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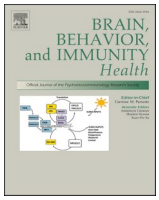

Examining vaccination-related adverse events in frequent neurodegenerative diseases

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ABSTRACT

This study investigates adverse events following vaccination in patients with four neurodegenerative diseases: Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease, Multiple Sclerosis (MS), and Parkinson's disease. We applied advanced data processing techniques to analyze symptom patterns and severity scores across these disease groups. Patients were identified through filtering, and symptom clusters were extracted to group similar symptoms into distinct clusters, and severity scores were computed based on hospitalization and death reports. A chi-squared test was performed to assess the statistical significance of adverse event distributions among the diseases for different vaccines. The results reveal that ALS patients exhibit severe respiratory symptoms post-vaccination, while Alzheimer's patients report significant respiratory and gastrointestinal issues. MS patients commonly experience general symptoms such as fatigue, while Parkinson's patients face exacerbated motor symptoms. Notably, our analysis showed no significant difference in adverse event reporting rates between COVID-19 and pneumococcal vaccines across these disease groups. This research provides new insights into disease-specific responses to vaccines, emphasizing the importance of personalized monitoring and treatment strategies to mitigate risks and improve clinical outcomes in these vulnerable populations.

1. Introduction

Vaccination is a critical tool in preventing infectious diseases, but it is essential to monitor and understand the adverse events that can occur post-vaccination. Neurodegenerative diseases present unique challenges due to their progressive nature and the complexities involved in their management. Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's Disease, is characterized by the degeneration of motor neurons, leading to severe muscle weakness and respiratory failure (Brown and Al-Chalabi, 2017). Alzheimer's Disease, the most common cause of dementia, involves the gradual loss of cognitive function and memory (Querfurth and LaFerla, 2010). Multiple Sclerosis or MS is an autoimmune disorder that affects the central nervous system, leading to a wide range of neurological symptoms (Sturm et al., 2014). Parkinson's Disease is marked by motor symptoms such as tremors, rigidity, and bradykinesia, resulting from the degeneration of dopamine-producing neurons in the brain (Kalia and Lang, 2015).

This study focuses on the analysis of vaccine-related events in patients with ALS, Alzheimer's, MS, and Parkinson's for the whole years 2022, 2023, and from January to July 2024 in the US. Given the immunocompromised state often associated with these diseases, understanding how vaccines affect these patients is crucial. Previous studies have highlighted the importance of monitoring vaccine safety in vulnerable populations (Orenstein et al., 2022). In other words, the objective of this study is to investigate and compare the symptom clusters and severity scores associated with adverse events following vaccination in patients with MS, ALS, Alzheimer's disease, and Parkinson's disease, by leveraging vaccine adverse event reporting system data (Shimabukuro et al., 2015; Center for Disease Control and Prevention CDC, 2024). By understanding these patterns, clusters, and their severity this research aims to provide insights into disease-specific responses to vaccination. Advanced data analysis techniques are used to identify common and unique symptom patterns across these four diseases and quantify their severity, which can assist physicians in tailoring treatment strategies for vaccination in patients with neurodegenerative diseases, thus providing insights that can improve patient care and inform clinical practices. The findings aim to inform healthcare providers and policymakers, ultimately contributing to safer vaccination practices and improved health outcomes for these vulnerable populations.

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2. Materials and methods

The dataset used in this study was derived from the Vaccine Adverse Event Reporting System (VAERS) for the whole years 2022, 2023, and from January to July 2024 (Center for Disease Control and Prevention CDC, 2024). The temporal distribution and other features of vaccine-related adverse events was analyzed for each disease.

2.1. Data processing

2.1.1. Identification of patients

Patients with Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease, and Parkinson's Disease were identified by filtering the dataset using relevant keywords. The keywords included "Multiple Sclerosis", "MS", "Amyotrophic Lateral Sclerosis", "ALS", "Alzheimer's Disease", "Alzheimers", "AD", "Dementia", "Parkinson's Disease", "Parkinsonism", and "PD".

2.1.2. Extraction and grouping of symptoms

Symptoms were extracted from the dataset, which lists symptoms reported for each adverse event. Each patient's symptoms were aggregated across up to five symptom columns (SYMPTOM1 to SYMPTOM5) to ensure comprehensive symptom coverage.

2.1.3. Calculation of severity scores

Severity indicators were extracted, including whether the patient died, was disabled, was hospitalized, or visited the emergency room. Each severity indicator was assigned a weight: death (5), disability (4), hospitalization (3), and ER visit (2) and summed to calculate a severity score for each symptom report.

