



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



No significant increase in Guillain-Barré syndrome after COVID-19 vaccination in adults: A vaccine adverse event reporting system study



M. Jaffry^a, F. Mostafa^b, K. Mandava^a, S. Rosario^c, Y. Jagarlamudi^d, K. Jaffry^a, J. Kornitzer^{a,e}, K. Jedidi^c, H. Khan^f, N. Souayah^{a,*}

^a Department of Neurology, Rutgers New Jersey Medical School, Newark, NJ, USA

^b Department of Mathematics and Statistics, Texas Tech University, Lubbock, TX, USA

^c Department of Marketing, Columbia Business School, New York City, NY, USA

^d Khoury College of Computer Science, Northeastern University, Boston, MA, USA

^e New Jersey Pediatric Neuroscience Institute, Morristown, NJ, USA

^f Department of Public Health, Texas Tech University Health Sciences Center, Lubbock, TX, USA

ARTICLE INFO

Article history:

Received 2 July 2022

Received in revised form 5 August 2022

Accepted 8 August 2022

Available online 22 August 2022

Keywords:

Guillain Barre syndrome

SARS-CoV-2

Machine learning

COVID-19 vaccination

Vaccine adverse events

ABSTRACT

Objective: To investigate the association between Guillain-Barré syndrome (GBS) and COVID-19 vaccination.

Background: On July 13, 2021, the US Food and Drug Administration (FDA) released a new warning that Johnson & Johnson COVID-19 vaccine could increase the risk of developing GBS.

Methods: The reporting rate of adult GBS after COVID-19 vaccination, ascertained with Brighton criteria, was compared with the reporting rate after other vaccinations during the same time period, and also compared with the reporting rate during control periods. Statistical methods such as proportion tests, and Pearson's chi-squared test were utilized to identify significant relationships. Self-controlled and case centered analyses were conducted. A machine learning model was utilized to identify the factors associated with a worse outcome defined as emergency room (ER) or doctor visits, hospitalizations, and deaths. **Results:** The reporting rate of GBS after COVID-19 vaccination was significantly higher than after influenza and other vaccinations (49.7, 0.19, 0.16 per 10 million, $p < 0.0001$). However, the reporting rate was within the incidence range of GBS in the general population. Using self-controlled and case centered analyses, there was a significant difference in the reporting rate of GBS after COVID-19 vaccination between the risk period and control period ($p < 0.0001$). There was an estimated 0.7–1.7 per million excess reports of GBS within 6 weeks of COVID-19 vaccination. Machine learning model demonstrated that female gender and age between 18 and 44 are associated with worse outcome. No association was found between the onset interval of GBS and its prognosis.

Conclusions: Although the reporting rate of GBS after COVID-19 vaccination was not statistically different than that of the general population, the increased reporting of GBS within the first 6 weeks after COVID-19 vaccination, more so than with other vaccinations, suggests that some cases of GBS are temporally associated with COVID-19 vaccination. However, there is a reduction in the reporting rate of GBS after other vaccines, compared to reporting rates pre-COVID-19, highlighting limitations inherent in any passive surveillance system. These findings warrant continuous analysis of GBS after COVID-19 vaccination. Further improvement of the machine learning model is needed for clinical use.

© 2022 Elsevier Ltd. All rights reserved.

1. Introduction

On July 13, 2021, the US Food and Drug Administration (FDA) announced that due to preliminary reports in the Vaccine Adverse

Event Reporting System (VAERS) data, the Johnson & Johnson COVID-19 vaccine could increase the risk of developing Guillain Barre Syndrome (GBS) [1]. At that time, about 100 preliminary reports of GBS had been detected after 12.8 million doses of J&J's COVID-19 vaccine. This FDA warning could fuel vaccine hesitancy which remains one of the largest barriers to administration in the United States. Thus, it is of great important to elucidate cause-effect associations, side effects, and adverse events related

* Corresponding author at: Department of Neurology, New Jersey Medical School, 90 Bergen Street DOC 8100, Newark NJ 07101, USA.

E-mail address: souayani@njms.rutgers.edu (N. Souayah).

to the COVID-19 vaccine [2]. We conducted this study using VAERS data to investigate whether there is sufficient evidence to determine an association between GBS and COVID-19 vaccinations. We also sought to identify patient variables that may be more likely to result in a worse outcome of GBS within these cases, using a machine learning model.

