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RESEARCH ARTICLE

Risk factors for respiratory failure in Guillain-Barré syndrome in Bangladesh: a prospective study

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Abstract

Objective: We investigated clinical, biological, and electrophysiological risk factors for mechanical ventilation (MV) and patient outcomes in Bangladesh using one of the largest, prospective Guillain-Barré syndrome (GBS) cohorts in developing world. **Methods**: A total of 693 GBS patients were included in two GBS studies conducted between 2006 and 2016 in Dhaka, Bangladesh. Associations between baseline characteristics and MV were tested using Fisher's exact test, χ^2 test, or Mann–Whitney *U*-test, as appropriate. Risk factors for MV were assessed using multivariate logistic regression. Survival analysis was performed using Kaplan–Meier method; comparisons between groups performed using log-rank test. **Results**: Of 693 patients, 155 (23%) required MV (median age, 26 years; interquartile range [IQR] 17–40). Among the ventilated patients, males were predominant (68%) than females. The most significant risk factor for MV was bulbar involvement (adjusted odds ratio [AOR]:19.07; 95% CI = 89.00–192.57, $P = 0.012$). Other independently associated factors included dysautonomia (AOR:4.88; 95% CI = 1.49–15.98, $P = 0.009$) and severe muscle weakness at study entry (AOR:6.12; 95% CI = 0.64–58.57, $P = 0.048$). At 6 months after disease onset, 20% of ventilated and 52% of non-ventilated patients ($P < 0.001$) had recovered completely or with minor symptoms. Mortality rate was significantly higher among ventilated patients than non-ventilated patients (41% vs. 7%, $P < 0.001$). **Interpretation**: Bulbar involvement, dysautonomia and severe muscle weakness were identified as the most important risk factors for MV among GBS patients from Bangladesh. The findings may help to develop predictive models for MV in GBS in developing countries to identify impending respiratory failure and proper clinical management of GBS patients.

Introduction

Guillain-Barré Syndrome (GBS), a common cause of acute neuromuscular paralysis, is often accompanied by respiratory failure that necessitates mechanical ventilation (MV).[1] About 20–30% of cases require respiratory support.[2–4] Major complications, including pulmonary infections, sepsis and pulmonary embolism, are reported in 60% of intubated patients with GBS.[5,6] The worldwide mortality rate for ventilated patients ranges from 15% to 30%, with survivors usually having poor outcomes.[7] Previous studies of Bangladeshi GBS cohorts showed the unavailability of ventilator support for patients with GBS with acute respiratory failure was the most significant risk factor for mortality, accounting for 20% of deaths among GBS patients.[8] This emphasizes the necessity of guidelines on allocation of patients with GBS to the appropriate unit (general ward or intensive care unit [ICU]) in low-resource settings to lower the risk of respiratory distress and consequent death. Multiple clinical and biological parameters have been identified as risk factors for impending respiratory failure in GBS,[9,10] including cranial

nerve involvement, disability grade on admission, rapidly progressive motor weakness, an absence of deep tendon reflexes, autonomic dysfunction, and features of nerve conduction block on electromyography.[11–14] Moreover, positive cytomegalovirus serology, anti-GQ1b antibodies, and increased liver enzymes have been associated with MV.[13–16] However, these associations have mostly been validated in developed nations, with only limited data available for patients in developing countries. Therefore, we aimed to identify the clinical and laboratory risk factors for MV in patients with GBS in a low-resource setting using one of the largest prospective cohorts from Bangladesh. Additionally, we also analyzed the outcomes of patients with GBS who required MV at standard follow-up time points.

Methods

Study subjects

Prospective data collected from 693 patients derived from two GBS studies in Bangladesh was used to assess risk factors for MV. The first study, a prospective multicenter study was conducted in Dhaka, Bangladesh, between July 2006 and June 2007 and enrolled 100 consecutive GBS cases (Fig. 1). The second study, a prospective observational study was conducted at Dhaka Medical College Hospital and the National Institute of Neurosciences and Hospital, Dhaka, Bangladesh from 2010 to 2016 and included 593 patients with GBS. The same inclusion and exclusion criteria were applied in both studies. All patients were recruited within 2 weeks of the onset of weakness and met the National Institute of Neurological Disorders and Stroke criteria.[17] After admission, a neurologist performed a complete neurological examination and validated the diagnosis. Patients were only enrolled in the study if they fulfilled the inclusion criteria and provided written informed consent. Serum and cerebrospinal fluid were collected following standard procedures at inclusion. Electrophysiological tests were performed within 1 week of the onset of neurological symptoms. After enrolment, patients underwent follow-up at standard time points (2 weeks, one, three, and 6 months, and 1 year) according to a predefined protocol.

