Guillain-Barré syndrome in association with COVID-19 vaccination: a systematic review

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Abstract
Since the beginning of worldwide vaccination against coronavirus disease 2019 (COVID-19), studies have reported a possible association between vaccination and Guillain-Barré syndrome (GBS). In this regard, we conducted a systematic review assessing different demographic, clinical, and neurophysiological aspects of patients with GBS following immunization with COVID-19 vaccines. A comprehensive search of PubMed, Web of Science, Scopus, and Google Scholar was performed. Articles in English between January 2020 and November 2021 were included. Data on demographics, clinical characteristics, vaccines information, treatment approaches, and outcomes were extracted. The data of a total of 88 patients out of 41 studies was included. The mean age of patients was 58.7 ± 16.6 years and 55 cases (62.5%) were male. AstraZeneca was the most-reported vaccine associated with GBS with 52 cases (59.1%) followed by Pfizer with 20 cases (22.7%). GBS occurred after the first dose of vaccination in 70 cases (79.5%). The mean time interval between vaccination and symptom onset was 13.9 ± 7.4 days. Limb weakness (47.7%), sensory disturbance (38.6%), and facial weakness (27.3%) were the most common reported symptoms, respectively. Albuminocytologic dissociation was seen in 65% of patients who underwent lumbar puncture (n = 65). Acute inflammatory demyelinating polyradiculopathy was the most common GBS subtype, which was reported in 38 patients (43.2%). While one-fifth of patients underwent intubation (n = 17), a favorable outcome was achieved in the majority of subjects (n = 46, 63%). Overall, a small rise in GBS incidence, following various COVID-19 vaccines, was observed. Notably, 85% of affected individuals experienced at least a partial recovery.

Keywords Guillain-Barré syndrome · Vaccination · COVID-19 · SARS-COV-2

Introduction
Guillain-Barré syndrome (GBS) is an autoimmune disease. In the majority of cases, the individual is affected by an infection or other immunological stimulants that results in an aberrant autoimmune response. The aberrated immunologic response targets the peripheral nerves and their spinal roots leading to a progressive neuropathic weakness [1, 2].

Typically, GBS is a monophasic disease and the disease onset often arises shortly (< 1 month) after an upper respiratory or gastrointestinal tract infection, usually without relapse. Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, mycoplasma pneumonia, influenza-like illness, HIV, and Zika virus are the most common infections reported to precede the onset of GBS [3]. Notably, the association of coronavirus disease 2019 (COVID-19) and different types of neuropathies, such as GBS, has been repeatedly described in the literature in recent years.
COVID-19-associated GBS was first brought to the attention of the medical community after a series of 5 patients who had GBS after the onset of COVID-19 was reported in Italy in early 2020 [4]. Since there has been a growing body of evidence introducing COVID-19 as a new infection that can cause GBS [4–6].

On the other hand, GBS has also been described following immunization with various vaccines, but not limited to Semple rabies vaccine and various types of influenza A virus vaccines [7, 8]. The potential link between influenza vaccine and GBS was noted during the H1N1 influenza vaccination campaign in 1976 where the increased risk was estimated roughly at one additional case of GBS for every 100,000 people who had been vaccinated [9]. The subsequent studies during 1992–2004 in USA and Canada confirmed this observation [10, 11]. Further multinational investigations revealed that influenza vaccines, both adjuvant or un-adjuvant forms, could increase the risk of GBS following vaccination [12–15].

Following the COVID-19 pandemic, several groups attempted to design effective vaccines against the virus. In late 2020, the first trials of vaccines showed promising results. Since the beginning of immunization with COVID-19 vaccines, some studies have implicated the association between the COVID-19 vaccine and GBS. In February 2021, Waheed et al. described the first case of GBS following immunization with BNT162b2 mRNA (Pfizer) vaccine [16]. More recently, several cases of GBS were reported following Pfizer, Oxford-AstraZeneca (AZV), and Johnson & Johnson (J&J) COVID-19 vaccines [17–20]. Since the beginning of the COVID-19 vaccination program, there have been databases designed to record all the COVID-19-related adverse events. The UK National Immunization Management System database revealed an increased risk of GBS following the first dose of ChAdOx1nCoV-19 (AZV) [21]. However, this risk was not higher than the risk of GBS following COVID-19 infection [21]. The US Vaccine Adverse Event Reporting System, which is a passive reporting system, showed a small but statistically significant risk of GBS associated with Ad26.COV2.S (J&J) COVID-19 vaccine [22]. Here, we systematically review the current literature regarding the risk of GBS after COVID-19 vaccination.