2. Methods

VAERS data on all reports filed under the symptom “Guillain-Barre Syndrome” from all vaccinations were collected from the publicly available VAERS website and divided into three main periods. The Brighton criteria was used to determine high and low diagnostic probability of GBS [3]. The Brighton criteria is graded on a level ranging from 4, the lowest diagnostic certainty to 1, and the highest. Level 4 is given when there is no alternative diagnosis available to explain weakness and one other finding related to GBS. These include a diminished or absent deep tendon reflex, monophasic time course, bilateral and flaccid weakness of limb, CSF cell count <50 cell/μL, CSF protein concentration greater than normal and nerve conduction studies suggestive of GBS. Level 3 includes the history and physical examination findings previously listed and no alternative diagnosis. Level 2 includes everything in level 3 in addition to nerve conduction studies. Level 4 include cases that are reported as GBS but do not include any of the above diagnostic information and do not meet any of the above levels. Level 1 includes every finding and adds CSF results. Cases were graded based on information given in the “Write-Up” and “Diagnostic Lab Data” section in the VAERS database. All GBS cases were graded and cases with levels 1–3 were included in the first analysis, with all statistics computed again including cases of level 4. The first period, considered to be the control period as it was before the beginning of the COVID-19 pandemic and all COVID-19 vaccinations, was all reported cases between January 1st, 2019, to November 31st, 2019. The next period was the COVID-19 pandemic period, before the administration of any COVID-19 vaccines: January 1st, 2020, to November 31st, 2020. The third period was the COVID-19 vaccination period: December 1st, 2020, to the end of the data collection period, which was October 31st, 2021. All demographic, nominal and descriptive data were collected for all reports of GBS. The reporting rate of GBS after COVID-19 vaccinations was compared to the reporting rate of GBS after influenza vaccinations and compared to the reporting rate of GBS after all other vaccinations. Adapted from Greene et al. 2012, self-controlled analysis and case centered analysis were used [4]. Self-controlled risk interval analysis compared GBS onset in the defined risk period, 3 days–6 weeks after vaccine administration to the control period which was 11–16 weeks after vaccination. 7–10 weeks was defined as a washout period. Case centered analysis was used to adjust for any independent variables that may affect both vaccination and GBS. The number of vaccine administrations that were between 3 days and 6 weeks before the onset of GBS was compared to those administrations that were 7–12 weeks before the onset. In this analysis, the null hypothesis was an equivalent computed risk in the risk period compared to the control period. A 6-week period was chosen due to prior studies, on the association with GBS and the influenza vaccine, demonstrating that most cases occurred within this interval [5]. Multiple proportion test was used to compare the reporting rates.

Machine learning, using a decision tree algorithm, was used to predict endpoints of the cases. These endpoints include emergency room (ER) and doctor visits, hospitalization, and death. These case characteristics are all reported within VAERS. A random forest classifier model was used to remedy any overfitting of data. For the 3 random forest models, the parameter of 100 decision trees was set.

Feature importance from the random forest model was placed on a scale from 0.0 to 1.0, with a higher value correlating to a higher impact on the prediction model. The feature importance classification for the model predicting death was conducted. A confusion matrix was constructed for endpoints of interest, noted earlier. Confusion matrices illustrate the results of the trained machine learning model on test data and used to test the accuracy of the machine learning model. In this case, the reports of GBS after COVID-19 vaccination in the vaccine time period was split into 80:20 where 80 % of the data was used to train the prediction model and 20 % was used to test. Accuracy of the model was obtained using the formula, Accuracy = (True Positive + True Negative)/(True Positive + True Negative + False Positive + False Negative). Due to the fact that classification accuracy alone can be misleading if there are an unequal number of observations in each class, confusion matrices were chosen to better illustrate the performance of the model. On the y axis of the matrix, 0 and 1 are the true characteristics of the patient, 0 being they did not have the endpoint and 1 being they did. The x-axis of the matrix is the output prediction of the machine learning model, 0 for prediction of not having the endpoint and 1 for prediction of having the endpoint. (0,1) is a false negative, (0,0) is a true negative, (1,1) is a true positive, (1,0) is a false positive.

Statistical methods such as multiple proportion test, and Pearson’s chi-squared test were used to compare the mean age of patients, the reporting rates, and relative risk or risk difference with its corresponding confidence intervals. Alpha level ($\alpha = 0.05$) was used to determine statistical significance.

3. Results

During the COVID-19 vaccination time period, VAERS reported a total of 1,310 cases of GBS, among those, 1,019 cases fulfilled the Brighton criteria level of 1–3. The mean age of patients was not significantly different from the vaccine period, when compared to the pre-pandemic and pre-vaccine time periods (52.6 ± 17.7 years vs 51.62 ± 24.9 years vs 55.8 ± 23.2 years, $p > 0.05$) respectively. In the vaccine period, 49.6 % were female, 49.2 % were male, and gender was unknown for 1.2 % of patients. In the vaccine period, for cases of GBS after COVID-19 vaccination, 10 % patients were reported to have acute illness symptoms such as cough, fever, diarrhea, congestion, or rhinorrhea that immediately preceded or were concurrent with the reported GBS symptoms and 1 % of patients reported these acute illness symptoms before vaccination. (1.2 %) 12 cases reported confirmed campylobacter, mycoplasma or active CMV, HIV or herpes zoster infection. No patients who developed GBS after influenza or all other vaccinations reported infectious

Table 1
The reporting rate of COVID-19, influenza, and all other vaccinations during the vaccine time period defined as December 1st, 2020, to October 31st, 2021. There were more reports of life-threatening events, hospitalizations, permanent disabilities, and deaths that resulted from COVID-19 vaccinations than both influenza and all other vaccinations in the COVID-19 vaccination period. Percentage is the number of cases with that endpoint over the total number of cases of GBS after that vaccination type. * denotes significance at $p < 0.0001$