2.1.4. Symptom vectorization and clustering

Symptoms were vectorized using Term Frequency-Inverse Document Frequency (TF-IDF) vectorization (Sammut and Webb, 2011). This method converts the textual symptom data into numerical format, reflecting the importance of each symptom within the dataset. *K*-means clustering was applied to the vectorized symptoms to group similar symptoms into clusters. The number of clusters (k) was set to 5, based on the Elbow method and domain knowledge (Pan et al., 2007; Marutho et al., 2018).

To evaluate adverse event reporting rates among patients with MS, ALS, Parkinson's, and Alzheimer's disease, we conducted a statistical test with the objective to determine if there is a significant difference in the percentage of adverse events reported for different vaccine types among patients with MS, ALS, Parkinson's, and Alzheimer's disease. We use the chi-squared test for independence to evaluate this.

We define specific keywords that are used to identify records related to each disease. Using the defined keywords, we filter the adverse event records to identify those that mention any of the keywords related to MS, Parkinson's, ALS, and Alzheimer's Disease. We calculate the total number of patients who received each type of vaccine. This is necessary to determine the baseline number of vaccine recipients for comparison.

Next, we constructed a contingency table to compare the ratios of adverse events for different diseases and two vaccine types of COVID19 and Pneumococcal Vaccines (since these vaccines protect against pneumonia, meningitis, and other serious infections caused by pneumococcal bacteria, which can be more severe in patients with chronic neurological conditions). For each vaccine type, we calculated the proportion of patients who reported adverse events related to MS, Parkinson's disease, ALS, and Alzheimer's Disease. This involves dividing the number of adverse event reports for each disease by the total number of patients who received that vaccine type.

Additionally, we use the chi-squared test for independence to evaluate the contingency table. This statistical test assesses whether there is a significant association between vaccine type and the occurrence of adverse events for the three diseases.

3. Theory/calculation

The theoretical foundation for this study lies in the assumption that adverse events following vaccination can be clustered into meaningful symptom groups. The clustering process converts textual symptom data into numerical format (Grootendorst, 2022) using *K*-means clustering (Zhuang et al., 2023). This helps in identifying patterns and associations among symptoms that may not be evident through simple observation. This method allows for the identification of common symptom patterns within each disease group. The severity score calculation quantifies the impact of each symptom based on the presence of severe outcomes, providing a metric for comparing the relative severity of different symptom clusters.

4. Results

The summary of adverse events for MS, Parkinson's, Alzheimer, and ALS patients by vaccine type is shown in Table 1.

The table in Supplementary Data contains the abbreviations for vaccine types in Table 1.

We further analyze the demographics, such as age and sex. Fig. 1 shows the age distributions of patients with reported vaccine adverse events for the four neurodegenerative diseases under study.

Fig. 2 shows the gender distributions among ALS, Alzheimer's, MS, and Parkinson's patients affected by adverse events of vaccinations.

Additionally, Fig. 3 presents the severity of adverse events of vaccinations among ALS, Alzheimer's, MS, and Parkinson's disease patients in terms of hospitalization or death.

Temporal information in Fig. 4 includes days post-vaccination for adverse events in patients with four diseases under study. In most cases adverse events either appear in the first week post-vaccination or at least 42 days post-vaccination.

The analysis for ALS, Alzheimer', MS, and Parkinson's patients shows some cases in adverse events within the first few days post-vaccination, with a gradual decline over time until the 6th week. The patterns of adverse events are more or less similar for the four diseases.

The temporal analysis across the four diseases indicates a common trend of adverse events shortly after vaccination and then tapering off and then reaching a peak. This pattern suggests that close monitoring of patients post-vaccination is crucial. Further research is needed to understand the underlying mechanisms and to develop strategies to mitigate these adverse events.

Table 2 contains the frequencies of top symptoms of vaccination adverse events among ALS, Alzheimer's, MS, and Parkinson's disease patients. Our analysis showed that the majority of reported symptoms were linked to COVID-19 vaccines, which emerged as a dominant factor in the results.

Our data mining analytics indicate the following observations:

4.1. ALS patients

- The most frequently reported symptom among ALS patients post-vaccination is COVID-19, with a smaller number reporting muscular weakness and decreased appetite.
- There are also cases of acute respiratory failure, which, while not the most common, is significant given the vulnerability of ALS patients.
- Overall, the symptom profile for ALS patients is less diverse, with fewer instances of common post-vaccination symptoms like chills or fever.

4.2. Alzheimer's patients

- Alzheimer's patients predominantly reported COVID-19 as a symptom post-vaccination, with a significant number also experiencing asthenia and pyrexia.

Table 1
Summary of adverse events of various vaccine types administered for MS, Parkinson's, Alzheimer's, and ALS patients.

