

Safety of SARS-CoV-2 vaccine in patients with autoimmune neurological conditions: a systematic review and meta-analysis

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Abstract

Risk of adverse effects and exacerbation in autoimmune neurological conditions(ANC)are frequently cited reasons for COVID-19 vaccine hesitancy. This study evaluates the ANC safety of COVID-19 vaccines in the real world. We selected studies that provided data on the occurrence of adverse effects and exacerbation of conditions related to ANC after vaccination. The pooled incidence rates for various adverse effects, stratified for the disease category, dosage, and type of vaccine were estimated. Twenty-eight studies (31 vaccination cohorts) were included. The pooled incidence rate of general adverse events was 0.35 (95%CI, 0.27–0.43, $I^2 = 100\%$). The pooled incidence rate of exacerbation adverse events was 0.05(95%CI, 0.04-0.07, $I^2 = 84\%$). The pooled incidence rates of local injection reaction, fatigue, weakness, myalgia, fever, headache, and chills were 0.27 (0.18–0.36, $I^2 = 98\%$), 0.16(0.11-0.21, $I^2 = 93\%$), 0.15(0.00-0.31, $I^2 = 97\%$), 0.13(0.08-0.19, $I^2 = 97\%$), 0.11(0.07-0.15, $I^2 = 95\%$), 0.11(0.07-0.16, $I^2 = 97\%$), and 0.09(0.03-0.16, $I^2 = 96\%$), respectively. According to available evidence, the administration of COVID-19 vaccines in individuals with ANC seems to be well-tolerated, with few reports of adverse events. Furthermore, exacerbation of ANC following vaccination appears to be infrequent.

1.INTRODUCTION

Since December 2019, COVID-19 infection caused by severe acute respiratory syndrome type 2 coronavirus (SARS-CoV-2) has rapidly spread worldwide, posing significant challenges to public health systems in various countries around the world. SARS-CoV-2 has undergone multiple rounds of variation since the outbreak. As of March 31, 2023, it has caused more than 6.8 million deaths worldwide, and the total medical costs and other economic setbacks caused by the prevention and treatment of COVID-19 are unprecedented. In addition, long-term chronic epidemics of the disease, as well as various anti-epidemic measures have caused a large number of psychological and social problems among the population, exacerbating social instability, particularly in less developed countries^[1].Presently, there are few specific drugs against this highly contagious ribonucleic acid virus, and widespread vaccination in the population is considered one of the effective interventions to substantially reduce morbidity and mortality and end the virus epidemic ^[2].As of 31 March 2022, more than 13 billion vaccine doses have been administered all over the world(<https://covid19.who.int>). Multiple large randomized controlled trials and real-world studies have demonstrated the safety and efficacy of COVID-19 vaccines in the general population^[3, 4]. However, the safety of COVID-19 vaccination for some patients with specific diseases, especially autoimmune diseases, has not been confirmed. Because these patients often have immune dysfunction and are immunocompromised by long-term use of immunosuppressants, they tend to be excluded from vaccine RCTs trial participant selection^[5].

ANC is a large group of autoimmune diseases characterized by an inappropriate immune response, in which the body mistakenly recognizes the nervous system as an immune target^[6], causing neurological damage, which often progresses or repeatedly exacerbates, resulting in disability or death. Common conditions include multiple sclerosis (MS), myasthenia gravis (MG), Guillain-Barre syndrome (GBS), neuromyelitis optica spectrum disorder (NMOSD) and chronic inflammatory demyelinating polyneuropathy (CIDP) , etc.

Infection is the most common cause of exacerbation in ANC^[7], SARS-CoV-2 may activate neuroinflammatory pathways^[8], and severe pneumonia rates and mortality are higher in ANC patients infected with SARS-CoV-2^[9]. In addition, immunosuppressive therapy (IST) also increases the chance of severe pneumonia post-infection in ANC patients. For these reasons, vaccination is necessary to protect these patients from SARS-CoV-2 infection. Paradoxically, the vaccine itself contains weakened or inactivated parts (antigens) of specific organisms that can trigger immune responses and induce antigen production in the body, and in general, this weakened version does not cause disease in healthy people receiving the vaccine, but immune abnormalities and hypo immunity are prevalent in people with autoimmune neurological diseases, and the vaccine may elicit or aggravate autoimmune diseases^[10]. Since the COVID-19 pandemic, multiple studies have reported that vaccines induce autoimmune diseases or exacerbate pre-existing conditions^[11, 12], however, more studies suggest that vaccination is safe for patients with neuroimmune diseases^[2, 13, 14]. These contradictory conclusions fuelled the hesitancy of patients with autoimmune diseases to vaccinate; Therefore, in the context of the long-term epidemic of COVID-19, it is essential to clarify the risks and benefits of post-inoculation for these patients.