	COVID-19 vaccinations	Influenza vaccinations	All other vaccinations
Reporting Rate per 1 million	4.97*	0.02	0.02
Emergency Room or Doctor Visits	299 (29 %)	0	3 (75 %)
Death	16 (1.6 %)	0	0
Hospitalizations:	747 (73 %)	1 (33 %)	3 (25 %)
Average Length of Stay if Hospitalized (days)	12	Unknown	10

symptoms or had a confirmed identified causative organism. The reporting rate of GBS after COVID-19 vaccination was 4.97 per 1 million, which is in the range expected in the general population (Table 1). 88 and 62 cases of GBS were reported in the pre-pandemic and pre-vaccine time periods. The reporting rate of GBS after influenza vaccination was also significantly different during the studied 3 time periods (0.25 vs 0.21 vs 0.02 per 1 million, $p < 0.0001$) for the pre-pandemic, pre-vaccine, and vaccine period respectively and was the lowest during the vaccine time period despite an approximately 10 % increase in the total number of doses administered of the influenza vaccination from the 2019–2020 season to the 2020–2021 season [6]. The reporting rate of GBS after other vaccines (0.17 vs 0.09 vs 0.02 per 1 million, $p < 0.0001$) for the pre-pandemic, pre-vaccine, and vaccine time period was also significantly different during the studied 3 time periods and was the lowest during the vaccine time period. This was paralleled by no significant decrease in rate of administered doses of vaccines analyzed [7]. When the cases were divided based on manufacturer of the COVID-19 vaccine, Johnson and Johnson had a significantly higher rate than either Pfizer/BioNTech or Moderna. The reporting rates were 11.51 vs 1.23 vs 2.55 per million for the Johnson and Johnson, Moderna, and Pfizer/BioNTech manufacturers respectively. Based on VAERS data, the reporting rate of non-GBS adverse events after COVID-19 vaccination was significantly higher compared to non-GBS events after influenza vaccines and all other vaccines during the vaccine time period (4100 vs 30 vs 100 per 1 million $p < 0.0001$) respectively. When onset intervals of the adverse event were available, their patterns in GBS and non-GBS events after COVID-19 vaccination were different: the median onset interval of GBS was 10 days and is longer than the median onset interval of non-GBS events, which was 1 day. 73.8 % of non-GBS events and only 43 % of GBS cases were reported within the first week after COVID-19 vaccination (Fig. 1). In the COVID-19 vaccine period, disregarding cases that began earlier than 3 days after vaccination, GBS occurred within six weeks of vaccination in 87 % of cases. The distribution of reported GBS cases within the first six weeks was imbalanced with 53 % occurring in the first 2 weeks: 25 % was reported in the first week, 28 % in the second week. 21 % of cases occurred between the third and sixth weeks of vaccination and 13 % after six weeks of vaccination. The likelihood of observing a distribution over six weeks with at least this degree of imbalance by chance alone is low ($p < 0.0001$).

There were 1,012 cases of GBS after COVID-19 vaccination, 3 cases after Influenza vaccination and 4 cases after all other vaccinations during the COVID-19 vaccination time period. The reporting rate of GBS after COVID-19 vaccination was significantly higher compared to GBS after influenza vaccination and all other vaccinations respectively. The reporting rate of GBS with 6 weeks after vaccination was significantly higher than the incidence of GBS in general population. The CDC estimates an incidence of GBS equivalent to 10–20 per 1 million people per year [8]. This is in agreement with previously published data that was calculated using widely accepted definitions of GBS, including the Brighton criteria as well as the National Institute of Neurological and Communicative Disorders and Stroke definition and others [9]. Between Brighton criteria level 1 and 3 and other definitions, case identification is comparable. We estimate 0.7 (95 % CI 0.62–0.80) per 1 million vaccinated to 1.7 (95 % CI 1.60–1.89) per 1 million vaccinated excess GBS reports vaccinated within 6 weeks after COVID-19 vaccination.

The self-controlled analysis demonstrated a greater relative risk within the risk period when compared to the control period. This showed a significant increase in cases in the risk period vs control period, 64 % vs 2 % respectively ($p < 0.0001$) (Fig. 2A). Similar results were observed with case centered analysis (Fig. 2B). It demonstrated significant increase in reporting rate of GBS in the risk time period (defined as the 6 weeks preceding the occurrence of GBS) compared to the control time period (7–12 weeks preceding the occurrence of GBS): 64 % vs 7 %, respectively ($p < 0.0001$).

A machine learning model using the random forest algorithm was created to compare and predict characteristics in the endpoints of the reported cases of GBS after COVID-19 vaccination. Patients who visited an ER or had a doctor visit, were hospitalized, or died were defined as having worse outcome and were compared to patients who did not (Fig. 3). The differences in patient characteristics were analyzed and the most important variables explaining the model were identified in a feature importance graph (Fig. 4).