Vaccine	MS Adverse Events (1700)	Parkinson's Adverse Events (3122)	Alzheimer's Adverse Events (3930)	ALS Adverse Events (135)
COVID19	1365 (80.29%)	2314 (74.13%)	3254 (82.81%)	118 (87.41%)
COVID19-2	111 (6.53%)	241 (7.72%)	302 (7.69%)	8 (5.93%)
DT	1 (0.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
DTAP	6 (0.35%)	1 (0.03%)	2 (0.05%)	0 (0.00%)
DTAPHEPBIP	2 (0.12%)	2 (0.06%)	1 (0.03%)	0 (0.00%)
FLU3	1 (0.06%)	3 (0.10%)	1 (0.03%)	0 (0.00%)
FLU4	26 (1.53%)	77 (2.47%)	50 (1.27%)	2 (1.48%)
FLUA4	10 (0.59%)	54 (1.73%)	111 (2.83%)	1 (0.74%)
FLUC4	4 (0.24%)	12 (0.38%)	6 (0.15%)	0 (0.00%)
FLUX	15 (0.88%)	29 (0.93%)	17 (0.43%)	0 (0.00%)
HEP	6 (0.35%)	8 (0.26%)	0 (0.00%)	0 (0.00%)
HEPA	4 (0.24%)	5 (0.16%)	3 (0.08%)	0 (0.00%)
HEPAB	1 (0.06%)	0 (0.00%)	2 (0.05%)	0 (0.00%)
HIBV	1 (0.06%)	6 (0.19%)	2 (0.05%)	0 (0.00%)
HPV4	5 (0.29%)	17 (0.54%)	4 (0.10%)	0 (0.00%)
HPV9	2 (0.12%)	17 (0.54%)	11 (0.28%)	0 (0.00%)
HPVX	1 (0.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
IPV	1 (0.06%)	5 (0.16%)	1 (0.03%)	0 (0.00%)
MEN	2 (0.12%)	3 (0.10%)	0 (0.00%)	0 (0.00%)
MENB	2 (0.12%)	11 (0.35%)	2 (0.05%)	0 (0.00%)
MMR	4 (0.24%)	5 (0.16%)	2 (0.05%)	0 (0.00%)
MNQ	2 (0.12%)	11 (0.35%)	5 (0.13%)	0 (0.00%)
PNC	1 (0.06%)	3 (0.10%)	0 (0.00%)	0 (0.00%)
PNC13	3 (0.18%)	7 (0.22%)	0 (0.00%)	0 (0.00%)
PNC20	9 (0.53%)	20 (0.64%)	17 (0.43%)	0 (0.00%)
PPV	9 (0.53%)	8 (0.26%)	2 (0.05%)	0 (0.00%)
RAB	1 (0.06%)	3 (0.10%)	2 (0.05%)	0 (0.00%)
RSV	9 (0.53%)	30 (0.96%)	25 (0.64%)	0 (0.00%)
SMALL	1 (0.06%)	1 (0.03%)	1 (0.03%)	0 (0.00%)
TDAP	8 (0.47%)	20 (0.64%)	8 (0.20%)	0 (0.00%)
TTOX	2 (0.12%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
TYP	2 (0.12%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
UNK	27 (1.59%)	83 (2.66%)	45 (1.15%)	4 (2.96%)
VARCEL	2 (0.12%)	3 (0.10%)	0 (0.00%)	0 (0.00%)
VARZOS	52 (3.06%)	97 (3.11%)	38 (0.97%)	2 (1.48%)
YF	2 (0.12%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ANTH	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
DTAPIPV	0 (0.00%)	1 (0.03%)	1 (0.03%)	0 (0.00%)
DTAPIPVHIB	0 (0.00%)	2 (0.06%)	0 (0.00%)	0 (0.00%)
DTPPVHBHPB	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
FLUA3	0 (0.00%)	1 (0.03%)	1 (0.03%)	0 (0.00%)
FLUC3	0 (0.00%)	4 (0.13%)	2 (0.05%)	0 (0.00%)
FLUN4	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
FLUR3	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
FLUR4	0 (0.00%)	2 (0.06%)	0 (0.00%)	0 (0.00%)
FLUX(H1N1)	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
RV5	0 (0.00%)	4 (0.13%)	2 (0.05%)	0 (0.00%)
RVX	0 (0.00%)	3 (0.10%)	0 (0.00%)	0 (0.00%)
SMALLMNK	0 (0.00%)	4 (0.13%)	2 (0.05%)	0 (0.00%)
EBZR	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
MMRV	0 (0.00%)	0 (0.00%)	4 (0.10%)	0 (0.00%)
TD	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

- Acute respiratory failure and acute kidney injury are also notably reported, reflecting the general frailty and complex health challenges in this patient group.
- Death and mental status changes are additional critical symptoms, highlighting the severe impact of vaccination-related adverse events and possibly age in Alzheimer's patients, indicating some overlap with common elderly health issues.