Due to the lack of direct safety evidence for SARS-CoV-2 vaccination in ANC patients, we conducted a systematic review and single-arm meta-analysis based on various eligible safety studies in ANC patients after vaccination to more fully assess the safety of SARS-CoV-2 vaccination in patients with autoimmune neurological diseases, eliminate these patients' hesitancy to vaccinate through evidence-based medicine, and improve the protection rate of vulnerable populations.

2. METHODS

This study is the first meta-data analysis to evaluate the safety of the COVID vaccine in ANC patients and was conducted in the light of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.

2.1 Search Strategy

The online literature search was conducted by two independent authors (FN and XC) from electronic databases including PubMed, Embase, and Web of Science from January 01, 2020, to December 31, 2022. The following sets of keywords were used for searching: Neuroimmune disorders, Central Nervous System Demyelinating Diseases, Multiple Sclerosis, Neuromyelitis Optica Spectrum Disorders, Myasthenia Gravis, Peripheral Nervous System Disease, chronic inflammatory demyelinating polyneuropathy combined using the operate 'AND' COVID 19 Vaccines, SARS Coronavirus 2 Vaccines or Vaccination. (The detailed search strategy is provided in Supplementary Table 1.) The eligible titles were combined and non-English-language titles and duplicates were removed. The titles and abstracts were then reviewed by two reviewers (FN and XC) independently. Full texts were screened after the preliminary screening of relevant titles and abstracts. Ambiguity was resolved after a discussion with a third reviewer (ZR).

2.2 Study selection

We included all associated observational studies about adverse events of COVID-19 vaccines in the systematic review. We included studies reporting at least one of the following outcomes in autoimmune neurological disorders ,mentioned below:

2.2.1. Adverse events or side effects after SARS-CoV-2 vaccination in patients with autoimmune neurological disorders;

2.2.2 exacerbation of underlying disorders after COVID-19 vaccination.

We excluded the studies that have one or more of the following criteria: 1) case, case series (the patient population of 5 participants or less), review, letter, conference abstract, guideline; 2) Studies on any species of vaccine other than SARS-CoV-2; 3) studies that did not include ANC patients. We also screening full text studies for vaccine efficacy study to look for any additional information regarding adverse events.

2.3 Data extraction

Data extraction and validity assessment by two researchers (FN and XC) independently screened and extracted data according to a predetermined proforma in Microsoft Excel Version 16, including: The data were extracted irrespective of the type of vaccine or number of vaccine doses. Data extraction and validity assessment by two researchers (FN and XC) independently screened and extracted data according to a predetermined proforma in Microsoft Excel Version 16, including: 1) bibliometric information: title, first author, date of publication, and the country conducting the studies; 2) details of intervention: type of the vaccine, number of participants receiving each dose of vaccine; 3) demographic information: age, sex, and disease; 4) general methodological details: length of follow up; 5) outcome information: outcomes of safety and details of adverse events. Any Disagreements during the process were resolved by the third researcher (ZR).

2.4 Outcomes

A single-arm, meta-analysis was performed because insufficiency of control arms. The pooled incidence rates of adverse events after the COVID-19 vaccine were calculated. The analysis was performed separately for several doses of the vaccine. We calculated the pooled incidence rates of adverse events for different types of ANC disease following vaccination. We also calculated the pooled rates of deterioration or recrudescence of underlying disease activity in ANC after COVID vaccination.

2.5 Data analysis

All analyses were conducted on R statistical software (version 4.2.2), in addition to the base package, meta, and metafor package was used^[15]. We used the random effects model to calculate the pooled incidence rate with the inverse variance approach and the corresponding 95% confidence intervals (CI) for the primary outcomes of interest. The I^2 value represents the percentage of total variation among studies due to heterogeneity rather than chance. After that, the random effects models were used because of the underlying heterogeneity in the studies, containing types of neuroimmune disorders, vaccines, and doses, and the reported outcomes (I^2 [?]50% or $p < 0.05$). We performed subgroup analyses to ascertain if results were effect by the type and dose of vaccine or the different disease types. The forest plot was used to represent the result of conducted subgroup meta-analysis graphically. Publication bias was assessed using funnel plots, visual inspection for funnel plot asymmetry, and Egger's test of funnel plot asymmetry. A sensitivity analysis was conducted to evaluate the robustness and reliability of the results.