The rates of the endpoints, including ER or doctor visits, hospitalizations and death were calculated for cases of GBS after COVID-19 vaccination with an onset interval within 6 weeks, and cases with an onset after 6 weeks. No significant difference was found between the two groups. The probability of these endpoints occurring was calculated using a logistic function and there was also no

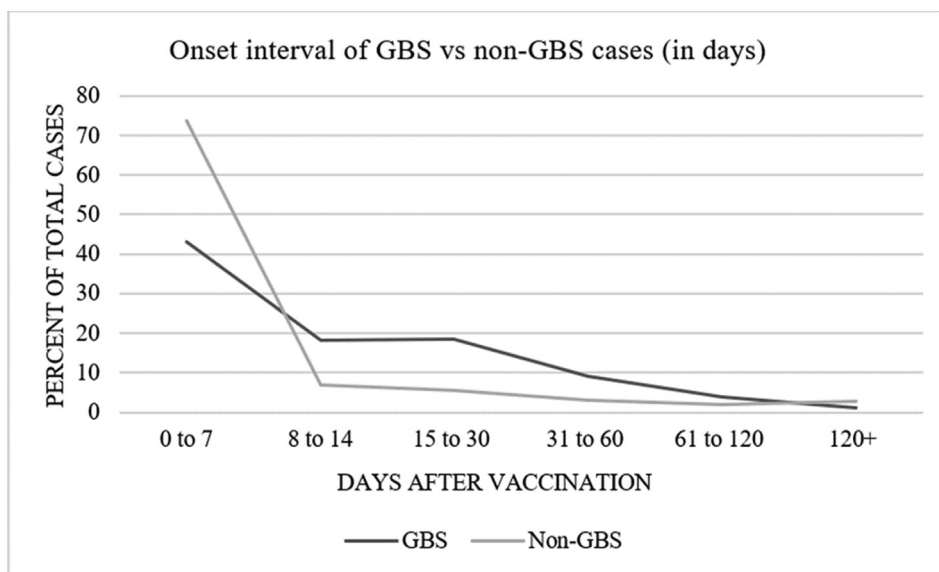


Fig. 1. Onset interval of GBS and non GBS events after COVID vaccination.

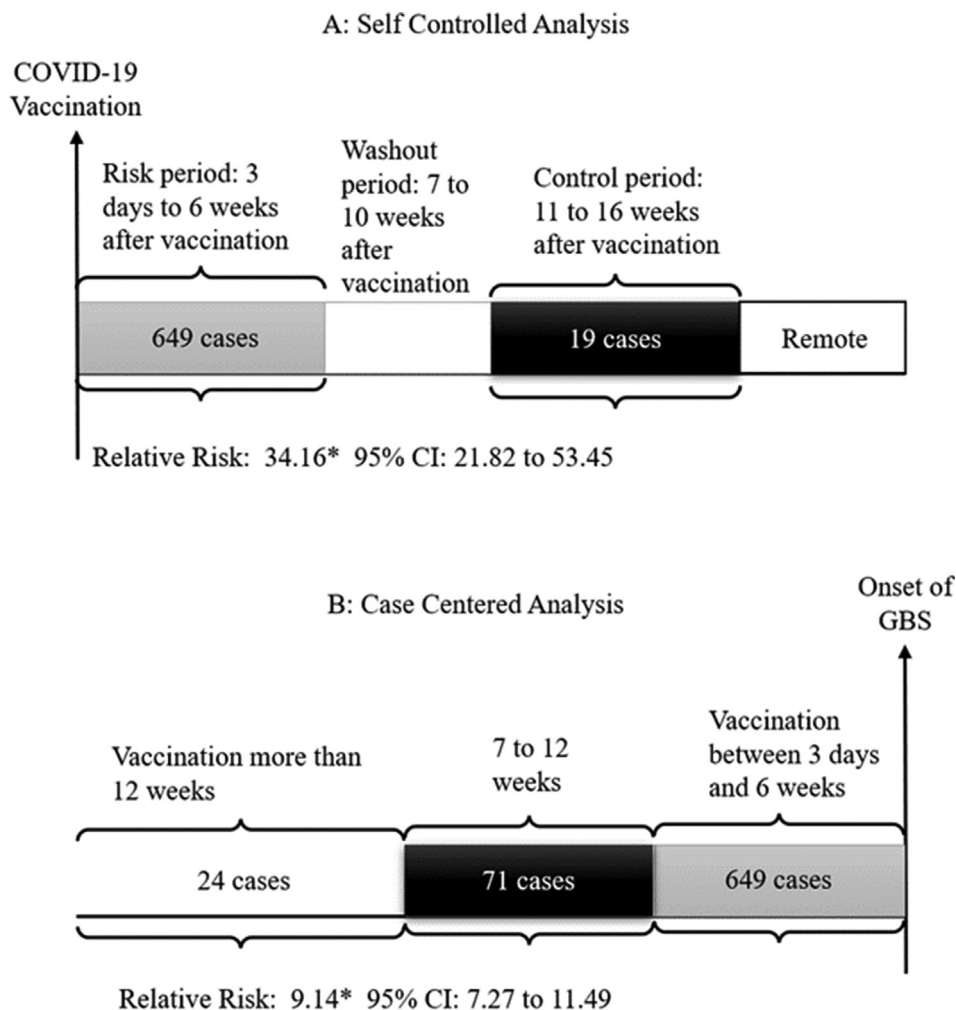


Fig. 2. Panel A: Using the self-controlled analysis, there was a significant difference in the reporting rate of GBS after COVID-19 vaccination between the risk period, which was 3 days–6 weeks and control period, which was 7 weeks to 10 weeks, $p < 0.0001$. The relative risk demonstrates that cases are 34.16 times more likely to occur 6 weeks after vaccination than the control period which was 11–16 weeks after vaccinations. Panel B: In case centered analysis the relative risk demonstrates vaccination was more likely to occur 9.14 times in the 3 days to 6-week period than the 7-to-12-week period.