4.3. MS patients

- The most common symptoms among MS patients post-vaccination are COVID-19 infection, asthenia, and arthralgia.
- Fatigue is also a notable symptom, aligning with the general experience of MS patients who often face chronic fatigue as part of their condition.
- There are specific instances of condition aggravation and multiple sclerosis relapses, suggesting a direct impact of vaccination on disease activity in MS patients.

4.4. Parkinson's patients

- Common symptoms reported by Parkinson's patients post-vaccination include tremor, chills, and asthenia, which align closely with the typical symptoms of Parkinson's disease.
- There is also a significant number of reports of fatigue and arthralgia, which may exacerbate the existing symptoms of Parkinson's disease.
- The occurrence of COVID-19 and related symptoms is prominent, with acute respiratory failure and pyrexia being reported, indicating the need for careful monitoring of these patients post-vaccination.

These findings indicate that ALS patients have a narrower symptom profile post-vaccination, primarily centered around COVID-19, while Alzheimer's patients report a broader range of severe symptoms, including acute respiratory and kidney issues. MS patients show a mix of COVID-19 related symptoms and specific disease-related aggravations, whereas Parkinson's patients experience symptoms that overlap with their pre-existing condition.

This variability underscores the importance of tailored medical attention and monitoring for different patient groups post-vaccination.

4.4.1. Comparative analysis of symptom clusters and severity in neurodegenerative and autoimmune diseases

Table 3 shows the clustering of symptom types among patients with the four diseases under study along with average severity score of symptoms. The severity score was calculated by multiplying the counts of death by 5, the counts of disabilities by 4, the counts of hospitalizations by 3, and the counts of emergency room visits by 2 and taking the average.

General Symptoms include fatigue, weakness, asthenia, and malaise, while Pain Symptoms include pain, arthralgia, myalgia, and headache. Moreover, Gastrointestinal Symptoms include nausea, vomiting, and diarrhea, while Neurological Symptoms are tremor, seizure, dizziness, insomnia, and confusion. Respiratory Symptoms include cough, shortness of breath, and dyspnea. Additionally, Skin Symptoms encompass rash, itching, swelling, and skin irritation, while Cardiovascular Symptoms include chest pain, palpitations, and hypertension. Also, fever, chills, and pyrexia are considered as Infection Symptoms.

Additionally, the results of the chi-square test conducted to compare the distribution of adverse events among patients with MS, Parkinson's disease, ALS, and Alzheimer's disease across different vaccine types, including COVID-19 (COVID19 and COVID19-2) and a combined group of Pneumococcal vaccines, indicate no statistically significant differences. The chi-square statistic was 0.00199 with a p-value of approximately 0.99, suggesting that the observed distribution of adverse events is consistent with what would be expected by chance alone. The degrees of freedom for the test contingency table were 6, and the expected frequencies closely matched the observed ratios across all conditions and vaccine types. The p-value indicates that the null hypothesis cannot be rejected, i.e., there is no significant difference in the percentage of adverse events reported for these vaccines among patients with MS, Parkinson's disease, ALS, and Alzheimer's disease. This finding suggests that the vaccines studied have a similar safety profile across these neurological conditions.

5. Discussion

The analysis of symptom clusters and severity scores reveals distinct patterns across neurological conditions, highlighting the unique

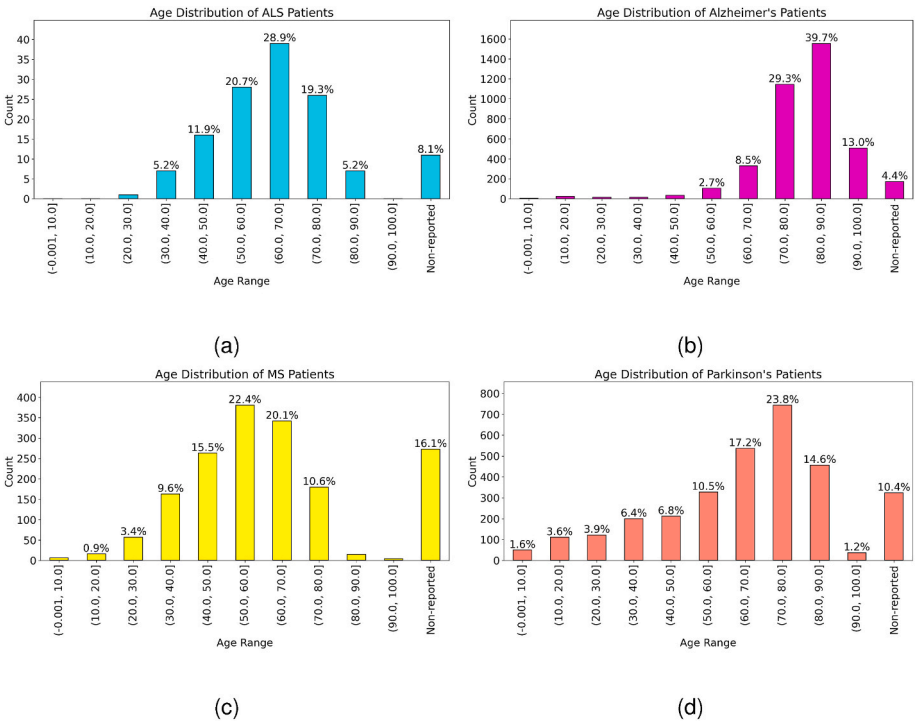

Fig. 1. Adverse events of vaccines affecting different age groups among (a) ALS, (b) Alzheimer's, (c) MS, and (d) Parkinson's disease patients.