Method and materials
This study was conducted by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23], a well-known tool to increase the transparency of reporting systematic reviews. To find relevant studies, we performed a comprehensive search in PubMed, Web of Science, and Scopus, as well as a manual search in Google Scholar to find relevant studies. The search query of each source was provided as supplementary materials; nonetheless, we used the following keywords: Guillain-Barré syndrome, COVID-19, SARS-COV-2, Vaccine. We included articles in English between January 2020 and November 2021. All published or pre-published studies that had data regarding the association of COVID-19 and neurological defects, especially GBS in adults who received vaccination against COVID-19, were considered eligible for inclusion regardless of vaccine type (Fig. 1). We also examined large-scale population-based cohort studies, case series, and case reports providing practical details regarding GBS incidence after COVID-19 vaccination.

After retrieving the relevant studies, two reviewers (M.A. and N.M.H.) independently extracted the data from the included studies. The extracted data included general information (author, year, geographic area, study design), demographics data (including age and gender), clinical data (vaccine type, vaccine dose number (first vs. second), the time interval between injection and symptom onset, presenting signs and symptoms, GBS subtype), electrophysiological findings, laboratory data (cerebrospinal fluid analysis, anti-ganglioside antibodies), treatment approaches, need for intubation, and clinical outcome. We classified patients’ outcomes into three categories (favorable, partial recovery, and poor). The patients who were discharged with no complications were categorized as “favorable” (complete recovery), those who recovered but needed assistance and further rehabilitation were listed as “partial recovery,” and patients who remained bedridden and intubated were classified as “poor” outcome. Moreover, the level of diagnostic certainty was evaluated via Brighton criteria for each case [24]. Due to the qualitative and summative nature of this review and significant variations in study designs and reporting of findings, a meta-analysis and statistical calculations were not performed.

Results
In this study, a total of 88 cases of COVID-19 vaccine–associated GBS were included from 41 studies in 17 countries. Two patients had a previous history of GBS [25, 26]. Five patients received the influenza vaccine in addition to the COVID-19 vaccination [27, 28]. The patients’ age ranged between 14 and 90 years and the mean age was 58.7 ± 16.6 years. The majority of the cases were male (62.5%). The demographic and clinical characteristics are shown in Table 1.

AZV was the most-reported vaccine with 52 cases (59.1%) and Pfizer was the second most-reported vaccine with 20 cases (22.7%). Each of the J&J, Sputnik V, Sinopharm, Moderna, and Sinovac vaccines was reported in 5, 4, 3, 2, and 1 patients, respectively. Most of the cases
occurred after the administration of the first dose (79.5%). The mean latency period from vaccination to the onset of the symptoms was 13.9 ± 7.4 days. Limb weakness was the most common symptom reported in 42 patients (47.7%). The sensory disturbance occurred in 34 patients (38.6%). Facial weakness was reported in 24 patients (27.3%). Incidence of bulbar weakness and ophthalmoplegia was 11.4% (10 patients) and 8% (7 patients), respectively. Only one patient suffered sphincter disturbance. Sixty-five patients underwent lumbar puncture. Albuminocytologic dissociation was shown in 65% of the patients. Anti-Ganglioside antibodies including anti-GQ1b, anti-GQ2b, anti-GM1, anti-GM2, anti-GM3, anti-GM4, anti-titin, and anti-sulfatide antibodies were found in 18% of patients who were tested for (5 out of 28).

The most common GBS subtype was acute inflammatory demyelinating polyradiculopathy reported in 38 patients (43.2%). Bifacial weakness with paresthesia (BFP) was the second most common subtype of GBS with an incidence of 15.9% (14 cases). Unspecified classic sensory-motor GBS was reported in 11 patients (12.5%).

Acute motor-sensory axonal neuropathy and acute motor axonal neuropathy were reported in 9 (10.2%) and 4 (4.5%) cases, respectively. Other rare subtypes were paraparetic GBS in 4 cases, Miller Fisher syndrome (MFS) in 3 cases, MFS-GBS overlap in 2 cases, pure sensory GBS in 2 subjects, and pure motor GBS in one patient. Patients were divided into four levels based on The Brighton Collaboration definitions with 41 cases in level 1 (46.6%), 24 in level 2 (27.3%), 4 in level 3 (4.5%), and 19 cases in level 4 (21.6%).