significant difference found between cases with an onset within 6 weeks and an onset after. Similar results were obtained with onset interval before and after 10 weeks. However, hospitalization was 60 % more likely in cases with an onset greater than 12 weeks, with no significant difference in death. The likelihood of being hospitalized was increased by 19 % with a reported comorbid condition of coronary artery disease and unchanged with other conditions, including diabetes mellitus, hypertension, and pulmonary chronic diseases. For the random forest model scale for death as end point, age, gender, ER or doctor visit, hospitalization, recovery, permanent disability, and days after vaccination were analyzed. The most important

variables to predict death were age, gender, ER or doctor visit (Fig. 4). Age was stratified as 18–44, 45–64 and 65+. Females aged 18–44 were more likely to visit a doctor or ER and were more likely to be hospitalized.

4. Discussion

There is no significant increase of the reporting rate of GBS after COVID-19 vaccination in the vaccine time period studied: December 1st, 2020, to October 31st, 2021, compared to the historical incidence of GBS in the general population. The latter incidence in the UK has fallen during the COVID-19 pandemic [10]. Similar

findings were observed with vaccines other than COVID-19 vaccines, where a significant reduction of reporting rate of GBS after the vaccine was observed during the pandemic and vaccination periods compared to the pre-pandemic period. This could be related to the measures implemented to reduce the transmission of COVID-19 infection: social distancing, hand washing, mask wearing, and lockdown measures caused a reduction in COVID-19 transmission that was paralleled by a prevention of the transmission of pathogens that may trigger GBS such as upper respiratory and gastrointestinal infection pathogens [11]. This may reduce the incidence of an overlooked triggering factor of GBS other than vaccination.

In our study, several lines of evidence suggest that in some cases, the association between GBS and COVID-19 vaccination is not entirely coincidental. Firstly, the increased reporting rate of GBS within the first 6 weeks after vaccination. 64 % of cases were reported after 6 weeks of COVID-19 vaccination. Self-controlled and case centered analyses confirmed a greater relative risk of GBS within the risk period compared to control period. Similar results were observed in several studies that suspected or established an association between some cases of GBS and vaccination [12–20]. Secondly, the unbalanced distribution of reporting rate of GBS during the first 6 weeks after vaccination, with 53 % of cases reported in the first 2 weeks. We computed a very low likelihood

Confusion Matrices of Endpoints

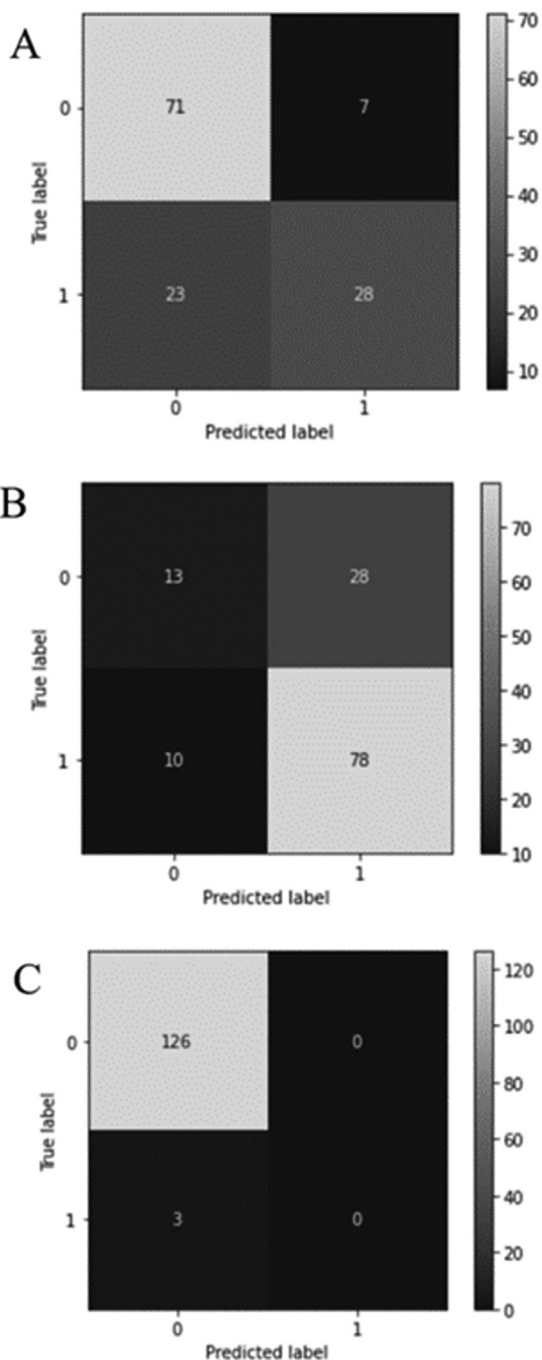


Fig. 3. Using this matrix, we classify the results of the predictive model. Panel A represents the ER or Doctor visit model, with a computed accuracy of 76.74%. Panel B is hospitalizations, with a computed accuracy of 70.54%. Panel C is death, with an accuracy of 97.67%. As can be seen in panel A, the model was able to accurately predict which cases would not result in an ER or doctor visit (sensitivity). But lower accuracy in cases that resulted in a visit (specificity). The same result was true for death, panel C, as an endpoint. For hospitalization, the model predicted with a high specificity for cases that would result in hospitalization, but a lower sensitivity, in identifying cases that did not result in hospitalization.