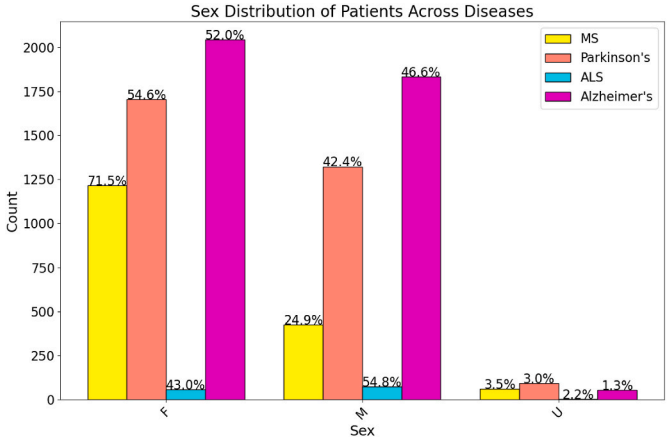

Fig. 2. Adverse events of vaccines affecting different genders of female (F), male (M), and unknown (U) among ALS, Alzheimer's, MS, and Parkinson's disease patients.

challenges faced by patients with MS, Alzheimer's disease, ALS, and Parkinson's disease following vaccination.

For MS patients, the most common symptom clusters include general symptoms such as fatigue, weakness, and asthenia, as well as respiratory symptoms like dyspnea and cough. Although the mean severity scores for MS patients are moderate, respiratory symptoms show a higher severity, indicating a need for careful monitoring of respiratory health in these patients post-vaccination. The presence of infection symptoms and cardiovascular symptoms, though less frequent, also presents a concern due to their potential impact on overall disease management.

Alzheimer's disease patients exhibit a broader range of symptoms, with respiratory, gastrointestinal, and neurological symptoms showing the highest severity scores. The prominence of severe respiratory symptoms underscores the vulnerability of Alzheimer's patients to complications from respiratory infections, particularly post-vaccination. The clustering of gastrointestinal and neurological symptoms further reflects the complex interplay of factors affecting these patients, necessitating comprehensive care that addresses both cognitive decline and physical health.

In ALS patients, the highest severity scores are observed in cardiovascular and neurological symptom clusters, with a severity score of 5.0, indicating critical issues in these areas. The significant severity of respiratory symptoms aligns with the progressive muscle degeneration characteristic of ALS, which often leads to life-threatening respiratory complications. These findings highlight the critical need for focused medical attention on respiratory and cardiovascular health in ALS patients, emphasizing the importance of personalized treatment strategies that address both the neurological and systemic aspects of the disease.

Parkinson's disease patients display a different pattern, with general and cardiovascular symptoms showing higher severity scores. The clustering of motor and movement issues, consistent with Parkinson's hallmark motor symptoms, suggests that these patients are particularly vulnerable to exacerbation of movement-related symptoms post-vaccination. While neurological symptoms have a lower severity score compared to other clusters, they remain a significant concern due to their potential to aggravate the underlying condition.

In other words, ALS patients require focused care on respiratory and cardiovascular health, while Alzheimer's patients need comprehensive management that addresses severe respiratory and gastrointestinal symptoms. MS and Parkinson's disease patients also show specific needs, with a focus on managing general and motor symptoms. This variability in symptomatology and severity highlights the necessity for personalized treatment strategies to improve patient outcomes and quality of life in these vulnerable populations.