3. RESULTS

As shown in **Fig.1** (PRISMA flow chart), summarizes the selection of studies. A total of 3063 citations were identified from databases, including PubMed, Web of Science and Embase, there were 1652 duplicates. After screening the title and abstract, 1241 citations were removed. Full-text copies of twelve articles could not be achieved and 158 full-text studies were finally reviewed. 113 studies excluded due to no safety index. Detailed exclusion reasons for other studies are shown in figure 1. Eventually, 28 studies were included in the final meta-analysis. Studies characteristics of the selected are shown in **Table 1** ^[12-14, 16-40].

Of the 28 articles included in the final analysis, 31 cohort, 129980 patients notified total adverse events after COVID-19 vaccination in patients with ANC. The diseases included were: MS (17/31, 54.8%), MG (10/31, 32.3%), and NMOSD (4/31, 12.9%). studies reported the incidence of adverse reactions after the first, second, and third dose vaccination was 20(71.4%), 17(60.7%), 6(21.4%) respectively. For different vaccine types, mRNA vaccines (either Pfizer-BioNTech or Moderna) accounted for 46.4%, inactivated vaccines (CoronaVac, Sinovac) accounted for 14.3%, and mixed vaccination types accounted for 39.3%.

3.1 The incidence of post-vaccination adverse events in general.

The meta-analysis of the pooled incidence rate of general adverse events following post-vaccination which contained 27 observational studies is shown in **Fig2**. The pooled incidence rate of general adverse events in ANC patients following COVID-19 vaccination was 0.35 (95% CI, 0.27–0.43, $I^2 = 100\%$). The most common type of adverse event was local injection reaction, with a pooled incidence rate of 0.27 (95% CI, 0.18 – 0.36, $I^2 = 98\%$); followed by fatigue 0.16 (95% CI: 0.11 – 0.21, $I^2 = 93\%$), weakness 0.15 (95% CI: 0.00 – 0.31, $I^2 = 97\%$), myalgia 0.13 (95% CI: 0.08 – 0.19, $I^2 = 97\%$), fever 0.11 (95% CI: 0.07 – 0.15, $I^2 = 95\%$), headache

0.11 (95% CI: 0.07 – 0.16, I2 = 97%), and chills 0.09 (95% CI: 0.03 – 0.16, I2 = 96%) (**Supplementary Fig1**).

3.2 The incidence of adverse events in subgroup

Subgroup analysis by disease type showed that the highest total adverse event pooled incidence rate of patients with MS at 0.43 (95% CI, 0.31–0.55, I2 = 100%). MG and NMOSD of 0.26 (95% CI, 0.15–0.37, I2 = 100%), and 0.30 (95% CI, 0.00–0.63, I2 = 91%), respectively. (**Supplementary Fig.2**). The pooled incidence rate of adverse reactions following different immunization doses was basically the same, 0.37 (95% CI, 0.25 – 0.49, I2 = 100%) after the first dose, 0.34 (95% CI, 0.21 – 0.47, I2 = 99%) after the second dose and 0.36 (95% CI, 0.27 – 0.44, I2 = 100%) after the third dose (**Supplementary Fig.3**). The pooled incidence rate of adverse events post-vaccination was similar across vaccine types, 0.35 (95% CI, 0.23–0.47, I2 = 100%) for mRNA vaccines, 0.34 (95% CI, 0.13–0.56, I2 = 99%) for inactivated vaccines, and 0.36 (95% CI, 0.19–0.53, I2 = 100%) for mixed vaccines (**Supplementary Fig.4**).