that this distribution occurred by chance alone. The peak occurrence of GBS was observed in the second week after vaccination and was followed by a decline to a value close to the incidence of GBS in the general population in the third to sixth weeks. The

greatest relative risk of GBS onset after a respiratory infection, a potential triggering factor, has also been reported in the first 2 weeks after infection [21]. Third, the median onset interval of GBS is 10 days and is different from non-GBS events which is 1 day. This protracted onset interval could conceivably be explained by the onset time of production of antibodies and the time when autoimmunity could occur. Additionally, the low reporting rate of triggering acute illnesses preceding GBS in COVID-19 vaccinated patients, which according to the reports seemed to be at least 10 % of the cases. This reporting rate is close to the prevalence on acute illness in Swine Flu related GBS investigations: acute illnesses preceded GBS in 33 % of vaccinated patients compared to 66 % in non-vaccinated cases [16]. These findings suggest that the vaccine may have replaced acute illness as a triggering factor of some cases of GBS. [14,16].

The low reporting rate of triggering acute illnesses and unbalanced distribution of GBS within the first 6 weeks in COVID-19 vaccinated patients suggest that some cases of GBS are temporally associated with COVID-19 vaccination, although no establishment of causation can be made. Molecular mimicry or other immune stimulation mechanisms may play a role in mediating GBS after vaccinations. Previous literature has also linked GBS to influenza vaccinations [22] and the Gardasil human papilloma virus vaccination [12]. Case reports and series have already observed associations between GBS and COVID-19 vaccinations [23–26]. The antigenicity of vaccine could trigger GBS in predisposed individuals [12].

The machine learning aspect of this study successfully predicted hospitalizations and ER, or doctor visits and death with an accuracy of more than 70 % (Fig. 3). No association between hospitalization, ER visits, doctor visits, and death with onset interval of GBS after vaccination was found, suggesting that the association between GBS and COVID-19 vaccination is incidental or did not cause an increase of morbidity and mortality of GBS. Furthermore, we observed hospitalization was 60 % more likely in cases with an onset greater than 12 weeks after vaccination and the likelihood for hospitalization increased by 19 % in patients with coronary artery disease supporting that the outcome of GBS depends on comorbid conditions rather than COVID-19 vaccination. Age, gender, ER and doctor visits are the most important predictors of death and women aged 18–44 years were more likely to be hospitalized. Similar results were reported by Almufty et al who investigated adverse effects of COVID-19 vaccines among the Iraqi population. They identified comorbidity, younger people, and female among the risk factors for side-effects of COVID-19 vaccination [27]. Younger adults and female gender were reported by several studies to more likely develop adverse reactions from COVID-19 vaccination [28–31]. Although a more intense immune reaction to COVID-19 vaccination in young subjects and women compared to older subjects and men respectively have been proposed as an explanation, other factors including genetic predisposition, hormonal factors, gender-related reporting bias, comorbidities, and prior COVID-19 infection need to be investigated [27,31].

Our study demonstrated that the likelihood of being hospitalized, a potential marker of severe reaction, was increased with the presence of coronary artery disease and unchanged with other conditions, including diabetes mellitus, hypertension, and pulmonary chronic diseases, well-known risk factors of poor prognosis of COVID-19 infection [32–34]. This contrast was observed with bronchial asthma, hypertension, and diabetes as comorbid conditions and risk factors of adverse reactions of vaccination by other authors [35]. Larger studies using active surveillance rather than passive surveillance are needed to clarify the association of comorbid conditions with COVID-19 vaccination adverse reactions.

The COVID-19 pandemic is currently the largest public health crisis of the last century, and one of the most important ways of

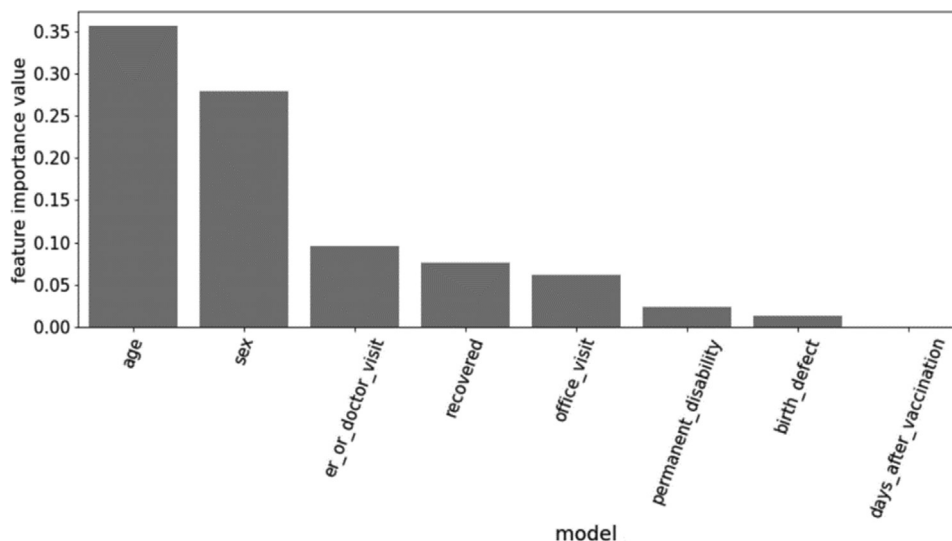


Fig. 4. This graph demonstrates the importance of each variable of the case of GBS and the percentage of the variance of the data that can be explained by each one. A higher value means that the feature has a higher impact on the model predicting a death. This indicates the percentage of importance in the classification model. As shown in this graph, the most important feature of the case, was the patient's age, which explains 35% of the prediction. Every feature used to train the random forest model is given a value on this scale. The most important variables were age, gender, and presence of an ER or doctor visit to predict death, with the cumulative sum of these explaining approximately 75% of the data.