The findings of this study contribute to the broader literature on vaccine safety and neurodegenerative diseases by highlighting the distinct adverse event profiles associated with various conditions. Previous research has indicated that neurodegenerative diseases like MS, ALS, Alzheimer's disease, and Parkinson's disease can influence immune responses to vaccinations, resulting in diverse adverse event patterns (Carvajal et al., 2024). This study aligns with existing literature by identifying disease-specific symptom clusters and severity scores, which underscores the need for tailored vaccine safety monitoring in these

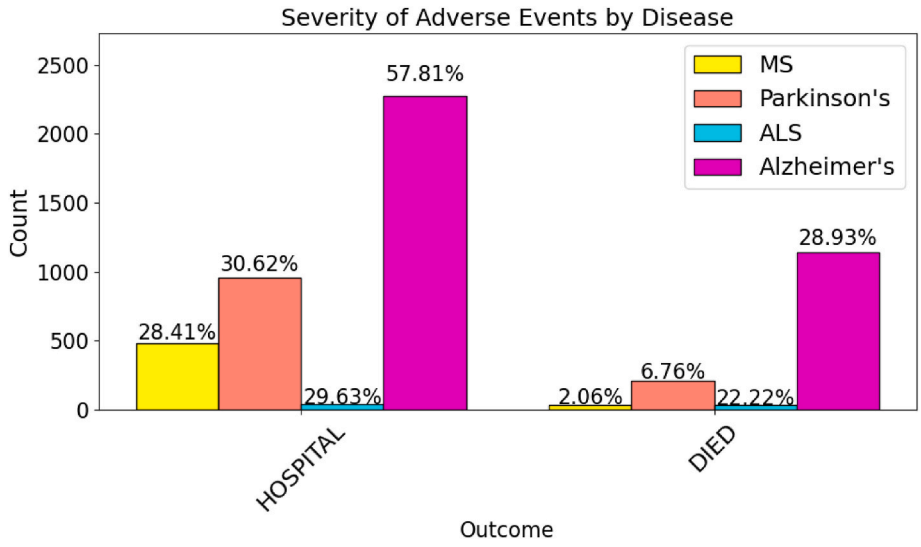

Fig. 3. Severity of adverse events (hospitalization or death) among ALS, Alzheimer's, MS, and Parkinson's disease patients.

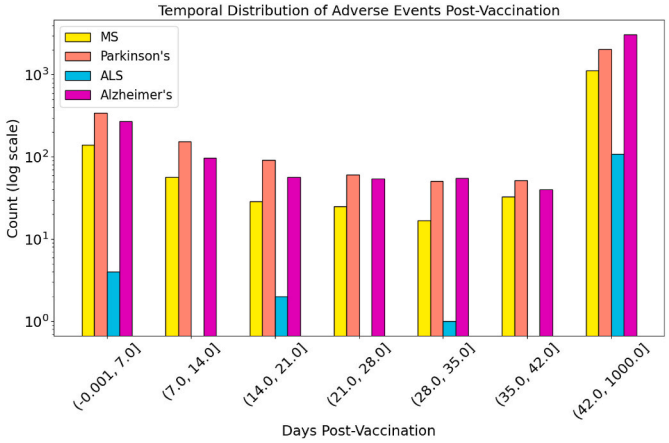

Fig. 4. Temporal distribution of adverse events in terms of days post-vaccination among ALS, Alzheimer's, MS, and Parkinson's disease patients in logarithmic scale.

populations. For instance, ALS patients in our study exhibited severe respiratory issues following vaccination, consistent with prior studies that highlight the critical vulnerability of respiratory function in ALS patients (Wijesekera and Leigh, 2009). Moreover, our findings show that MS patients experienced higher severity in respiratory symptoms, while Alzheimer's patients showed severe respiratory and gastrointestinal symptoms post-vaccination. Additionally, the higher symptom counts reported among females with MS and Parkinson's disease align with previously observed gender differences in immune responses and vaccine reactions (Klein et al., 2010; Fischinger et al., 2019) These results underscore the importance of considering individual patient characteristics, including underlying neurodegenerative conditions and gender, in vaccine safety assessments. Future research should continue exploring these interactions to enhance vaccine recommendations and mitigate adverse events in these vulnerable populations.

The statistical analysis revealed differences in the adverse event profiles and severity scores among patients with MS, ALS, Alzheimer's Disease, and Parkinson's Disease. ALS patients exhibited the highest likelihood of severe adverse events, which is consistent with the known progression of ALS. This finding underscores the need for heightened monitoring and possibly different vaccination strategies for ALS patients to mitigate these severe outcomes.

Table 2
Frequencies of top symptoms post-vaccination among ALS, Alzheimer's, MS, and Parkinson's patients.

Vaccine	SYMPTOM	MS Count	Alzheimer	Parkinson	ALS
COVID19	COVID-19	49.0%	42.7%	20.9%	22.0%
COVID19	Asthenia	13.0%	14.2%	16.3%	7.3%
COVID19	SARS-CoV-2 test positive	7.2%	11.8%	5.9%	0
COVID19	Fatigue	6.9%	0	7.8%	7.3%
COVID19	Multiple sclerosis	5.7%	0	0	0
COVID19	Condition aggravated	5.3%	0	0	0
COVID19	Arthralgia	5.0%	0	6.7%	0
COVID19	Chills	4.1%	0	8.2%	0
COVID19	Pyrexia	3.8%	2.7%	5.5%	0
COVID19	Acute respiratory failure	0	8.4%	4.9%	19.5%
COVID19	Acute kidney injury	0	7.4%	0	0
COVID19	Death	0	6.9%	0	0
COVID19	Dyspnoea	0	3.2%	0	0
COVID19	Mental status changes	0	2.8%	0	0
COVID19	Tremor	0	0	19.8%	0
COVID19	Anxiety	0	0	4.1%	0
COVID19	Muscular weakness	0	0	0	24.4%
COVID19	Decreased appetite	0	0	0	9.8%
COVID19-2	Amyotrophic lateral sclerosis	0	0	0	9.8%