The most frequent treatment used as the first-line therapy was intravenous immunoglobulin (IVIG) (n = 61, 69.3%). Plasmapheresis (PLEX) was performed in 13.6% of the cases (n = 12, four cases received PLEX solely, seven received PLEX following IVIG, and one case received PLEX prior to IVIG). Six patients have received corticosteroids (6.8%) while 3 patients were managed conservatively (3.4%). Almost one-fifth of patients were intubated (n = 17). The majority of the patients experienced favorable outcomes (n = 46, 6%) and roughly 22% of the patients had partial improvement (n = 16). Poor outcome was reported in 10
| No | Authors                  | Country   | Age/sex | Vaccine/dose | Onset time (day) | GBS subtype       | Electro-physiologic finding | Albumino-cytological dissociation | Ganglioside Ab | MRI                          | Brighton collaboration level | Treatment            | Intubation | Outcome |
|----|-------------------------|-----------|---------|--------------|------------------|--------------------|----------------------------|-------------------------------|----------------|-----------------------------|--------------------------|-------------------|------------|---------|
| 1  | Abičić et al. [29]       | Croatia   | 24/F    | Pfizer/1     | 18               | MFS                | NR                         | + (anti GQ1b)                | NP             | 4                           | - Prednisolone, IVIg | - CR              | -          | CR      |
| 2  | Allen et al. [30]         | UK        | 54/M    | AZV/1        | 16               | BFP                | See below<sup>a</sup>      | +                             | -              | 4                           | - Prednisolone, IVIg | - CR              | -          | CR      |
|    |                         |           | 20/M    | AZV/1        | 26               | BFP                | See below<sup>b</sup>      | +                             | -              | 4                           | - Prednisolone, IVIg | - CR              | -          | CR      |
|    |                         |           | 57/M    | AZV/1        | 21               | BFP                | Normal                     | +                             | -              | 4                           | - Prednisolone, IVIg | - CR              | -          | CR      |
|    |                         |           | 55/M    | AZV/1        | 29               | BFP                | NT                         | +                             |                | 4                           | IVIg, Conservative | -                | -          | CR      |
| 3  | Añor-Millán et al. [17]  | Spain     | 77/M    | Pfizer/1     | 3                | AMSAN              | AMSAN                      | -                            | -              | 2                           | - IVIg, PLEX           | - CR              | -          | CR      |
| 4  | Azam et al. [31]          | UK        | 67/M    | AZV/1        | 15               | AIDP               | AIDP                       | +                            | -              | 1                           | - IVIg                | - CR              | -          | NR      |
| 5  | Bax et al. [32]           | Italy     | 90/M    | Pfizer/2     | 3                | AMSAN              | AMSAN                      | +                            | +<sup>d</sup>    | 2                           | - IVIg                | - CR              | -          | CR      |
|    |                         |           | 51/F    | AZV/1        | 10               | AIDP               | AIDP                       | -                            |                | 1                           | - IVIg                | - CR              | -          | CR      |
|    |                         |           | 66/M    | AZV/1        | 17               | BFP                | Demyelinating             | +                            | -              | 4                           | - IVIg                | CR               | -         |        |
|    |                         |           | 43/M    | AZV/1        | 17               | BFP                | Demyelinating             | +                            | -              | 4                           | - IVIg                | PR               | -         |        |
|    |                         |           | 51/M    | AZV/1        | 14               | BFP                | Demyelinating / +/GM3     | +                            | -              | 4                           | - NR                 | CR               | -         |        |
|    |                         |           | 71/F    | AZV/1        | 15               | BFP                | Demyelinating             | +                            | -              | 1                           | - NR                 | CR               | -         |        |
| 6  | Bonifacio et al. [33]     | UK        | 62/F    | AZV/1        | 18               | AIDP               | AIDP                       | +                            | -              | 2                           | - IVIg                | - CR              | -          | CR      |
| 7  | Bouattour et al. [34]     | Tunisia   | 67/M    | Pfizer/1     | 7                | AIDP               | AIDP                       | +                            | -              | 1                           | - IVIg                | CR               | -          |        |