Ethical considerations

The project protocol was reviewed and approved by the Institutional Review Board and ethical committees at icddr,b, and Dhaka Medical College and Hospital Dhaka, Bangladesh. Written informed consent was obtained from all participants or their legal representatives.

Socio-demographic and clinical data

All patients included were evaluated for respiratory failure that required MV. MV was defined as a GBS disability score of 5 at inclusion or within 7 days of inclusion of the study. Baseline characteristics included socio-demographic characteristics, history of preceding infection, and detailed clinical and neurological features including GBS disability score and Medical Research Council (MRC) sum score. The decision to provide MV and other treatments (intravenous immunoglobulin [IVIg] or plasma exchange [PE]) was at the discretion of the consultant/neurologist at the hospital in charge of the patient.

The GBS disability score was defined by Hughes et al. as a widely accepted scale used to assess the functional status of patients with GBS, ranges from 0 (healthy) to 6 (death).[18] The MRC sum score was defined as the sum of the MRC score for six muscles in the upper and lower limbs on both sides, and ranges from 60 (normal) to 0 (quadriplegic).[19] During analysis we have categorized MRC sum score into three categories: 0–20 (severe weakness), 21–40 (moderate weakness), and 41–60 (mild weakness). Nadir was defined as the highest GBS disability score or lowest MRC sum score (excluding small fluctuations of less than five points within the margins of inter-observer variation).[18,19] A good outcome was defined as the ability to ambulate without assistance (GBS disability score $\leq$2); a poor outcome, as the inability to ambulate independently (GBS disability score $\geq$3).[7]

Campylobacter and anti-ganglioside serology

Campylobacter jejuni serology and detection of antiganglioside antibodies against ganglioside GM1 were performed for all included patients. Serum antibodies against *C. jejuni* were determined by an indirect enzyme-linked immunosorbent assay (ELISA) for IgG and by antibody class capture ELISA for IgM and IgA antibodies. Sera were tested for IgM and IgG antibodies against the ganglioside GM1 using ELISA, following the previously described method and criteria.[20]

Electrophysiological examination

Electrophysiological testing was performed by an experienced neurophysiologist for 479 (69%) patients using a Viking Select Electromyography (EMG) system (CareFusion, San Diego, CA, USA). Nerve Conduction Study at onset and follow-up were classified according to the GBS criteria proposed by Hadden et al. (1998).[21]

Statistical analysis

The outcome variable (ventilated or nonventilated) was considered dichotomous. Categorical variables were