Gender differences were noteworthy, with females showing a higher likelihood of severe adverse events compared to males across most diseases. This result aligns with previous research indicating that females often have stronger immune responses to vaccines, which can result in higher rates of adverse events (Klein et al., 2010). Understanding these gender-based differences is critical for developing tailored approaches to vaccination that minimize adverse events in females.

Age was another factor, with older patients being more susceptible to severe adverse events. This is particularly relevant given the increased vaccination rates in older populations and their heightened vulnerability to severe disease outcomes. The higher likelihood of severe adverse events associated with COVID-19 vaccines suggests that these vaccines might provoke stronger immune responses, particularly in older patients, necessitating careful monitoring and potentially adjusted dosing or follow-up schedules for high-risk groups.

Table 3
Symptom clusters and severity scores for various patients.

Disease Group	CLUSTER	PERCENT	MEAN SEVERITY SCORE
MS	Respiratory Symptoms	4.76%	2.948755
MS	Cardiovascular Symptoms	1.35%	1.875000
MS	Other	51.65%	1.841356
MS	General Symptoms	11.06%	1.672014
MS	Infection Symptoms	8.35%	1.616800
MS	Neurological Symptoms	3.65%	1.523810
MS	Pain Symptoms	12.59%	0.652381
MS	Gastrointestinal Symptoms	4.53%	0.573691
MS	Skin Symptoms	2.06%	0.250000
Alzheimer's	Respiratory Symptoms	5.01%	3.916288
Alzheimer's	Gastrointestinal Symptoms	2.06%	3.815027
Alzheimer's	Neurological Symptoms	1.93%	3.773366
Alzheimer's	General Symptoms	9.9%	2.864603
Alzheimer's	Cardiovascular Symptoms	0.87%	2.541667
Alzheimer's	Infection Symptoms	5.19%	2.470779
Alzheimer's	Other	71.01%	2.095340
Alzheimer's	Pain Symptoms	2.7%	1.355303
Alzheimer's	Skin Symptoms	0.33%	0.875000
ALS	Cardiovascular Symptoms	2.22%	5.000000
ALS	Neurological Symptoms	0.74%	5.000000
ALS	Infection Symptoms	2.96%	1.833333
ALS	Other	83.70%	1.692972
ALS	General Symptoms	4.44%	1.666667
ALS	Pain Symptoms	3.7%	1.375000
ALS	Respiratory Symptoms	2.22%	1.000000
Parkinson's	General Symptoms	8.42%	2.861302
Parkinson's	Cardiovascular Symptoms	1.06%	2.846032
Parkinson's	Other	70.0%	2.661268
Parkinson's	Respiratory Symptoms	4.0%	2.341145
Parkinson's	Infection Symptoms	4.87%	1.695610
Parkinson's	Gastrointestinal Symptoms	2.11%	1.121457
Parkinson's	Neurological Symptoms	3.75%	0.933694
Parkinson's	Pain Symptoms	4.68%	0.682124
Parkinson's	Skin Symptoms	0.67%	0.482143

These findings emphasize the importance of personalized vaccination strategies that consider individual risk factors such as underlying neurological condition, gender, and age to enhance vaccine safety and efficacy.

Based on the results, the clinical focus recommendations include:

MS treatments should focus on general discomfort and sleep issues. Clinicians should prioritize managing symptoms such as fatigue, weakness, and insomnia, which were found to be the most frequent and moderately severe in MS patients. Interventions could include sleep hygiene education, cognitive-behavioral therapy for insomnia, and pharmacological treatments to alleviate discomfort and improve sleep quality. Additionally, strategies to manage general discomfort, such as pain management and fatigue-reducing therapies, should be integrated into the treatment plan.

ALS requires urgent attention to respiratory issues. Given the high severity scores associated with respiratory symptoms in ALS patients, it is crucial to monitor and support respiratory function rigorously. Regular pulmonary function tests, early intervention with non-invasive ventilation, and prompt management of respiratory infections are recommended. Healthcare providers should educate patients and caregivers about the signs of respiratory distress and the importance of timely medical intervention. Proactive respiratory care, including the use of respiratory assistive devices and advanced planning for potential respiratory complications, is essential to improve patient outcomes.