| 8  | Dang et al. [35]          | Australia | 63/M    | AZV/1        | 14               | MF&GBS overlap     | +                            | -              | 3                           | - IVIg                | - PR              | -          |        |
|    |                         |           |         |              |                  |                    |                            |                |                |                            |                    |                  |            |         |
| 9  | da Silva et al. [36]       | Brazil    | 62/F    | AZV/1        | 18               | Classic SM         | NT                         | +                            | NR             | 2                           | - IVIg                | - CR              | -          | CR      |
| No | Authors                          | Country | Age/sex | Vaccine/dose | Onset time (day) | GBS subtype | Electro-physiologic finding | Albuminocytological dissociation | Ganglioside Ab | MRI | Brighton collaboration level | Treatment | Intubation | Outcome |
|----|---------------------------------|---------|---------|--------------|------------------|-------------|-----------------------------|-------------------------------|----------------|------|------------------------------|-----------|------------|---------|
| 10 | Finsterer et al. [26]           | Austria | 32/M    | Vector based/1 | 8                | AIDP        | AIDP                        | +                             | NR             | NR   | 1                           | - IVIg     | -          | PR      |
| 11 | García-Grimshaw et al. [27]     | Mexico  | 33/M    | Pfizer/1     | 28               | AIDP        | AIDP                        | +                             | NR             | NR   | 1                           | - IVIg     | -          | CR      |
|    |                                 |         | 25/M    | Pfizer/1     | 12               | AIDP        | AIDP                        | +                             | NR             | NR   | 1                           | - IVIg     | -          | PR      |
|    |                                 |         | 53/F    | Pfizer/1     | 6                | AMAN        | AMAN                        | -                             | NR             | NR   | 2                           | - IVIg     | Poor       |         |
|    |                                 |         | 72/M    | Pfizer/1     | 4                | AMAN        | AMAN                        | NT                            | NR             | NR   | 2                           | - IVIg     | PR         |         |
| 12 | Hasan et al. [37]               | UK      | 62/F    | AZV/1        | 11               | AIDP        | AIDP                        | +                             | NR             | Normal | 1                           | - IVIg     | Poor       | CR      |
| 13 | Hughes et al. [38]              | USA     | 65/M    | Pfizer/1     | 2                | AIDP        | AIDP                        | +                             | NR             | Normal | 1                           | - IVIg     | -          | CR      |
| 14 | Introna et al. [39]             | Italy   | 62/F    | AZV/1        | 10               | AIDP        | AMSAN                       | +                             | /GMI           | Normal | 1                           | - IVIg     | -          | PR      |
| 15 | Jain et al. [20]                | USA     | 65/F    | J & J        | 19               | BFP         | NT                          | +                             | -              | Normal | 4                           | - IVIg, IVMP| -          | CR      |
| 16 | James et al. [19]               | India   | 60/M    | AZV/1        | 11               | AMSAN       | AMSAN                       | +                             | NT             | -Normal| 2                           | - IVIg, IVMP| -          | CR      |
|    |                                 |         | 66/M    | AZV/1        | 12               | AIDP        | AIDP                        | +                             | NT             | -Nonspec-| 1                           | - IVIg, IVMP| -          | CR      |
|    |                                 |         | 54/F    | AZV/1        | 13               | AIDP        | AIDP                        | NT                            | -              | Normal | NR, NP                      | - IVIg, IVMP| -          | CR      |
| 17 | Kanabar et al. [40]             | UK      | 61/F    | AZV/1        | 10               | AIDP        | AIDP                        | +                             | NR             | NP    | 1                           | - IVIg     | -          | CR      |
|    |                                 |         | 56/M    | AZV/1        | 11               | AIDP        | AIDP                        | +                             | NR             | NP    | 1                           | - IVIg     | -          | CR      |
| 18 | Karimi et al. [41]              | Iran    | 38/M    | Sputnik V    | 14               | BFP         | Prolong R1                  | +                             | NT             | -Normal| 4                           | - PLEX     | -          | CR      |
|    |                                 |         | 38/M    | Sputnik V/1  | 8                | AIDP        | and R2                      | +                             | NR             | -Normal| 1                           | - PLEX     | -          | PR      |