combatting this has been administration of the COVID-19 vaccine. Concerns regarding GBS following COVID-19 vaccination may lead to underutilization of the vaccine and increased hesitancy, possibly prolonging the pandemic. With the most common reasons being concerns for safety and side effects, concerns of a rushed process, and lack of trust in vaccine efficacy [36,37]. In our study, although there is an increased reporting rate of GBS within the first 6 weeks after vaccination, it did not exceed 1.7(95 % CI 1.60–1.89) extra GBS reports per 1 million subjects vaccinated. Similar results were observed by Frontera et al. who reported <1 GBS case per 1,000,000 vaccine doses [11]. They demonstrated that the ratio of observed GBS rate reported after COVID-19 vaccination to expected GBS rate during the acute phase of SARS-CoV-2 infection was 0.004 and that the chances of having a neurological event after acute SARS-CoV-2 infection were 617 times higher than that of after COVID-19 vaccination [11]. These findings support the fact that the risk of GBS after COVID-19 vaccination is insignificant compared to the risk of GBS and other neurological complications after SARS-CoV-2 infection.

This study has the limitation of being based solely on VAERS data. VAERS is a passive surveillance system which relies on healthcare professionals, patients, and their caregivers to report unusual or unanticipated events that occur after administration of a vaccine. VAERS strengths include prompt reporting of events, which can increase the speed and processing of vaccine safety issues, public availability, and the ability to have detailed reports on what exactly occurred. Due to the inherent nature of passive surveillance systems, VAERS also has a number of limitations which include under-reporting, over-reporting, differential reporting, lack of background incidence as well as control groups, stimulated reporting which can occur after large media responses, and lack of validity of report [38]. Importantly, events that occurred closer to vaccine administration are more likely to be reported and reports to VAERS are not a sample of all events, and thus causation is usually not able to be assessed [39]. Furthermore, cases of GBS triggered by unreported or undiagnosed COVID-19 infection, other infections, autoimmunity, and other triggering factors cannot be excluded. The significant reduction of the reporting rate of GBS after influenza vaccination and other vaccinations during the COVID-19 pandemic time period without significant reduction in

the vaccinated rate illustrated the limitation of the VAERS database in establishing causation: assuming a cause-effect relationship between vaccines and GBS, no significant variation in GBS after vaccination is expected in such a short timeframe of the COVID-19 pandemic time period. The observed significant reduction of reporting rate of GBS could be related to reduction of other causes of GBS that are overlooked prior to the COVID-19 pandemic and masked by the temporal association with vaccination.

This study seeks to add to the body of knowledge surrounding the association between COVID-19 vaccination and GBS, so that healthcare providers may explain the risk/benefit ratio to patients to aid adherence to vaccination guidelines. These findings are in alignment with other studies supporting the safety and efficacy of COVID-19 vaccination. Our results warrant continuous and careful analysis of GBS after COVID-19 vaccination. Because of the lack of a case cohort control group in our study, further controlled and larger studies using active surveillance to further the association of GBS after COVID-19 vaccination and elucidate the role of comorbid conditions and identify the risk factors and prognosis of GBS after COVID-19 vaccination should be attempted.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Rosenblum HG et al. Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna): update from the Advisory Committee on Immunization Practices - United States, July 2021. *MMWR Morb Mortal Wkly Rep* 2021;70(32):1094–9.
- [2] Jaseem J et al. Guillain-Barre syndrome as a cause of acute flaccid paralysis in Iraqi children: a result of 15 years of nation-wide study. *BMC Neurol* 2013;13:195.