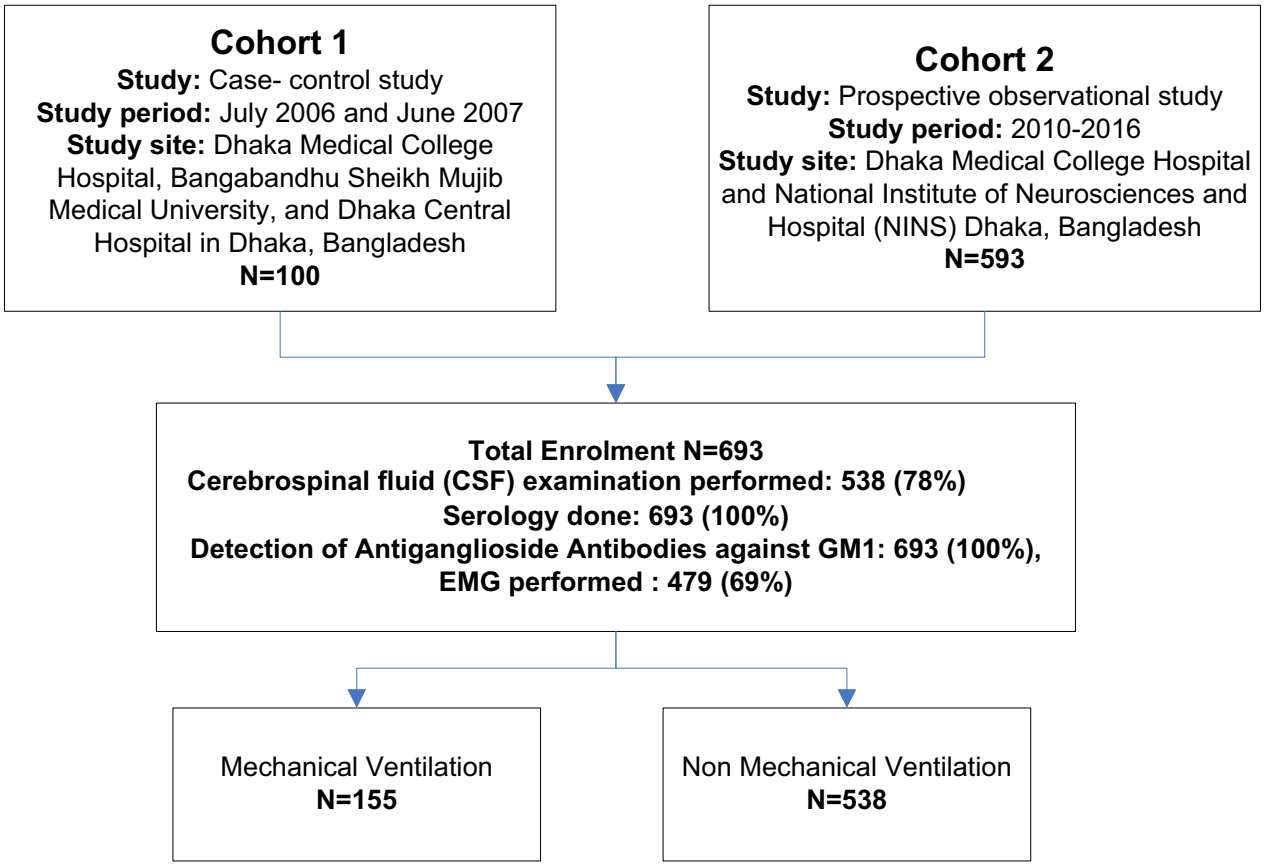

Figure 1. Inclusion of GBS patients. Flow chart indicating the process of enrolment of study subjects from two separate cohorts showing the details of each cohort and the final sample included in the analyses reported here.

presented as numbers (percentages) and continuous variables as means with standard deviation if normally distributed. If the distribution was not normal, median values and interquartile ranges (IQR) were calculated. Associations between baseline characteristics (categorical variables) and MV were tested using Fisher's exact test or the χ^2 test, as appropriate. Two independent sample *t*-tests were performed to compare continuous variables among groups. The Mann–Whitney *U*-test was performed for non-normally distributed data. Risk factors for MV were assessed using univariate logistic regression analysis. Factors that were significant in univariate analysis were further accessed via multivariate logistic regression, and adjusted odds ratios (AOR) were calculated with 95% CI. Thus, the final model only included predictors that showed some evidence of association with the outcome variable. A separate analysis was performed to compare the associations between baseline characteristics and mortality among ventilated patients using Fisher's exact test or the χ^2 test. For all analyses, variables with a two-sided $P < 0.05$ were considered potential risk factors. Survival analysis was performed using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. Data were entered and analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Results

In this cohort, 155 (23%) of the 693 patients were mechanically ventilated; 136 (20%) patients were ventilated at the time of enrollment and 19 (3%) patients required ventilation within 1 week of hospital admission. The median age of the ventilated patients was 26-year-old (IQR 17, 40); 68% of ventilated patients were male. The socio-demographic characteristics of the ventilated and nonventilated patients were similar; the baseline characteristics of all patients and the groups of ventilated and nonventilated patients are presented in Table 1.

Patients who required MV were more likely to have cranial nerve involvement, such as facial palsy ($P < 0.001$) or bulbar dysfunction ($P < 0.001$), autonomic dysfunction ($P < 0.001$), and had a lower MRC score, indicating greater muscle weakness ($P < 0.001$). Electrophysiology revealed the acute motor and sensory axonal neuropathy

Table 1. Baseline clinical, biological, and electrophysiological features of all patients and the ventilated and nonventilated groups of patients with Guillain-Barré syndrome.