3.3 The exacerbation pooled incidence rate of post-vaccination adverse events in different neuroimmune diseases.

23 (82.1%) studies reported an exacerbation of pre-existing ANC post-vaccination .The pooled incidence rate of exacerbation of pre-existing disease in ANC patients following COVID-19 vaccination was calculated to be 0.05(95%CI,0.04–0.07,I2 = 84%) (**Fig.3-bottom panel**). Subgroup analysis by disease type showed that the pooled incidence rate of MS exacerbation after vaccination was the lowest at 0.05 (95% CI, 0.03–0.07, I2 = 89%). MG and NMOSD of (95% CI, 0.05–0.10, I2 = 0%), and 0.06 (95% CI, 0.05–0.08, I2 = 32%), respectively(**Fig.4**);Subgroup analysis by vaccination dose showed that the incidence of exacerbation of pre-existing disease was the lowest after the first dose, 0.04 (95% CI, 0.02 – 0.05, I2 = 77%), and was basically the same after the second dose and the third dose, 0.07 (95% CI, 0.04 – 0.11, I2 = 67%) and 0.07 (95% CI, 0.04 – 0.10, I2 = 0%)(**Fig5**); Subgroup analysis by vaccine type showed that the incidence of pre-existing disease exacerbations was 0.06 (95% CI, 0.04–0.08, I2 = 83%) after mRNA vaccination, 0.04 (95% CI, 0.00–0.10, I2 = 94%) for inactivated vaccines, and 0.06 (95% CI, 0.02–0.09, I2 = 79%) for mixed vaccines(**Fig6**). Four (14.3%) studies reported post-vaccination neurologic adverse events, with a pooled incidence of 0.11 (95% CI, 0.01 – 0.21, I2 = 96%) (**Fig.3-Top Panel**).

3.4 Risk of bias and sensitivity analysis

Visual inspection of the funnel plot showed no evidence of a significant publication bias(**Fig.7**), confirmed by Egger’s test for publication bias (P = 0.9008) (**Supplementary Fig.5**).

Leave one out sensitivity analysis was performed to re-estimate the pooled incidence rate of adverse events. The results revealed that no single study had a significant impact on the overall effect (**Supplementary Fig.6**).

4.DISCUSSION

This study reviewed the safety studies of COVID-19 vaccination in patients with autoimmune neurological conditions and conducted a systematic review and meta-analysis. The results of the study showed that the general adverse event pooled incidence rate of ANC patients post-vaccination with COVID-19 was similar to the healthy people(35%:25%-38%), vaccination had little effect on the original neurological autoimmune disease, the disease exacerbation rate caused by the vaccine was very low(5%), and COVID-19 vaccination was generally safe for ANC patients.

Infection is a clear predisposing or aggravating factor for some autoimmune diseases, and it has been documented that COVID-19 infection induces neuroimmune diseases or leads to the aggravation of pre-existing diseases^[41]. Patients with ANC are at increased risk of acute respiratory distress syndrome and multiple organ failure after infection with the SARS-CoV-2 virus because of their immunosuppressed status^[42], therefore, the protection of this group of patients is a priority, and some international consensus also recommends that people with neuroimmune diseases be vaccinated against SARS-CoV-2 as soon as possible^[43].However,

it is troubling that vaccination activates autoimmune responses, and theoretically, the vaccine may also induce ANC or lead to deterioration or recurrence of the disease in ANC patients. Although more than 5 billion people have been vaccinated worldwide(<https://covid19.who.int.>), results from some investigative studies demonstrate that there are still 10%-20% of patients with neuroimmune diseases are hesitant to vaccinate^[44], and there are many reasons for hesitation, but the most common reasons were concerns about vaccine safety^[45]. A better clarification of the safety of COVID-19 vaccination in ANC patients is therefore crucial to help reduce their vaccine hesitancy and bring the COVID-19 pandemic under control.

After vaccination, we found a pooled incidence rate of general adverse events to be approximately 35%. Most of the symptoms were characterized by transient post-vaccination adverse reactions, such as pain, swelling, redness, fever, chills, fatigue, headache, myalgia and weakness at the injection site, and the incidence of these common adverse reactions was similar to that in healthy people^[4]. Subgroup analysis of disease category showed that patients with multiple sclerosis had a slightly higher general adverse event rate (43%) than those with neuromyelitis optica and myasthenia gravis, but less than half overall. Due to ethnic and geographical differences in the prevalence of different diseases, and large heterogeneity between studies, the incidence of adverse events in the three common neuroimmune diseases cannot be directly compared. In general, a similar incidence of general adverse events in all three diseases to that observed with healthy people, with no significant difference. Subgroup analysis of different vaccinations showed that the incidence of general adverse reactions caused by different doses was essentially the same for patients with neuroimmune diseases. Because the virus mutates continuously during transmission, breakthrough infections occur at a high incidence in patients receiving routine doses of the vaccine, and many studies have shown that universal booster vaccination could be a current strategy to prevent breakthrough infections from COVID-19^[46]. From the pooled analysis, there was no increase in the incidence of general adverse reactions in patients with ANC who received three vaccinations, this finding could be considered that providing booster needles to further enhance the protective effect of ANC patients. Currently, the most widely used vaccine types worldwide are mRNA vaccines and inactivated vaccines, and subgroup analysis results show that there is little overall difference in the incidence of general adverse events between these two vaccines, so it is reasonable to recommend these two types of vaccines to patients with neuroimmune diseases from a safety point of view.