|    |                                 |         | 87/M    | Sinopharm/1  | 4                | AIDP        | latency                     | +                             | NR             | -Normal| 1                           | - IVIg     | -          | PR      |
|    |                                 |         | 52/M    | Sputnik V    | 21               | AIDP        | AIDP                        | +                             | NR             | -Normal| 1                           | - IVIg     | -          | CR      |
|    |                                 |         | 48/F    | Sputnik V    | 17               | Classic SM | AIDP                        | NT                            | NR             | -NP    | 3                           | - IVIg, PLEX| -          | PR      |
| 19 | Ling et al. [25]                | Canada  | 63/M    | AZV/1        | 12               | AIDP        | AIDP                        | +                             | NT             | Normal| 1                           | - IVIg, PLEX| -          | PR      |
| No | Authors              | Country | Age/sex | Vaccine/dose | Onset time (day) | GBS subtype | Electro-physiologic finding | Albumino-cytological dissociation | Ganglioside Ab | MRI | Brighton collaboration level | Treatment               | Intubation | Outcome |
|----|---------------------|---------|---------|--------------|------------------|-------------|----------------------------|----------------------------------|----------------|-----|----------------------------|--------------------------|------------|---------|
| 20 | Loza et al. [42]    | USA     | 60/F    | J&J          | 10               | MFS and classic overlap | Absent F waves and H reflex | +                  |     |     | 1                           | - IVIg                   | -          | CR      |
| 21 | Malamud et al. [43] | USA     | 14/M    | Pfizer/2     | 30               | AIDP         | AIDP                      | +                  | NR  | NP  | 1                           | - IVIg                   | -          | CR      |
| 22 | Maramottom et al. [44] | India | 43/F    | AZV/1        | 10               | AIDP         | AIDP                      | +                  | NT  | NP  | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 67/F    | AZV/1        | 14               | AMSAN        | AMSAN                     | +                  |     |     | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 53/F    | AZV/1        | 12               | AIDP         | AIDP                      | +                  |     |     | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 68/F    | AZV/1        | 14               | AIDP         | AIDP                      | +                  |     |     | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 70/M    | AZV/1        | 11               | AIDP         | AIDP                      | NT                 | NT  | NP  | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 69/F    | AZV/1        | 12               | AIDP         | AIDP                      | NT                 | NT  | NP  | 1                           | - IVIg                   | +          | Poor    |
|    |                     |         | 69/F    | AZV/1        | 13               | AIDP         | AIDP                      | NT                 | NT  | NP  | 1                           | - IVIg                   | +          | Poor    |
| 23 | Masuccio et al. [45] | Italy   | 80/M    | Moderna/2    | 44               | AIDP         | AIDP                      | +                  |     |     | 1                           | - IVIg                   | -          | CR      |
| 24 | Matarneh et al. [46] | Qatar   | 61/M    | Moderna/2    | 4                | Pure motor   | Demyelinating motor neuropathy | +                  | NT  | NR  | 4                           | - IVIg                   | -          | CR      |
| 25 | McKean et al. [47]  | Malta   | 48/M    | AZV/1        | 10               | AIDP         | AIDP                      | +                  |     |     | 1                           | - IVIg, Prednisolone     | -          | CR      |
| 26 | Michaelson et al. [48] | USA  | 78/M    | Pfizer/2     | 14               | MFS          | MFS                       | +                  |     |     | 4                           | - IVIg                   | -          | CR      |
| 27 | Min et al. [49]     | Korea   | 58/M    | AZV/1        | 15               | Sensory GBS | Sensory GBS               | See below | +   |     | 4                           | - Gabapentin, Duloxetine, Tramadol | -          | CR      |
|    |                     |         | 37/F    | AZV/1        | 18               | Sensory GBS | Sensory GBS               | See below | -   |     | 4                           | - Gabapentin, Duloxetine, Tramadol | -          | CR      |
| 28 | Morehouse et al. [50] | USA    | 49/F    | J&J          | 5                | Classic SM   | NT                        | -                  | NT  |     | 3                           | - IVIg, PLEX             | +          | Poor    |
| 29 | Nasuelli et al. [51] | Italy   | 59/M    | AZV/1        | 10               | AIDP         | AIDP                      | +                  |     |     | 1                           | - IVIg                   | -          | CR      |
| 30 | Nishiguchi et al. [52] | Japan | 71/M    | Pfizer/1     | 18               | MFS          | MFS                       | +                  |     |     | 4                           | - IVIg                   | -          | CR      |