Variable	All (n = 693)	MV (n = 155)	Non-MV (n = 538)	P-value
Age (years), median (IQR)	26 (17, 40)	27 (17, 40)	27 (17, 40)	0.775
0–18 years, n (%)	228 (33%)	53 (34%)	175 (33%)	
19–40 years, n (%)	298 (43%)	66 (43%)	232 (43%)	
41–60 years, n (%)	143 (21%)	29 (19%)	114 (21%)	
>60 years, n (%)	24 (4%)	7 (5%)	17 (3%)	
Sex				
Male, n (%)	469 (68%)	103 (67%)	366 (68%)	0.711
Female, n (%)	224 (32%)	52 (33%)	172 (32%)	
Symptoms of preceding infection in 4 weeks preceding onset of weakness		109 (70%)	391 (73%)	
Diarrhea, n (%)	320 (46%)	71 (46%)	249 (46%)	0.768
Respiratory tract infection, n (%)	122 (18%)	31 (20%)	91 (17%)	0.271
Other, n (%)	64 (9%)	9 (6%)	55 (10%)	
Sensory deficit, n (%)	123 (18%)	29 (19%)	94 (17%)	0.232
Cranial nerve involvement				
Facial, n (%)	224 (32%)	82 (53%)	142 (26%)	<0.001
Bulbar nerve involvement, n (%)	333 (48%)	133 (86%)	200 (37%)	<0.001
Autonomic dysfunction, n (%)	110 (16%)	57 (37%)	53 (10%)	<0.001
MRC score				
0–20, n (%)	326 (47%)	139 (90%)	187 (35%)	<0.001
21–40, n (%)	243 (35%)	13 (8%)	230 (43%)	
41–60, n (%)	124 (18%)	3 (2%)	121 (22%)	
Mean cerebrospinal fluid protein (mg/dL) (N = 538)	165.74 ± 146.09	157.51 ± 162.71	167.99 ± 141.33	0.538
Electromyography classification (n = 479)				
Acute motor axonal neuropathy (AMAN), n (%)	258 (54%)	40 (53%)	218 (54%)	<0.001
AMSAN, n (%)	37 (8%)	15 (20%)	22 (6%)	
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), n (%)	134 (28%)	17 (22%)	117 (29%)	
Unclassified, n (%)	40 (8%)	4 (5%)	36 (9%)	
Normal, n (%)	10 (2%)	0	10 (2%)	
Campylobacter jejuni serology				
Positive, n (%)	402 (58%)	79 (51%)	323 (60%)	0.119
Negative, n (%)	291 (42%)	76 (49%)	215 (40%)	
Antiganglioside IgM/IgG antibodies				
GM1 antibody-positive, n (%)	270 (39%)	39 (25%)	231 (43%)	<0.001
Specific treatment for GBS	98 (14%)	31 (20%)	67 (13%)	0.018
IVIg, n (%)	76 (11%)	24 (16%)	52 (10%)	
PE, n (%)	22 (3%)	7 (4%)	15 (3%)	

AMSAN, acute motor and sensory axonal neuropathy; GBS, Guillain-Barré Syndrome; IQR, interquartile range; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; PE, plasma exchange; MV, mechanical ventilation in the first week after hospital admission.

subtype of GBS was more prevalent among patients requiring MV compared to the nonventilated group (20% vs. 6% $P < 0.001$). Moreover, 25% of ventilated patients had antibodies against the GM1 ganglioside compared to 43% of nonventilated patients ($P < 0.001$). Ventilated patients were more likely to receive treatment with either IVIg or PE than nonventilated patients (20% vs. 13%; $P = 0.018$; Table 1).

The variables associated with MV were included in regression analysis (Table 2). In multivariate logistic regression analysis, involvement of the cranial nerves (IX, X, XI, XII) supplying bulbar muscles was the most significant risk factor for MV (AOR: 19.07; 95% CI=89.00–192.57, $P = 0.012$). Autonomic dysfunction was associated with about fivefold increase in the risk of MV (AOR: 4.88; 95% CI=1.49–15.98, $P = 0.009$). Moreover, MRC sum scores of 0–20 and 21–40 were associated with six- and twofold increases in the risk of respiratory insufficiency, respectively, compared to a MRC sum score of 41–60 ($P = 0.048$). The axonal variant of GBS and GM1 antibody-positivity were significant risk factors for MV in univariate regression, but not in multivariate analysis.

At 6 months after disease onset, 41% ($n = 53$) of ventilated patients had died compared to 7% ($n = 31$) of nonventilated patients ($P < 0.001$). The factors associated with mortality among ventilated patients are presented in

Table 2. Risk factors for MV in the patients with Guillain-Barré syndrome.