Whether COVID-19 vaccination leads to the exacerbation of underlying neuroimmune diseases has been a controversial topic and a significant cause of vaccine hesitation in patients with neuroimmune diseases. A questionnaire survey on vaccination willingness conducted on South Korean people with myasthenia gravis by researchers KIM et al reported that patients who had experienced myasthenic crises were more resistant to vaccination in 160 questionnaire results, which may be related to their greater concern about the exacerbation of underlying diseases^[47]. Yap, S. M. et al. surveyed COVID-19 vaccination willingness among people with multiple sclerosis in Northern Ireland, and the results showed that about 20% of MS patients are antipathy to vaccines^[48]. Most of this antipathy stems from concerns that vaccination may trigger or aggravate the disease^[49]. The association of vaccination with disease recurrence has been reported previously in several studies. A review incorporated 10 observational articles with a total of 1299 myasthenia gravis patients revealed that only 60 (4.26%) patients developed an acute exacerbation of MG after vaccination^[9]. In a study conducted in Kuwait, the probability of disease worsening and recurrence was carried out a 5.5% and 1.8% following Vaccination in MS patients, respectively^[2]. Giannoccaro et al. reported no difference in the recurrence rate of NMOSD before and after vaccination^[29]. In a multicenter prospective clinical study conducted by Ad'aja E. Baars et al, 1152 patients with neurological autoimmune diseases including GBS, CIDP, or multifocal motor neuropathy (MMN) were enrolled. The results showed that the exacerbation rates of these three underlying diseases after vaccination were 0%, 3%, and 4%, respectively. Those studies suggest that vaccination does not increase the risk of disease exacerbation and provides evidence of the safety of vaccination in patients with ANC^[50]. Despite the majority of research indicating no significant exacerbation of pre-existing neurological and immunological conditions following vaccination, divergent outcomes exist due to variations in the disease under study, population inclusion criteria, sample size, geographic location, and vaccine type employed. Our meta-analysis demonstrate that the rate of recurrence or exacerbation of underlying diseases after SARS-CoV-2 vaccination is low, at approximately 7%. Due to the lack of control

groups in most vaccine studies and the proportion may be even lower given that mass vaccination of the population may coincide with natural deterioration or relapse of the disease. Furthermore, for patients with exacerbations of pre-existing conditions, most have a good prognosis, and there are almost no reports of severe deterioration (requiring adjustment of current treatment plans) reported, and this exacerbation is mostly transient, after the steroid of treatment, patients can partially or completely return to baseline values^[16, 32]. Exacerbating symptoms have also been reported to be self-limiting in some patients and recover without the need for any medical treatment^[29]. In addition, we also found that the proportion of neurological adverse reactions caused by vaccination is relatively low(around 11%), which further confirmed that vaccination had a minor impact on the course of ANC and that COVID-19 vaccination was safe for patients with neurological autoimmune diseases. Due to significant heterogeneity between studies, we conducted categorical subgroup analysis based on vaccination dose, vaccine type, and different ANC types. However, the heterogeneity did not significantly decrease, suggesting that it may be due to factors such as age, gender, ethnicity, and different study countries, which could introduce systematic errors and result in high heterogeneity. This is consistent with our research conclusion, which demonstrates that SARS-CoV-2 vaccines are safe in patients with neuroimmune disorders.

4.1 Study limitations

There are some limitations to this study. Firstly, due to the unique nature of vaccine research, all studies included had no control group. Although it was a single-arm meta-analysis, the extremely low pooled incidence rate can still reflect the safety of the vaccine. Secondly, the overall heterogeneity in the analysis of the results of this study was large, and despite the use of a random-effects model, there may still exist the presence of uncontrollable confounding factors. We tried to conduct multiple subgroup analyses stratified by confounding factors such as age, sex, comorbidities, etc to test the stability of the results, but these factors could not be further corrected due to the lack of raw data; and we also performed bias analysis and sensitivity analysis to examine the influence of a specific study on the overall results, confirming that our included studies were large and of high quality and that individual studies had little effect on the overall results, so we judged the results to remain reliable. Thirdly, due to the significant variation in the number of publications for different diseases, we ultimately included only three types of diseases (MS, MG, NMOSD) after the screening, mainly because these diseases are rare and thus have fewer relevant studies. Finally, most of the studies were conducted in 2022, during which the Omicron variant was dominant, and the incidence of adverse events may differ across different strains of the virus.