| 31 | Ogbebor et al. [53] | USA     | 86/F    | Pfizer/1     | 1                | Paraparetic  | NT                        | +                  | NT  |     | 2                           | - IVIg                   | -          | CR      |
| No | Authors | Country | Age/sex | Vaccine/dose | Onset time (day) | GBS subtype | Electro-physiologic finding | Albuminocytological dissociation | Ganglioside Ab | MRI | Brighton collaboration level | Treatment | Intubation | Outcome |
|----|---------|---------|---------|--------------|-----------------|--------------|----------------------------|--------------------------------|----------------|-----|-----------------------------|------------|------------|---------|
| 32 | Oo et al. [28] | Australia | 51/M | AZV/1 | 14 | AIDP | AIDP | + | NT | NR | 1 | - IVlg, + | Poor |
|    |         |         | 65/F | AZV/1 | 7 | AIDP | AIDP | + | - | Nonspecific | 1 | - PLEX, + | PR |
|    |         |         | 66/M | AZV/1 | 21 | AIDP | AIDP | + | NT | NR | 1 | - IVlg | CR |
| 33 | Osowicki et al. [54] | Australia | 75/F | AZV/1 | 17 | AIDP | AIDP | NR | NR | NR | 1 | - NR | NR |
|    |         |         | 77/F | AZV/1 | 17 | AIDP | AIDP | NR | NR | NR | 1 | - NR | NR |
|    |         |         | 57/F | AZV/1 | 13 | AIDP | AIDP | NR | NR | NR | 1 | - NR | NR |
|    |         |         | 57/M | AZV/1 | 12 | Paraparetic | NR | NR | NR | 2 | - NR | NR |
|    |         |         | 52/F | AZV/1 | 20 | BFP | NR | NR | NR | 4 | - NR | NR |
|    |         |         | 54/M | AZV/1 | 10 | AIDP | AIDP | NR | NR | NR | 1 | - NR | NR |
|    |         |         | 80/F | AZV/1 | 21 | Paraparetic | NR | NR | NR | 2 | - NR | NR |
|    |         |         | 72/M | AZV/1 | 14 | Classic | NR | NR | NR | 3 | - NR | NR |
|    |         |         | 59/M | AZV/1 | 25 | Classic | NR | NR | NR | 4 | - NR | NR |
|    |         |         | 69/M | AZV/1 | 16 | Classic | NR | NR | NR | 2 | - NR | NR |
|    |         |         | 72/F | AZV/1 | 11 | Classic | NR | NR | NR | 2 | - NR | NR |
|    |         |         | 66/M | AZV/1 | 11 | Classic | NR | NR | NR | 1 | - NR | NR |
|    |         |         | 63/M | AZV/1 | 14 | Classic | NR | NR | NR | 2 | - NR | NR |
|    |         |         | 70/M | AZV/1 | 14 | AMSAN | AMSAN | NR | NR | 1 | - NR | NR |
| 34 | Patel et al. [55] | UK | 37/M | AZV/1 | 14 | Classic SM | Patchy attenuation of motor response | + | NT | Prominent ventral Cauda equina nerve root enhancement | 2 | - IVlg | CR |
| 35 | Prasad et al. [56] | USA | 41/M | J&J | 15 | BFP | demyelinating + | - | Normal | 1 | - IVlg | PR |
| 36 | Razok et al. [57] | Qatar | 73/M | Pfizer/2 | 16 | Paraparetic | Absent bilateral H reflex | + | NR | Bilateral lumbar nerve root enhancement | 1 | - IVlg | CR |
| No | Authors                  | Country | Age/sex | Vaccine/dose | Onset time (day) | GBS subtype | Electrophysiologic finding | Albumino-cytological dissociation | Ganglioside Ab | MRI | Brighton collaboration level | Treatment | Intubation | Outcome |
|----|--------------------------|---------|---------|--------------|-----------------|-------------|--------------------------|---------------------------------|----------------|-----|--------------------------|-----------|------------|---------|
| 37 | Rossetti et al. [58]     | USA     | 38/M    | J&J          | 30              | BFP         | +                       | NR                              |                |     |                         | - IVIg     | −          | CR      |
|    |                          |         |         |              |                 |             |                         |                                 |                |     |                          |           |            |         |
| 38 | Scendoni et al. [59]     | Italy   | 82/F    | Pfizer/2     | 14              | AIDP        | AIDP                    | +                               | +                | NP  | 1                        | - IVIg     | −          | PR      |
|    |                          |         |         |              |                 |             |                         |                                 |                |     |                          |           |            |         |
| 39 | Trimboli et al. [60]     | Italy   | 25/F    | Pfizer/2     | 8               | AIDP        | AIDP                    | −                               | NR               | NP  | 2                        | - IVIg     | −          | CR      |
|    |                          |         |         |              |                 |             |                         |                                 |                |     |                          |           |            |         |
| 40 | Tutar et al. [61]        | Turkey  | 76/M    | CoronaVac/2  | 8               | AMSAN       | AMSAN                   | −                               | −                | Normal | 2                        | - IVIg     | −          | CR      |
|    |                          |         |         |              |                 |             |                         |                                 |                |     |                          |           |            |         |
| 41 | Waheed et al. [16]       | USA     | 82/F    | Pfizer/1     | 14              | Classic SM  | NT                      | +                               | NT               | Cauda equina nerve root enhancement | 2         | - IVIg     | PR      |