Variable	Univariate odds ratio (95% confidence interval)	*P*-value	Multivariate odds ratio (95% confidence interval)	*P*-value
Age				
0–18 years	1	0.777		
19–40 years	0.94 (0.62–1.42)			
41–60 years	0.84 (0.51–1.40)			
>60 years	1.36 (0.54–3.45)			
Sex				
Male	1			
Female	1.07 (0.74–1.57)	0.711		
Symptoms of preceding infection in 4 weeks preceding onset of weakness				
Diarrhea	1.06 (0.73–1.53)	0.768		
Respiratory tract infection	1.29 (0.82–2.04)	0.272		
Sensory deficit at entry	133 (0.83–2.13)	0.233		
Cranial nerve involvement at entry				
Facial	2.18 (1.42–3.34)	<0.001	0.99 (0.30–3.25)	0.985
Bulbar nerve involvement	5.98 (3.51–10.21)	<0.001	19.07 (1.89–192.57)	0.012
Autonomic dysfunction at entry	5.98 (3.81–9.37)	<0.001	4.88 (1.49–15.98)	0.009
MRC score at entry		<0.001		0.048
41–60	1			
21–40	2.28 (0.64–8.16)		1.61 (0.15–17.42)	
0–20	29.98 (9.34–96.25)		6.12 (0.64–58.57)	
Electromyography classification				
Axonal	1.78 (1.04–3.05)	0.037	1.84 (0.60–5.65)	0.287
AIDP acute inflammatory demyelinating polyradiculoneuropathy	0.52 (0.25–1.07)	0.075		
Positive *Campylobacter jejuni* serology	0.74 (0.50–1.08)	0.12		
GM1 antibody-positive	0.43 (0.28–0.66)	<0.001	0.88 (0.34–2.31)	0.795

MRC, Medical Research Council; MV, mechanical ventilation.

Table 3. The age, sex, clinical, and electrophysiological features of patients who died and survived after MV were similar. Current analysis found no socio-demographic or clinical factors to be associated with the mortality of the ventilated GBS patients.

After 3 months, 33% of nonventilated patients had achieved a complete recovery or recovery with minor symptoms (GBS disability score 0–1) compared to only 12% of the ventilated group ($P < 0.001$) (Fig. 2A). At 6 months, 20% of ventilated patients and 52% of nonventilated patients had a GBS disability score of 0–1 ($P < 0.001$) (Fig. 2A). After 3 and 6 months of onset of weakness the MRC sum scores revealed that nonventilated patients exhibited significantly better recovery of muscle power than ventilated patients ($P < 0.001$) (Fig. 2B).

Kaplan–Meir analysis showed ventilated patients required a significantly longer time to regain independent locomotion (primary endpoint, recovery to GBS disability score ≤2) compared to nonventilated patients (Fig. 3; log-rank test, $P < 0.001$). The estimated probability of not being able to walk independently at 6 months of onset of weakness was ~31% for ventilated patients and 18% for nonventilated patients.

Discussion

This study investigated the risk factors for MV among patients with GBS in the early stages of disease, along with patient outcomes, in the context of a developing country. The most significant risk factors for MV were bulbar nerve involvement, autonomic dysfunction and severe muscle weakness. The mortality rate was significantly higher for ventilated patients than nonventilated patients. At 6 months after disease onset, ventilated patients had poorer outcomes with more residual symptoms and greater muscle weakness compared to the nonventilated group.

We found bulbar nerve involvement was most significant risk factor for MV. Bulbar weakness has been established as a predictor of artificial ventilation in several studies from developed and developing countries.[9,11,22] Similarly, a study in Thailand found bulbar weakness was the only prognostic factor for compromised respiratory function that subsequently required MV in patients with GBS.[22] Paul et al. also identified bulbar weakness as an independent predictor of MV in an Indian cohort of patients with GBS.[9] Dysautonomia was five times more

Table 3. Clinical, biological, and electrophysiological features of patients with Guillain-Barré syndrome who died or survived after MV.

Variable	Died (n = 53)	Survived (n = 75)	P-value
Age, median (IQR)			
0–18 years	12 (23%)	27 (36%)	0.443
19–40 years	26 (49%)	30 (40%)	
41–60 years	12 (23%)	15 (20%)	
>60 years	3 (5%)	3 (4%)	
Sex			
Male	36 (68%)	54 (72%)	0.619
Female	17 (32%)	21 (28%)	
Symptoms of preceding infection in 4 weeks preceding onset of weakness			
Diarrhea	23 (49%)	34 (47%)	0.855
Respiratory tract infection	9 (19%)	16 (22%)	0.687
Sensory deficit	11 (28%)	18 (28%)	0.945
Cranial nerve involvement			
Facial	30 (65%)	41 (71%)	0.552
Bulbar nerve involvement	48 (92%)	68 (93%)	0.857
Autonomic dysfunction	22 (49%)	31 (45%)	0.679
MRC score			
0–20	50 (94%)	62 (83%)	0.111
21–40	3 (6%)	10 (13%)	
41–60	0 (0)	3 (4%)	
Electromyography classification			
Axonal	10 (67%)	31 (67%)	0.430
Acute inflammatory demyelinating polyradiculoneuropathy	3 (20%)	13 (28%)	

