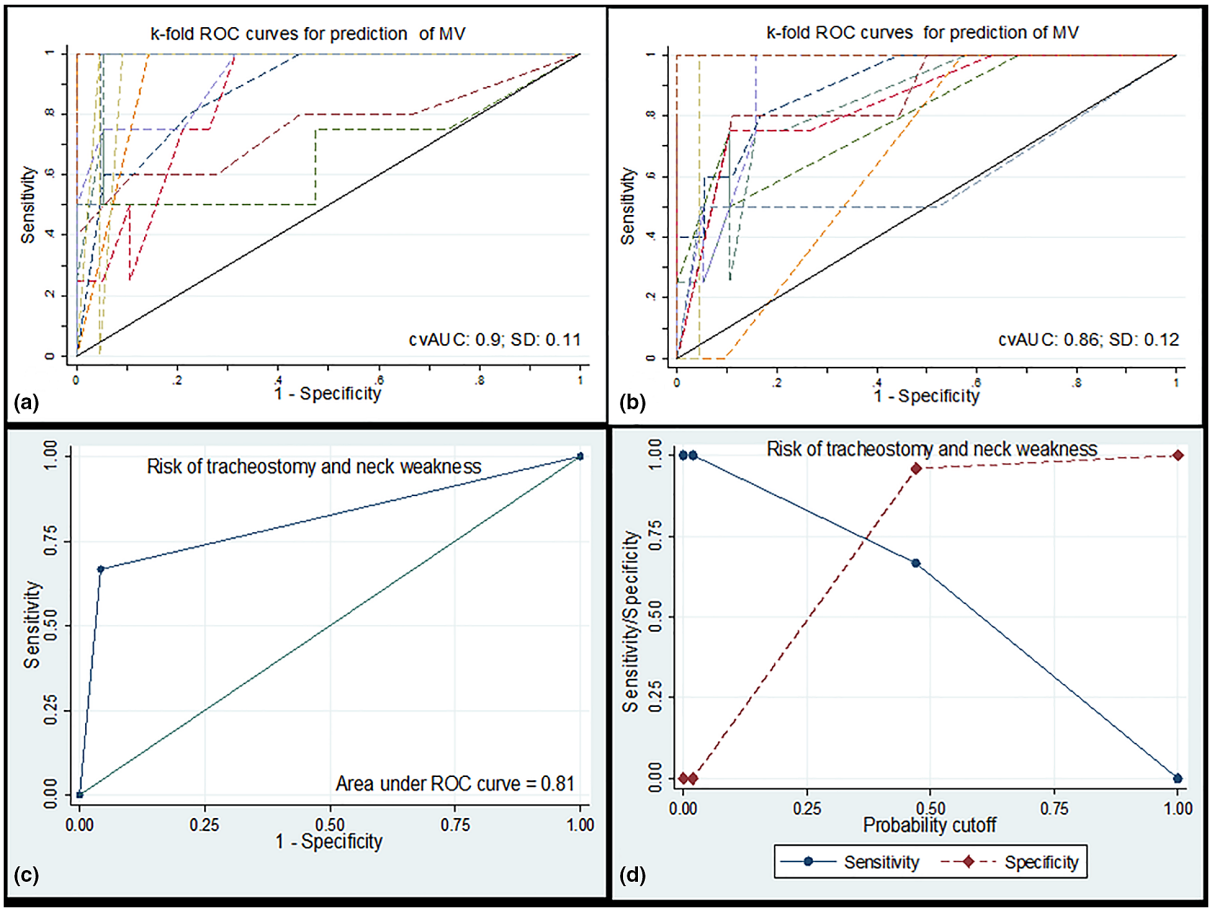

FIGURE 2 (a) *k*-fold cross-validation, internal validation. The AUC (0.9; SD ±0.11) measures the accuracy of the model, which included as predictors of mechanical ventilation the age over median value, the bulbar, and neck flexor weakness, the dysautonomia. (b) *k*-fold cross-validation, internal validation. The AUC (0.85; SD ±0.12) measures the accuracy of the model, which included as predictors of mechanical ventilation the age over median value, the presence of axonal features on NCS, the plasma exchange as therapy, the bulbar weakness. (c) The ROC curves show the discrimination of neck weakness as predictor for tracheostomy need. (d) The ROC curves show sensitivity and specificity for the best cut-off of neck weakness as predictor for tracheostomy need. Abbreviations: cvAUC, area under the curve; MV, mechanical ventilation; NCS, nerve conduction study; ROC, receiver operating characteristic; SD, standard deviation.

ICU patients were ventilated within the first week [17, 33]. Wang et al. [23] concluded that nearly 25% of cases needed MV. A recent meta-analysis [19] showed that the MV prevalence varied from 7% to 65%. Considering the heterogeneity of these data, a key point is the primary outcome definition; indeed, the initiation of MV might be influenced by physician decisions and diverse guidelines in the management of respiratory failure over time and countries [10, 15, 17–19, 24, 33]. Ginanneschi et al. [7] reported that 5 patients amongst their 7 admitted to ICU (8.3%) were treated with