GBS, Guillain–Barré syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MRI, magnetic resonance imaging; AZV, AstraZeneca vaccine; J&J, Johnson & Johnson; NR, not reported; NT, not tested; NP, not performed; AIDP, acute inflammatory demyelinating polyradiculopathy; AMAN, acute motor axonal neuropathy; BFP, bifacial weakness with paresthesia; MFS, Miller Fisher syndrome; IVIg, intravenous immunoglobulin; PLEX, plasmapheresis; CR, complete recovery; PR, partial recovery; SM, sensory-motor; rt, right; lt, left; SNAP, sensory nerve action potential; CMAP, compound muscle action potential; IVMP, intravenous methylprednisolone; CN, cranial nerve. Decreased facial CMAP amplitude, denervation in facial muscles. Decreased rt/lt sural SNAP amplitude, temporal dispersion in Lt, and absent rt peroneal CMAP. Decreased Rt/Lt sural SNAP amplitude, temporal dispersion in Lt, and absent Rt peroneal CMAP. Nonspecific white matter hyperintensities. Anti-sulfatide, anti-GM2, anti-GM4.
cases (~14%) and one person died due to GBS complications (1.1%; Table 2).

Discussion

Here, we characterized 88 patients who developed GBS following the administration of the COVID-19 vaccine. The majority of cases occurred after receiving a vector-based vaccine with the AZV vaccine being the most reported. The motor deficit was the most common finding among patients who received the AZV vaccine. The latency between vaccination and the onset of neurological symptoms was highly variable (2–30 days; 13.9 ± 7.41 days). The severity of the complications ranged from mild symptoms to severe life-threatening conditions. Thirteen patients required mechanical ventilation. While the favorable outcome was achieved in most cases, some patients had partial recovery and poor outcomes such as unconsciousness and prolonged mechanical ventilation via tracheostomy. A favorable prognosis with a high chance of response to IVIG therapy was in line with our own experience, i.e., we recently reported three cases of post-COVID-19 vaccination GBS of acute motor axonal neuropathy subtype with a considerable short-term recovery in response to treatment with IVIG suggestive for a temporal association between GBS incidence and COVID-19 vaccination [62].

Notably, a high proportion of patients with BFP variant was reported with COVID-19 vaccine–associated GBS, compared to previous studies of non-vaccine-associated GBS. In the current study, the BFP variant was seen in 15.9% of patients while it generally constitutes less than 5% in GBS cases [63].

General pain and weakness were reported to be the most common adverse events of the AZV COVID-19 vaccine in a recently published large-scale phase III study. Interestingly, only two patients who received the vaccine have shown nervous system disorders, i.e., one patient developed chronic inflammatory demyelinating polyradiculoneuropathy and the other suffered from hypoesthesia [64]. The Pfizer vaccine ranked second for COVID-19 vaccine–associated GBS in our study while no neurological adverse events were described in the phase III study [65]. Another interesting notion was that the majority of GBS cases occurred after the second dose of the Pfizer vaccine which was in contrast to the other observations.

In earlier studies, a higher incidence of GBS was observed among those vaccinated with AZV compared to the general population [21, 66] while this was not the case in Pfizer-vaccinated individuals. In a self-controlled case study using the English national immunization database of COVID-19 vaccination, a total of 187 cases of GBS (out of more than 32 million subjects) have been observed during 1–28 days following vaccination with the first dose of either AZV or Pfizer vaccines (incidence ~ 0.6 cases per 100,000 first dose vaccination). No association was found between the Pfizer vaccine and the risk of GBS in this period. However, an increased risk of GBS was found after AZV vaccination (IRR, 2.04; 95% CI: 1.60–2.60). Nevertheless, the risk of GBS was substantially higher within 28 days of a positive COVID-19 test (IRR, 5.25; 95% CI: 3.00–9.18) [21].

In an interim analysis of surveillance data of COVID-19 vaccines, Hanson et al. compared the adjusted rate ratio (RR) of GBS incidence in the other vector-based vaccine (J&J) vs. mRNA vaccines (Pfizer, Moderna) during the 1–21 days post-vaccination period. The adjusted RR (adjusted for age, sex, race/ethnicity, and calendar day) of GBS following J&J vs. mRNA vaccines was 20.56 showing a significantly higher risk for J&J recipients compared to mRNA vaccines with 15.5 excess GBS cases per million J&J vaccines (95% CI: 6.94–64.66, P < 0.001) [67].

Very rarely central nervous system autoimmune diseases were also described in association with the COVID-19 vaccine [68]. Different potential mechanisms can be suggested for the possible association of autoimmune diseases after vaccination. This may include the similarity of vaccine epitopes with myelin or axon epitopes and triggering cellular and humoral immune responses, degradation of axon or myelin membranes due to direct exposure of vaccine virus or vaccine-related products, and chances of genetic predisposition [69]. The presence of a temporal association between vaccination and GBS is by no means adequate evidence for a causal relationship between the two, however suggestive of one. Regardless, a wide range of time intervals between the vaccination and the occurrence of GBS symptoms (3 h to 39 days) seen in this study again suggests a complex multifactorial relationship rather than a direct link between the two.