IQR, interquartile ranges; MRC, Medical Research Council; MV, mechanical ventilation.

common among ventilated patients than nonventilated patients in this study. Sundar et al. also reported development of autonomic dysfunction was an independent predictor of respiratory insufficiency in a cohort from India.[23] These findings suggest that GBS follows a similar clinical course in both developed and developing countries.[6,11,12] Patients with severe muscle weakness had a higher risk of progression to requirement for ventilator support. A French study suggested weakness in both the upper and lower limbs was associated with the requirement for assisted ventilation.[13] Similarly, study conducted by Hadden et al. also asserted MRC sum score was an independent predictor of MV in GBS.[21] Walgaard et al. developed a scoring system "The Erasmus GBS Respiratory Insufficiency Score" which was based on three predictors of respiratory insufficiency: MRC sum score at admission, days between onset of weakness and hospital entry, and facial and/or bulbar weakness at admission. Though the clinical applicability of this score for the GBS patients from developing countries could not be confirmed by this study, but the risk factors for MV among GBS patients from Bangladesh were quite similar as compared to the developed countries.[1]

Age and a preceding history of diarrhea were not associated with MV among patients with GBS in this study, consistent with previous findings.[1,11] In Bangladesh, recent diarrhea among patients with GBS is mostly due to antecedent *C. jejuni* infection, which is associated with development of the severe axonal forms of GBS. The axonal form does not usually involve proximal muscle weakness or cranial nerve impairment, features that are significantly associated with development of respiratory failure. Hughes et al. supported the observation that the frequency of MV is lower in cohorts where the axonal forms of GBS predominate.[24] On the other hand, demyelinating GBS has been associated with respiratory insufficiency.[12,14] However, we did not find any significant association between EMG classification and MV in our cohort of patients with GBS from Bangladesh. The current analysis found that significantly fewer ventilated patients had GM1 antibody-positivity compared to the non-MV group. These findings reflect the fact that GM1 antibody-positivity is significantly associated with the axonal variant of GBS, the predominant form of GBS in Bangladeshi patients,[25] which does not usually require MV.

The mortality rate among the ventilated patients in this Bangladeshi cohort was 41%, which is much higher than that of ventilated patients with GBS in the Western world; the mortality rate for ventilated patients in developed countries ranges from 12% to 20%.[7,26–28] Much higher mortality rates have been reported (47%) by studies from developing countries, including studies in India.[29,30] This could possibly be related to the lack of or poorly resourced intensive care facilities and lack of specialties in most low-income countries compared to hospitals in the developed world. Moreover, no data on the electrolyte and pulmonary complications experienced by the patients during and after ventilation were available for this cohort. These variables may significantly affect the outcome of ventilated patients and need to be assessed in future studies. However, we observed ventilated patients had poorer outcomes than the nonventilated group, in accordance with previous findings that mechanically ventilated patients account for a major proportion of patients with GBS who have a poor outcome or prolonged recovery.[7]

We acknowledge that the observational nature of this study and the possibility of unassessed confounding factors do not allow us to infer a cause and effect relationship between potential risk factors for MV and patient outcomes. This study did not assess vital capacity, which indicates severe respiratory involvement and has been associated with MV among patients with GBS in other studies.[11,12] Moreover, the lack of data on ICU complications for the ventilated patients is another