NIV. In our study, all patients requiring ventilation underwent endotracheal intubation; thus our population was probably more severely affected. NIV is an unsafe therapeutic option in GBS for several reasons: first, a persisting decline of respiratory muscle weakness, followed by prolonged nadir, makes NIV temporization meaningless; secondly, patients with dysautonomia have high risks of emergency intubation, due to labile blood pressure and arrhythmias; thirdly, patients may need ventilation for long periods and respiratory failure worsens dysautonomia [15, 23, 25, 35–37].

Cranial nerve involvement and neck flexor weakness as predictors for MV

Bulbar dysfunction predicted respiratory failure in several studies [4–10, 15–18, 20, 23–27, 33, 36]. Our study confirms bulbar and neck weakness as significant predictors of MV. The latter finding provides insights into the pathology of GBS, where inflammatory endoneurial oedema, from early stages, predominates in proximal nerves, where spinal roots unite to form spinal nerves, suggesting that root involvement is highly threatening for breathing [45]. Patients with bulbar palsy are at high risk of aspiration and airway occlusion [15, 23, 37, 38]; therefore, in the presence of relevant dysphagia, early hospitalization is necessary to protect airways from aspiration pneumonia. In this subset of patients, endotracheal intubation is recommended to protect the airways [15]; however, in a recent trial, early MV was unable to prevent pneumonia in patients with increased risk of respiratory failure [46].