CONCLUSIONS

This study further confirms the safety of COVID-19 vaccination in the neuroimmune disease population, especially those with autoimmune neurological conditions. Stable patients with neuroimmune disorders should be encouraged to receive COVID-19 vaccination. Further research should monitor for serious adverse events following vaccination and the long-term impact of vaccination on patients with neuroimmune diseases.

Abbreviations: ANC:autoimmune neurological conditions; SARS-CoV-2 :severe acute respiratory syndrome type 2 coronavirus; MS: multiple sclerosis; MG: myasthenia gravis; NMOSD: neuromyelitis optica spectrum disorder; GBS: Guillain-Barre syndrome; CIDP: chronic inflammatory demyelinating polyneuropathy; IST: immunosuppressive therapy; MMN: multifocal motor neuropathy

AUTHOR CONTRIBUTIONS

TC and ZR contributed to designing the study and take responsibility for the integrity of the data. FN and XC contributed to running the search strategy, selecting articles, and extracting data. FN, XC, QW, and ZL contributed to reviewing and editing the manuscript All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data from this study are available from the corresponding author upon reasonable request.

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Fig 1. PRISMA flow chart depicting the study screening and selection of the systematic review

Fig 2. Forst maps of General adverse events following COVID-19 vaccination in patients with ANC.

Fig 3. Top-panel: Forst maps of adverse events causing Neurological symptoms \in ANC patients following COVID-19 vaccination ; **bottom panel :** Forst maps of causing exacerbation of disease following COVID-19 vaccination.

Fig 4. Forst maps of causing exacerbation of disease following COVID-19 vaccination with subtyped for type of ANC.

Fig 5. Forst maps of causing exacerbation of disease following COVID-19 vaccination with subtyped for type of vaccine.

Fig 6. Forst maps of causing exacerbation of disease following COVID-19 vaccination with subtyped for dose of vaccine.

Fig 7. The funnel plot of included studies.

Table.1 Characteristics of included studies.

Abbreviate: ANC: autoimmune neurological conditions; MS : multiple sclerosis; MG: myasthenia gravis; NMOSD :neuromyelitis optica spectrum disorder; CI: confidence interval;

Supplementary Figure 1: Pooled incidence of adverse events in patients with ANC subtyped for type of Symptoms.

Supplementary Figure 2: Adverse events following COVID-19 vaccination in patients subtyped for type of ANC.

Supplementary Figure 3: Adverse events following COVID-19 vaccination in patients with ANC subtyped for dose of vaccine.

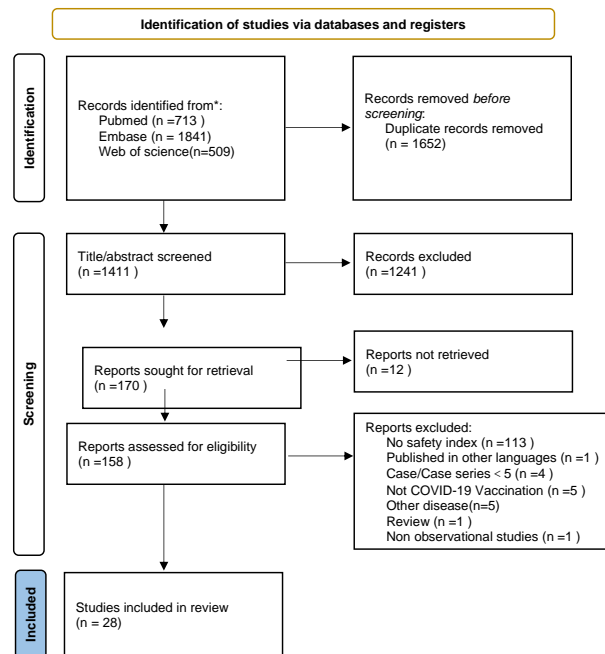
Supplementary Figure 4: Adverse events following COVID-19 vaccination in patients with ANC subtyped for type of vaccine.