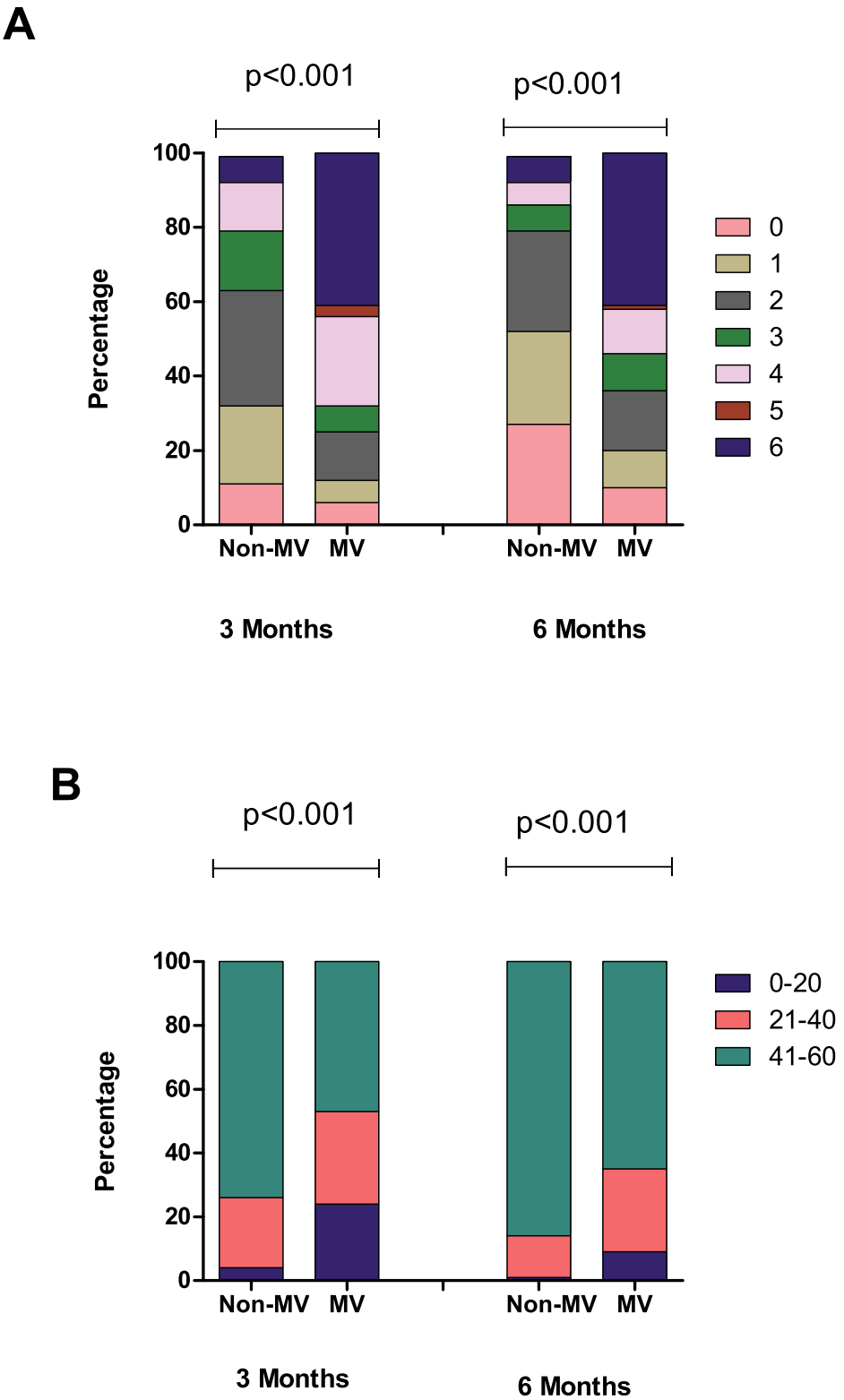

Figure 2. Outcomes of the ventilated and nonventilated patients with GBS. Bar diagram showing comparison of outcome of GBS among ventilated and nonventilated patients at 3 and 6 months of onset of disease with regard to (A) GBS disability score and (B) MRC sum score. After 3 and 6 months of onset of weakness revealed that nonventilated patients exhibited significantly better recovery in GBS disability score and MRC sum scores than ventilated patients ($P < 0.001$). MRC, Medical Research Council