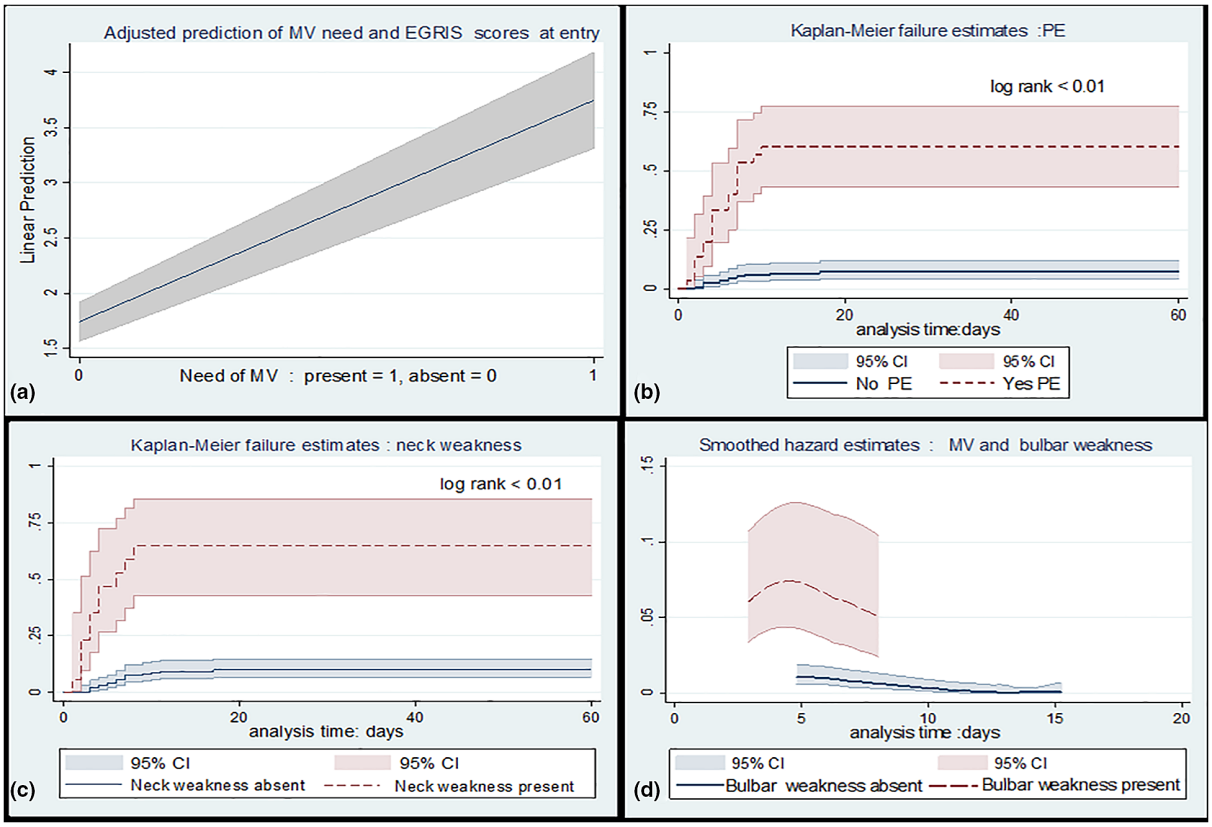

FIGURE 3 (a) Adjusted prediction: the graph depicts the adjusted prediction of mechanical ventilation in relation to EGRIS scores at entry. The band represents the 95% confidence interval. (b) Survival analysis: Kaplan–Meier failure curves representing the probability of mechanical ventilation in patients treated or not with plasma exchange. $p < 0.01$ at log rank test. The bands for both groups represent 95% confidence intervals. (c) Survival analysis: Kaplan–Meier failure curves expressing the probability of mechanical ventilation in patients with neck weakness. $p < 0.01$ at log rank test. The bands for both groups represent 95% confidence intervals. (d) Smoothed hazard estimates: the graph represents the instantaneous event rate of mechanical ventilation for the survivors in the absence or in the presence of bulbar weakness. The bands represent the 95% confidence intervals. Abbreviations: CI, confidence interval; EGRIS, Erasmus GBS Respiratory Insufficiency Score; GBS, Guillain–Barré syndrome; MV, mechanical ventilation; PE, plasma exchange.

Dysautonomia as predictor of MV

Involvement of the autonomic nervous system occurs in about two-thirds of GBS patients and increases mortality, due to several factors including fatal arrhythmias and stress-induced cardiomyopathy [15, 17, 35–37]; interestingly, dysautonomia may resolve in the recovery phase, preceding the motor improvement [35, 36]. The mechanism of dysautonomia is thought to be due to an imbalance in sympatho-vagal transmission, shifted toward a sympathetic predominance, mediated by afferent fibres from arterial baroreceptors, efferent parasympathetic fibres innervating the heart and in preganglionic sympathetic fibres controlling sudomotor and vasomotor functions [36–38]. Previous studies interestingly suggested that dysautonomia might cause respiratory deterioration also through a different mechanism: the inflammatory demyelination of vagal afferent fibres results in an excessive sympathetic outflow, leading to hyperdynamic pulmonary circulation, which in turn causes worsening of hypoxaemia through an increase in intrapulmonary shunt [47]. Increased intrapulmonary shunt is common in ICU patients, where dysautonomia and intrapulmonary shunts show a parallel time course [47].