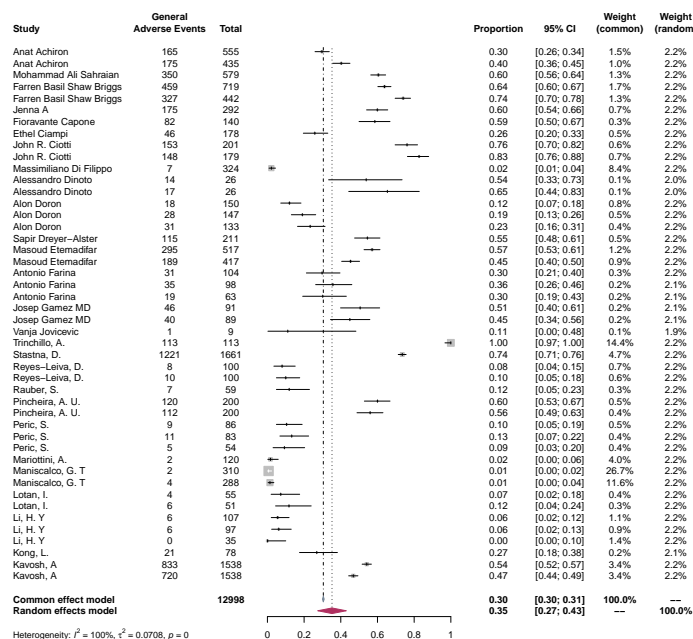
Supplementary Figure5: Egger’s test for publication bias.

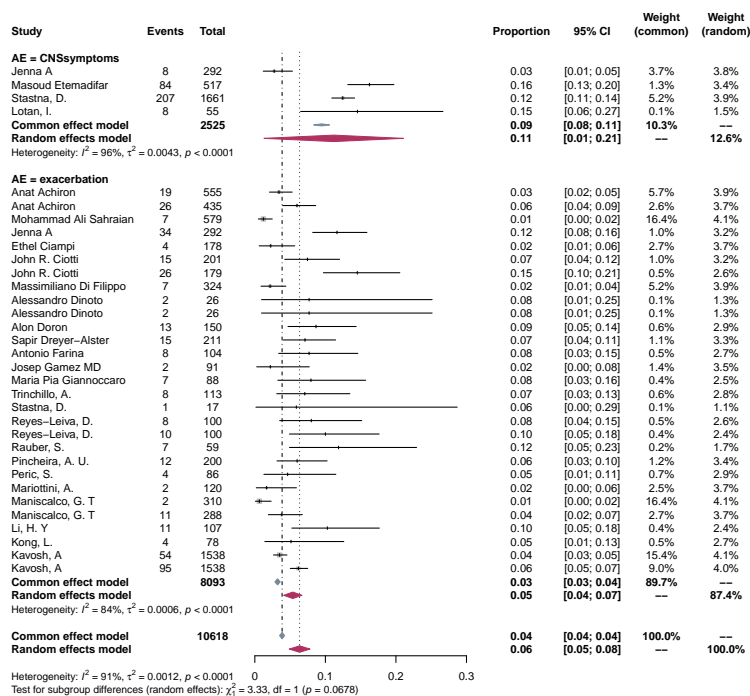
Supplementary Figure 6: Leave one out sensitivity analysis was performed to re-estimate the pooled incidence rate of adverse events.

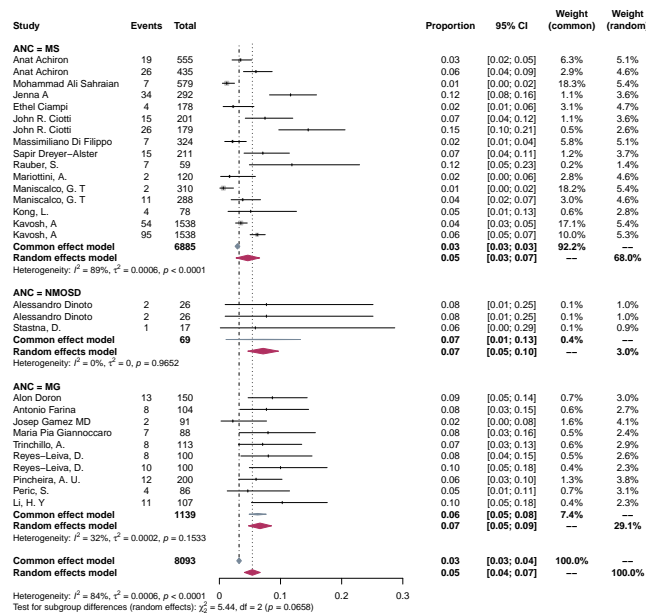
Supplementary Table 1: Detailed search strategy for the systematic review.