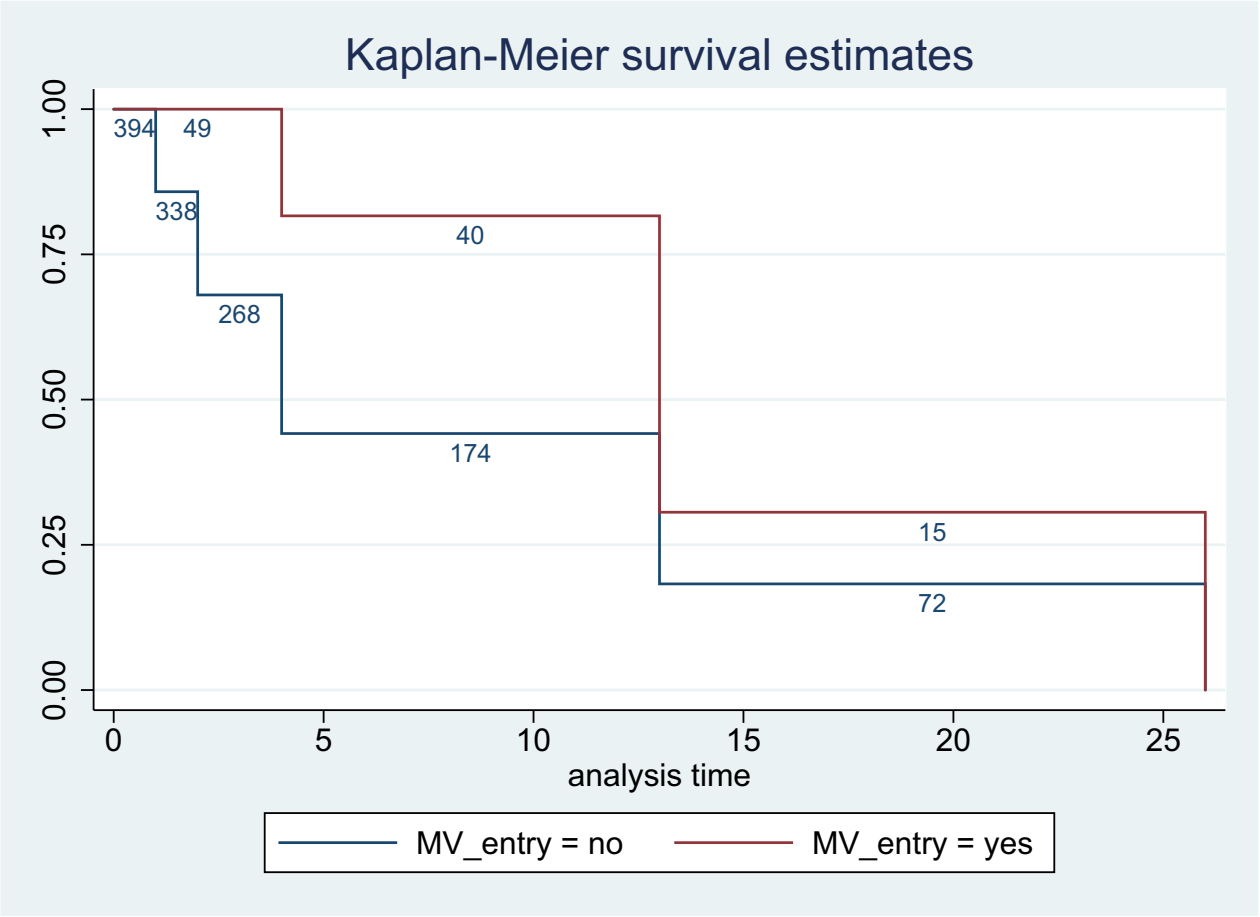

Figure 3. Kaplan–Meir analysis. Graph showing the time to recovery of independent locomotion (primary endpoint, recovery to GBS disability score ≤2) for ventilated and nonventilated patients with GBS. It revealed ventilated patients required a significantly longer time to regain independent locomotion compared to nonventilated patients (log-rank test, $P < 0.001$).

potential limitation of this study. Despite these limitations, it is worth noting our analysis was based on one of the largest prospective GBS cohorts from a developing nation.

In conclusion, this study identified bulbar nerve involvement, autonomic dysfunction, and severe muscle weakness as potential risk factors for MV among patients with GBS from Bangladesh. The presence of these factors alone or in combination may not necessitate immediate support with MV, but may be helpful when making the decision to transfer a patient to the ICU. In addition, considering the high mortality rates and poor outcomes of ventilated patients, physicians need to take further precautions to reduce morbidity and mortality among ventilated patients with GBS. However, the results of this study should be confirmed by additional rigorous studies and predictive models for respiratory insufficiency for patients with GBS in developing countries urgently need to be developed.

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Author Contributions

ZI, NP, GA, and QD conceived and designed the study. TI, AUA, IJ, and BI contributed in data acquisition. ZI, NP, GA, and TI performed data analyses. NP, ZI, TI, and QD

interpreted data and drafted the manuscript, which was critically reviewed by all other authors. All authors read and approved the final manuscript before submission.

Conflict of Interests

None declared.

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