Electrophysiological subtype and respiratory failure

Axonal features significantly predicted respiratory failure: bulbar dysfunction was detected in 10% of our AIDP cases and in 30% of AMAN cases. Axonal subtype was associated with poor recovery in the first IGOS studies [4, 20], whereas other authors [21] concluded that risk of respiratory failure was highest in patients carrying the demyelinating subtype. In AMAN, the immune-mediated injury to the axolemma at Ranvier nodes damages the sodium voltage channel clusters, leading, if the attack progresses, to protease activation and calcium entry into axons, followed by axonal degeneration, which accounts for the poor outcome [48].

Tracheostomy in GBS

Our study delineates the predictors of tracheostomy in subjects treated with MV. Walgaard et al. [49] addressed this issue and concluded that early tracheostomy does not seem to shorten the duration of MV. However, Shang et al. [15] considered tracheostomy

TABLE 4 Crude and adjusted hazard ratios for risk of mechanical ventilation (MV) in 230 GBS patients.

	Crude HR (95% CI)	*p* value	Adjusted HR* (95% CI)	Adjusted *p* value*
Demographics				
Age (years above median age)	3.50 (1.51–8.1)	**0.03**	2.77 (1.1–6.9)	**0.020**
Gender (ref male)	1.31 (0.63–2.64)	0.43	1.43 (0.69–2.98)	0.33
Antecedent event				
Respiratory tract symptoms	1.05 (0.51–2.19)	0.87	1.3 (0.61–3.0)	0.43
Gastro-intestinal symptoms	0.8 (0.36–1.9)	0.70	0.69 (0.27–1.71)	0.42
Neurological features at admission				
Cranial nerve involvement				
Oculomotor	2.27 (0.98–5.2)	0.054	1.75 (0.72–4.26)	0.21
Bulbar	7.71 (3.87–15.3)	**<0.001**	4.59 (2.19–9.59)	**<0.001**
Facial	4.3 (2.09–9.00)	**<0.001**	3.04 (1.45–6.38)	**<0.001**
Neck weakness	10.5 (5.5–22.03)	**<0.001**	8.04 (3.71–17.4)	**<0.001**
Autonomic dysfunction	7.30 (3.3–15.7)	**<0.001**	5.10 (2.29–11.3)	**<0.001**
Comorbidities overall > 3 (respiratory, neoplastic, metabolic, autoimmune, renal disorders)	2.83 (1.54–5.7)	**0.003**	1.3 (0.62–2.84)	0.46
Associated cardiovascular disorders	4.27 (1.9–9.12)	**<0.001**	3.1 (1.42–6.74)	**0.004**
Electrophysiological features (ref AIDP)				
AMAN/AMSAN	4.19 (2.0–8.4)	**<0.001**	4.4 (22.1–9)	**<0.001**
Cerebrospinal fluid features				
Albumino-cytological dissociation	1.29 (0.52–3.1)	0.57	1.26 (0.47–3.32)	0.63
Therapy				
PE	11.9 (5.92–24.1)	**<0.001**	7.0 (3.40–14.4)	**<0.001**

Note: Overview of the results obtained with the Cox regression analyses. The 95% confidence interval is reported in parentheses. Significant values are in bold.

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAM, acute motor sensory axonal neuropathy; CI, confidence interval; GBS, Guillain–Barré syndrome; HR, hazard ratio; MV, mechanical ventilation; PE, plasma exchange.

*Adjusted *p* value.

useful to provide earlier oral nutrition, easier communication and out-of-bed mobilization of patients.

Treatment outcomes

Guillain–Barré syndrome treatment is based on PE and IVIG [2–6, 12, 15, 22, 31, 48]. The use of IVIG has increased in recent years, due to its easier management compared to PE. IVIG was the first-line therapy in the majority of our patients; however, our results suggested that PE was preferred by treating physicians in patients with faster neurological deterioration and loss of autonomy.