Conclusion

GBS is a rare neurologic disease and a few cases of GBS have been reported worldwide in association with vaccination against COVID-19. The available data is insufficient to determine the precise pathophysiology behind this observation. In this review, we provided a summary of current evidence on clinical and neurophysiological characteristics of post-COVID-19 vaccination GBS. This information helps physicians in early diagnosis and appropriate management of this rare type of GBS and enables them to have an evidence-based discussion with patients, particularly when dealing with vaccine hesitancy. Furthermore, our data add to the growing body of evidence suggestive of an association between various COVID-19 vaccines and the occurrence of GBS. Nonetheless, the benefits of vaccines against
Table 2  Summary of types of vaccine injections and related clinical findings

| Variable                                      | Total cases |
|-----------------------------------------------|-------------|
| Sex (%)                                       | 88          |
| Female                                        | 33 (37.5)   |
| Male                                          | 55 (62.5)   |
| Age, years, mean ± SD                        | 57.80 ± 16.59|
| Vaccine name (%)                              | 88          |
| AstraZeneca                                   | 52 (59.1)   |
| Pfizer & BioNTech                             | 20 (22.7)   |
| Moderna                                       | 2 (2.3)     |
| Johnson & Johnson                             | 5 (5.7)     |
| Sputnik                                       | 4 (4.5)     |
| Sinopharm                                     | 3 (3.4)     |
| SinoVac                                       | 1 (1.1)     |
| Unknown vector-based                          | 1 (1.1)     |
| Vaccination dose                              |             |
| First                                         | 70 (79.5)   |
| Second                                        | 10 (11.4)   |
| Latency period, days, mean ± SD (from vaccination to symptom onset) | 87          |
| Facial weakness                               | 24 (27.3)   |
| Limb weakness                                 | 42 (47.7)   |
| Bulbar palsy                                  | 10 (11.4)   |
| Ophthalmoplegia                               | 7 (8)       |
| Sensory disturbances                          | 34 (38.6)   |
| Sphincter weakness                           | 1 (1.1)     |
| CSF protein (%)                               | 65          |
| Elevated                                      | 57 (87.7)   |
| Normal                                        | 8 (12.3)    |
| Ganglioside antibody (%)                      | 28          |
| Positive                                      | 5 (17.9)    |
| Negative                                      | 23 (82.1)   |
| GBS subtype (%)                               | 88          |
| AIDP                                          | 38 (43.2)   |
| AMAN                                          | 4 (4.5)     |
| AMSAN                                         | 9 (10.2)    |
| BFP                                           | 14 (15.9)   |
| Paraparetic                                   | 4 (4.5)     |
| MFS-GBS overlap syndrome                      | 2 (2.2)     |
| Pure motor                                    | 1 (1.1)     |
| Pure sensory                                  | 2 (2.3)     |
| Unspecified classic sensory-motor             | 11 (12.5)   |
| Miller Fisher Syndrome                        | 3 (3.4)     |
| Treatment (%)                                 | 88          |
| IVIg                                          | 61 (69.3)   |
| Glucocorticoids                               | 6 (6.8)     |
| Plasmapheresis                                | 12 (13.6)   |
| Conservative                                  | 3 (3.4)     |
| Intubation (%)                                | 67          |
| Yes                                           | 17 (25.4)   |
| No                                            | 50 (74.6)   |
| Outcome (%)                                   | 73          |
| Favorable                                     | 46 (63)     |
| Partial improvement                           | 16 (21.9)   |
| Poor                                          | 10 (13.7)   |
| Death                                         | 1 (1.4)     |
| Brighton collaboration level (%)               | 88          |
| 1                                             | 41 (46.6)   |
| 2                                             | 24 (27.3)   |
| 3                                             | 4 (4.5)     |
| 4                                             | 19 (21.6)   |

*CSF*, cerebrospinal fluid; *GBS*, Guillain–Barre syndrome; *AIDP*, acute inflammatory demyelinating polyradiculopathy; *AMAN*, acute motor axonal neuropathy; *AMSAN*, acute motor-sensory axonal neuropathy; *BFP*, bifacial weakness with paresthesia; *MFS*, Miller Fisher syndrome; *IVIg*, intravenous immune globulin
COVID-19 certainly outweigh the potential risk of GBS with a prognosis that proved to be favorable in the majority of cases.

**Author contribution** All authors contributed to the study conception and design. Material preparation, data extraction, and assessment were performed by Meysam Abolmaali, Arman Karimi Behnagh, and Negin Mahmoudi Hamidabad. The first draft of the manuscript was written equally by Zahra Mirzaasgari, Meysam Abolmaali, Arman Karimi Behnagh, and Negin Mahmoudi Hamidabad and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

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