- [3] Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. *Brain* 2014;137(1):33–43.
- [4] Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, et al. Risk of confirmed Guillain-Barre syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009–2010. *Am J Epidemiol* 2012;175(11):1100–9.
- [5] Stratton K et al. Immunization safety review: influenza vaccines and neurological complications. Institute of Medicine (US) Immunization Safety Review Committee; 2004.
- [6] Kuehn BM. Influenza vaccination increased during the COVID-19 pandemic. *JAMA* 2021;326(24):2465. <https://doi.org/10.1001/jama.2021.22390>.
- [7] Hill HA, Yankey D, Elam-Evans LD, Singleton JA, Sterrett N. Vaccination coverage by age 24 months among children born in 2017 and 2018 - National Immunization Survey-Child, United States, 2018–2020. *MMWR Morb Mortal Wkly Rep* 2021;70(41):1435–40.
- [8] “GBS (Guillain-Barré Syndrome) and Vaccines.” Centers for Disease Control and Prevention, 25 Aug. 2021. Available from: <https://www.cdc.gov/vaccinesafety/concerns/guillain-barre-syndrome.html>.
- [9] Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 36, 123–33.
- [10] Keddie S et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barre syndrome. *Brain* 2021;144(2):682–93.
- [11] Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, et al. Coronavirus disease 2019 pandemic: impact caused by school closure and national lockdown on pediatric visits and admissions for viral and nonviral infections—a time series analysis. *Clin Infect Dis* 2021;72(2):319–22.
- [12] Souayah N et al. Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006–2009. *Vaccine* 2011;29(5):886–9.
- [13] Lasky T et al. The Guillain-Barre syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med* 1998;339(25):1797–802.
- [14] Haber P et al. Guillain-Barre syndrome following influenza vaccination. *JAMA* 2004;292(20):2478–81.
- [15] Schonberger LB et al. Guillain-Barre syndrome: its epidemiology and associations with influenza vaccination. *Ann Neurol* 1981;9(Suppl.):31–8.
- [16] Schonberger LB et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol* 1979;110(2):105–23.
- [17] Schonberger LB et al. Guillain-Barre syndrome after administration of killed vaccines. *Dev Biol Stand* 1977;39:295–6.
- [18] Souayah N et al. Guillain-Barre syndrome after H1N1 vaccination in the United States: a report using the CDC/FDA Vaccine Adverse Event Reporting System (2009). *Neuroepidemiology* 2012;38(4):227–32.
- [19] Souayah N et al. Guillain-Barre syndrome after influenza vaccination in the United States, a report from the CDC/FDA vaccine adverse event reporting system (1990–2009). *J Clin Neuromuscul Dis* 2012;14(2):66–71.
- [20] Souayah N, Nasar A, Suri MFK, Qureshi AI. Guillain-Barre syndrome after vaccination in United States a report from the CDC/FDA vaccine adverse event reporting system. *Vaccine* 2007;25(29):5253–5.
- [21] Winer JB, Hughes RA, Anderson MJ, Jones DM, Kangro H, Watkins RP. A prospective study of acute idiopathic neuropathy. II. Antecedent events. *J Neurol Neurosurg Psychiatry* 1988;51(5):613–8.
- [22] Sanz Fadrigue R et al. Guillain-Barre syndrome and influenza vaccines: current evidence. *Rev Esp Quimioter* 2019;32(4):288–95.
- [23] Oo WM, Giri P, de Souza A. AstraZeneca COVID-19 vaccine and Guillain-Barre syndrome in Tasmania: a causal link? *J Neuroimmunology* 2021;360:577719.
- [24] Rao SJ, Khurana S, Murthy G, Dawson ET, Jazebi N, Haas CJ. A case of Guillain-Barre syndrome following Pfizer COVID-19 vaccine. *J Commun Hosp Intern Med Perspect* 2021;11(5):597–600.
- [25] Marquez Loza AM et al. Guillain-Barre syndrome in the placebo and active arms of a COVID-19 vaccine clinical trial: temporal associations do not imply causality. *Neurology* 2021.
- [26] Finsterer J, Scorza FA, Scorza CA. Post SARS-CoV-2 vaccination Guillain-Barre syndrome in 19 patients. *Clinics (Sao Paulo)* 2021;76:e3286.
- [27] Almufty HB, Mohammed SA, Abdullah AM, Merza MA. Potential adverse effects of COVID19 vaccines among Iraqi population; a comparison between the three available vaccines in Iraq; a retrospective cross-sectional study. *Diabetes Metab Syndr* 2021;15(5):102207.
- [28] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397(10269):99–111.
- [29] Singhai A, Budhiraja A. Guillain-Barre syndrome following SARS-COVID-19 Infection: a case report from India. *Case Rep Infect Dis* 2021;2021:4676659.
- [30] Riad A, Pokorná A, Attia S, Klugarová J, Koščik M, Klugar M. Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech Republic. *J Clin Med* 2021;10(7):1428.
- [31] Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID symptom study app in the UK: a prospective observational study. *Lancet Infect Dis* 2021;21(7):939–49.
- [32] Lisco G, De Tullio A, Giagulli VA, Guastamacchia E, De Pergola G, Triggiani V. Hypothesized mechanisms explaining poor prognosis in type 2 diabetes patients with COVID-19: a review. *Endocrine* 2020;70(3):441–53.
- [33] Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: a systematic review. *Diabetes Metab Syndr* 2020;14(5):1133–42.
- [34] Parohan M, et al. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Aging Male* 2020:1–9.
- [35] Choi WS, Cheong HJ. COVID-19 vaccination for people with comorbidities. *Infect Chemother* 2021;53(1):155–8.
- [36] Khubchandani J, Sharma S, Price JH, Wiblishauser MJ, Sharma M, Webb FJ. COVID-19 vaccination hesitancy in the United States: a rapid national assessment. *J Commun Health* 2021;46(2):270–7.
- [37] Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. *Public Health* 2021;194:245–51.
- [38] Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the vaccine adverse event reporting system (VAERS). *Vaccine* 2015;33(36):4398–405.
- [39] Chen R, Rastogi S, Mullen J, Hayes S, Cochi S, Donlon J, et al. The vaccine adverse event reporting system (VAERS). *Vaccine* 1994;12(6):542–50.