CONCLUSION AND LIMITATIONS

Our study identified the predictors of MV in an Italian cohort of GBS patients. Our research, although based on longitudinal assessments over 22 years, has several limitations: first, it is a single-centre study, and therefore the enrolled population can be subject to hospital and country-specific case mix. Secondly, our model was only internally validated; therefore the study of the patients followed in our hospitals could be biased, compared to the general population, including more severely affected cases [4, 10, 32]. Thirdly, patients aged below 16 years and with follow-up shorter than 8 weeks were excluded; fourthly, the respiratory functional assessment was unavailable.

The clinical applicability of the original EGRIS could be confirmed, as a simple and accurate tool for prediction of MV [10, 18, 32, 33]. Future research is needed to establish the potential value of other clinical, biological and electrophysiological predictors.

AUTHOR CONTRIBUTIONS

Giuliana Galassi: Conceptualization; methodology; data curation; investigation; validation; formal analysis; supervision; visualization; writing—original draft; writing—review and editing. Marco Mazzoli: Conceptualization; methodology; data curation; investigation; validation; supervision; visualization; writing—review and editing; writing—original draft. Alessandra Ariatti: Conceptualization; methodology; data curation; investigation; validation;

writing—review and editing; supervision; visualization. Roberta Bedin: Conceptualization; methodology; investigation; validation; data curation; supervision; writing—original draft. Donato Marzullo: Investigation; validation; supervision; writing—original draft. Elisabetta Bastia: Conceptualization; methodology; data curation; investigation; validation; formal analysis; visualization; writing—original draft. Virginia Agnoletto: Methodology; investigation; validation; writing—review and editing; conceptualization. Manuela Gozzi: Conceptualization; methodology; data curation; investigation; validation; formal analysis; visualization; supervision; writing—original draft. Franco Valzania: Conceptualization; methodology; visualization; writing—review and editing; writing—original draft. Stefano Meletti: Methodology; validation; visualization; writing—review and editing; writing—original draft; conceptualization. Alessandro Marchioni: Conceptualization; methodology; investigation; validation; visualization; writing—original draft; writing—review and editing; data curation; supervision.