Alzheimer's disease management should consider physical symptoms with high severity. Physical symptoms, particularly those related to mobility, respiratory issues, and musculoskeletal pain, should be a primary focus to enhance patient comfort and functionality. This could involve physical therapy, regular exercise programs tailored to the patient's abilities, and pain management strategies. Attention to these aspects can help improve the overall quality of life and potentially slow the progression of physical decline. Additionally, respiratory care and monitoring are vital, given the severity of respiratory symptoms observed in these patients.

Parkinson's disease interventions need to address motor and movement issues primarily. Treatments should focus on improving motor function and managing symptoms such as tremors, rigidity, and bradykinesia. This can be achieved through a combination of medication (e.g., levodopa), physical therapy, and exercise programs designed to enhance strength, flexibility, and balance. Occupational therapy can help patients maintain independence in daily activities, while speech therapy may be necessary to address communication difficulties. Additionally, interventions should be personalized to each patient's stage of disease progression and specific symptomatology to optimize treatment outcomes.

The proportion of deaths relative to hospitalizations is notably higher among ALS and Alzheimer's patients. This suggests that when these groups require vaccination, there should be heightened vigilance to closely and aggressively monitor them for adverse events and to provide timely care or medication as needed. Surprisingly, however, Parkinson's patients exhibited a lower morbidity rate compared to those with Alzheimer's and ALS. This unexpected finding could warrant further research into the role of acetylcholine and dopamine neurotransmitters in immune response to vaccine-related adverse events. In Alzheimer's disease, acetylcholine levels decrease relative to dopamine, while in Parkinson's disease, acetylcholine levels are higher compared to dopamine. Among MS patients, the death-to-hospitalization ratio was the lowest. This may be partly because MS patients are generally younger than those in the other three groups studied, and it could also be influenced by the use of immune-modulating medications, such as steroids.

The results of this study are time-specific, reflecting the period during which the data were collected, particularly with the presence of COVID-19 vaccines and related symptoms. Period effects in the reporting of adverse events are crucial to consider, as the prevalence and types of vaccines administered, as well as public health circumstances, can vary significantly over time. For instance, the current study period includes data influenced by the global COVID-19 pandemic, which would not have been present in data collected five years ago.

It is crucial to consider that many of the symptoms observed may align with the natural progression of the patients' underlying conditions. The temporal relationship between vaccination and the onset of symptoms, however, does suggest a need for further investigation to discern whether these effects are attributable to the vaccine or are due to the disease's inherent trajectory. Future research exploring this distinction could provide valuable insights, especially in understanding the safety profile of vaccines in individuals with pre-existing health concerns.

Additionally, it is noteworthy that the data indicate some exacerbation of symptoms related to underlying conditions in certain cases following vaccination. This observation underscores the necessity for continued monitoring, particularly among vulnerable populations, to ensure any potential vaccine-related risks are identified and managed appropriately.

6. Conclusion

This study provides a comprehensive analysis of adverse events following vaccination in patients with MS, ALS, Alzheimer's Disease, and Parkinson's Disease. We also performed a hypothesis test to determine if there is a significant difference in the percentage of adverse events between two different vaccine types. The findings highlight

disease-specific adverse event profiles and underscore the importance of considering differences in vaccine safety monitoring. These insights could inform clinical practice and potentially guide future research into the mechanisms underlying vaccine-related adverse events in these populations. The findings could help healthcare providers better anticipate and manage risks, potentially improving patient safety and outcomes.

The results reveal distinct symptom clusters and severity patterns for each disease, highlighting the variability in adverse event profiles among different neurological conditions. MS and Alzheimer's Disease show a predominance of general symptoms, with Alzheimer's patients also experiencing significant respiratory and gastrointestinal issues. ALS is characterized by severe respiratory symptoms and some muscle/joint pain, which is consistent with the known progression of the disease affecting respiratory function. Parkinson's Disease is primarily marked by motor and movement issues, such as tremors and rigidity. The severity scores indicate that ALS patients experience the most severe symptoms, particularly in respiratory function, underscoring the critical need for targeted respiratory care in this population. Future studies should consider longitudinal analyses to capture the evolving nature of vaccine-related adverse events over different time periods. Mechanistic studies are needed to investigate the underlying biological mechanisms that contribute to differences in vaccine-related adverse events among patients. Additionally, exploring the reasons behind differences in adverse event reporting and outcomes, focusing on hormonal, genetic, and immunological factors, is crucial. Assessing the efficacy and safety of different vaccine types in patients, considering factors such as disease progression and comorbidities, would also be valuable. Finally, developing personalized vaccination strategies based on patient characteristics, such as genetic predispositions and existing health conditions, could minimize adverse events and enhance vaccine efficacy.

CRediT authorship contribution statement

Shabnam Sodagari: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Nassim Sodagari:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100902.

Data availability

public data

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