ACKNOWLEDGEMENTS

The authors thank Dr Riccardo Cuoghi Costantini, University of Modena and Reggio Emilia, for critical advice on the statistical methods and results.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. *Ann Neurol*. 1990;27(Suppl):S21-S24.
2. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain–Barré syndrome and validation of Brighton criteria. *Brain*. 2014;137:33-43.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain–Barré syndrome. *Lancet*. 2016;388:717-727.
4. Doets AY, Verboon C, van den Berg B, et al. Regional variation of Guillain–Barré syndrome. *Brain*. 2018;141:2866-2877.
5. Doets AY, Jacobs BC, van Doorn PA. Advances in management of Guillain–Barré syndrome. *Curr Opin Neurol*. 2018;31:541-550.
6. Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. *Nat Rev Neurol*. 2019;15:671-683.
7. Ginanneschi F, Giannini F, Sicurelli F, et al. Clinical features and outcome of the Guillain–Barré syndrome: a single-center 11-year experience. *Front Neurol*. 2022;29(13):856091.
8. Zhai Q, Guo C, Xue F, Qiang J, Li C, Guo L. Guillain–Barré syndrome in northern China: a retrospective analysis of 294 patients from 2015 to 2020. *J Clin Med*. 2022;11:6323.
9. Verboon C, Harbo T, Cornblath DR, et al. Intravenous immunoglobulin treatment for mild Guillain–Barré syndrome: an international observational study. *J Neurol Neurosurg Psychiatry*. 2021;92:1080-1088.
10. Doets AY, Lingsma HF, Walgaard C, et al. Predicting outcome in Guillain–Barré syndrome: international validation of the modified Erasmus GBS outcome score. *Neurology*. 2022;98:e518-e532.
11. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. *Lancet*. 1978;2:750-753.
12. Hadden RD, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain–Barré syndrome. *Neurology*. 2001;56:758-765.
13. Hadden RD, Cornblath DR, Hughes RA, et al. Electrophysiological classification of Guillain–Barré syndrome: clinical associations and outcome. PlasmaExchange/Sandoglobulin Guillain–Barré Syndrome Trial Group. *Ann Neurol*. 1998;44:780-788.
14. Helfferich J, Roodbol J, de Wit MC, et al. Acute flaccid myelitis and Guillain–Barré syndrome in children: a comparative study with evaluation of diagnostic criteria. *Eur J Neurol*. 2022;29:593-604.
15. Shang P, Feng J, Wu W, Zhang HL. Intensive care and treatment of severe Guillain–Barré syndrome. *Front Pharmacol*. 2021;12:608130.
16. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain–Barré syndrome. *Neurology*. 2011;76:968-975.
17. 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;6:324-332.
18. Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain–Barré syndrome. *Ann Neurol*. 2010;67:781-787.
19. 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;208:181-188.
20. Benedetti L, Briani C, Beronio A, et al. Increased incidence of axonal Guillain–Barré syndrome in La Spezia area of Italy: a 13-year follow-up study. *J Peripher Nerv Syst*. 2019;24:80-86.
21. Durand MC, Porcher R, Orlikowski D, et al. Clinical and electrophysiological predictors of respiratory failure in Guillain–Barré syndrome: a prospective study. *Lancet Neurol*. 2006;5:1021-10288.
22. Hosseininezhad M, Khatami SS, Saadat S, et al. Ten years evaluation of epidemiology- and mortality-related factors in adults and children with Guillain–Barré syndrome in the north of Iran. *Neurol Sci*. 2022;43:1929-1938.
23. Wang Y, Zhang HL, Wu X, Zhu J. Complications of Guillain–Barré syndrome. *Expert Rev Clin Immunol*. 2016;12:439-448.
24. Papri N, Islam Z, Leonhard SE, Mohammad QD, Endtz HP, Jacobs BC. Guillain–Barré syndrome in low-income and middle-income countries: challenges and prospects. *Nat Rev Neurol*. 2021;17:285-296.
25. Cheng Y, Liu K, Li C, Zhang W, Wu X, Fang S. Risk factors for mechanical ventilation in patients with Guillain–Barré syndrome. *Neurocrit Care*. 2022;37:121-128.
26. Kumar M, Kalita J, Kant Misra U, Dhar N. Prediction models for mechanical ventilation and outcome in Guillain–Barré syndrome. *J Clin Neurosci*. 2021;92:131-135.
27. Doets AY, Walgaard C, Lingsma HF, et al. International validation of the Erasmus Guillain–Barré Syndrome Respiratory Insufficiency Score. *Ann Neurol*. 2022;91:521-531.
28. Alanazy MH, Bakry SS, Alqahtani A, et al. Clinical features and outcome of Guillain–Barré syndrome in Saudi Arabia: a multicenter, retrospective study. *BMC Neurol*. 2021;21:275.
29. Ruts L, Drenthen J, Jacobs BC, van Doorn PA, Dutch GBS Study Group. Distinguishing acute-onset CIDP from fluctuating Guillain–Barré syndrome: a prospective study. *Neurology*. 2010;74:1680-1686.
30. Arnold LM, Hehir MK, Tandan R, Kolb N, Waheed W. Neck flexion strength as a predictor of need for intubation in Guillain–Barré syndrome. *J Clin Neuromuscul Dis*. 2022;23:119-123.

31. Hughes RA, Raphaël JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain–Barré syndrome. *Cochrane Database Syst Rev*. 2006;(1):CD002063.
32. Luijten LWG, Doets AY, Arends S, et al. Modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain–Barré syndrome. *J Neurol Neurosurg Psychiatry*. 2023;94:300-308.
33. Papri N, Doets AY, Mohammad QD, et al. Validation and adjustment of modified Erasmus GBS outcome score in Bangladesh. *Ann Clin Transl Neurol*. 2022;9:1264-1275.
34. Yamagishi Y, Suzuki H, Sonoo M, et al. Markers for Guillain–Barré syndrome with poor prognosis: a multi-center study. *J Peripher Nerv Syst*. 2017;22:433-439.
35. Chakraborty T, Kramer CL, Wijdicks EFM, Rabinstein AA. Dysautonomia in Guillain–Barré syndrome: prevalence, clinical spectrum, and outcomes. *Neurocrit Care*. 2020;32:113-120.
36. Rabinstein AA. Acute neuromuscular respiratory failure. *Continuum (Minneap Minn)*. 2015;21:1324-1345.
37. Bazán-Rodríguez L, Ruiz-Avalos JA, de Saráchaga AJ, Martinez-Jimenez E, López-Hernández JC, Vargas-Cañas S. Dysautonomia and related outcomes in Guillain–Barré syndrome. *Auton Neurosci*. 2023;245:103070.
38. 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;20(99):e1299-e1313.
39. Arends S, Drenthen J, van den Bergh P, et al. Electrodiagnosis of Guillain–Barré syndrome in the International GBS Outcome Study: differences in methods and reference values. *Clin Neurophysiol*. 2022;138:231-240.
40. Chan YC, Punzalan-Sotelo AM, Kannan TA. Electrodiagnosis of reversible conduction failure in Guillain–Barré syndrome. *Muscle Nerve*. 2017;56:919-924.
41. López-Hernández JC, Galnares-Olalde JA, Jorge de Saráchaga A, et al. Very low peroneal nerve compound muscle action potential amplitude predicts poor outcome in patients with Guillain–Barré syndrome: a prospective cohort. *Neurol Sci*. 2022;43:3923-3928.
42. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. *Am J Epidemiol*. 2010;171:624-632.
43. Verboon C, Doets AY, Galassi G, et al. Current treatment practice of Guillain–Barré syndrome. *Neurology*. 2019;93:e59-e76.
44. Granieri E, Andreasi NG, de Martin P, et al. Incidence study of Guillain–Barré syndrome in the province of Ferrara, northern Italy, between 2003 and 2017. A 40-year follow-up. *Neurol Sci*. 2019;0:603-609.
45. Berciano J, Sedano MJ, Pelayo-Negro AL, et al. Proximal nerve lesions in early Guillain–Barré syndrome: implications for pathogenesis and disease classification. *J Neurol*. 2017;264:221-236.
46. Melone MA, Heming N, Meng P, et al. Early mechanical ventilation in patients with Guillain–Barré syndrome at high risk of respiratory failure:a randomized trial. *Ann Intensive Care*. 2020;10:128.
47. Sykora M, Diedler J, Hacke W, Veltkamp R. Intrapulmonary right–left shunts in Guillain–Barré syndrome with severe dysautonomia. *Neurocrit Care*. 2008;9:374-377.
48. Querol L, Lleixà C. Novel immunological and therapeutic insights in Guillain–Barré syndrome and CIDP. *Neurotherapeutics*. 2021;18:2222-2235.
49. Walgaard C, Lingsma HF, van Doorn PA, van der Jagt M, Steyerberg EW, Jacobs BC. Tracheostomy or not: prediction of prolonged mechanical ventilation in Guillain–Barré syndrome. *Neurocrit Care*. 2017;26(1):6-13.

SUPPORTING INFORMATION

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

How to cite this article: Galassi G, Mazzoli M, Ariatti A, et al. Predictors of respiratory failure in Guillain–Barré syndrome: a 22 year cohort study from a single Italian centre. *Eur J Neurol*. 2024;31:e16090. doi:10.1111/ene.16090