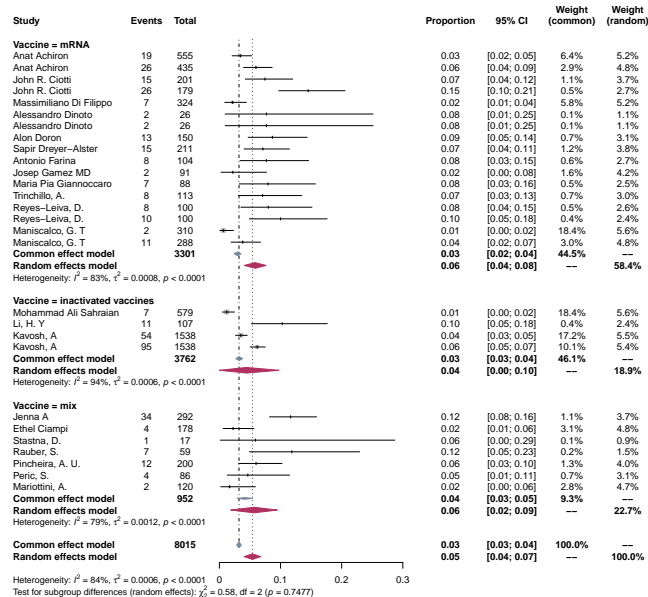
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only











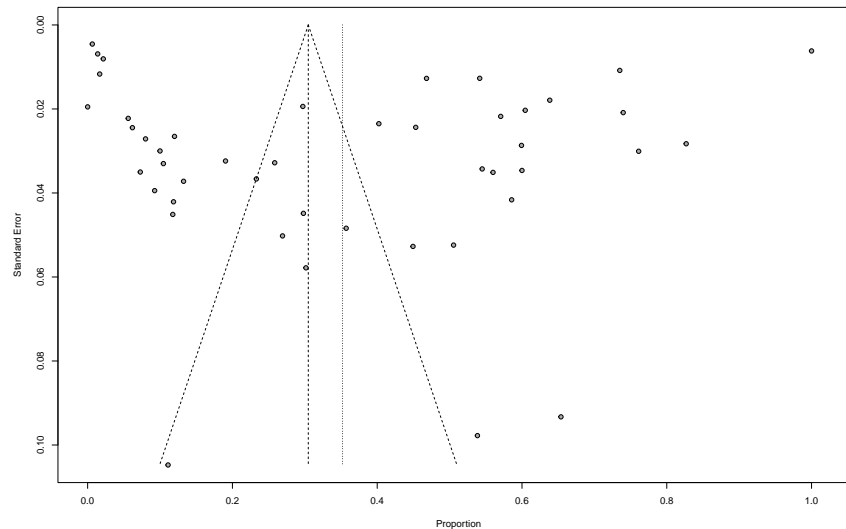
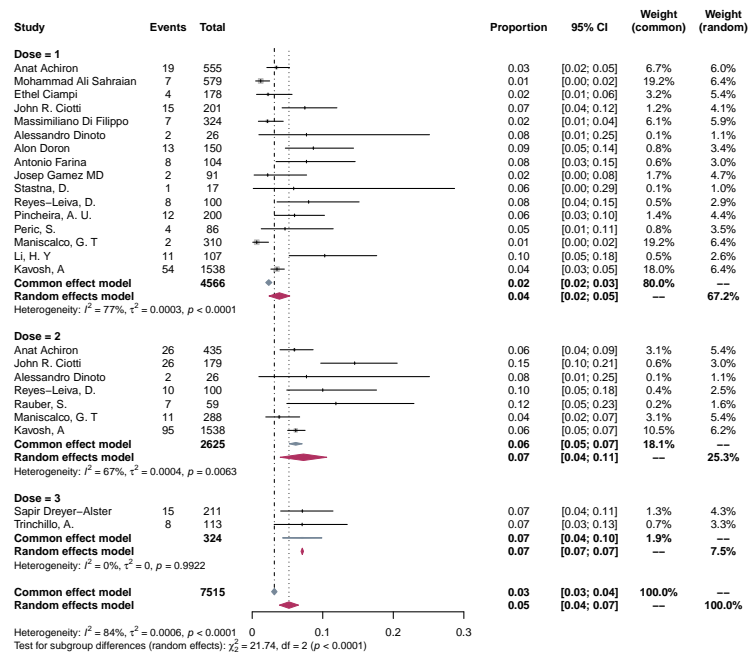


Table 1 Characteristics of included studies.

Authors	country	Study design	Patients(n)	Mean age(SD)(years)	Type of ANC	Name of the vaccine	COVID-19 vaccine dosa(n)			Follow up days
							D1	D2	D3	
Anat Achiron	Israel	observational study	555		MS	mRNA vaccine	555	435		67
Mohammad Ali Sahraian	Iranian	observational study	579		MS	inactivated vaccines	579	350		21
Farren Basil Shaw Briggs		Retrospective, observational study	719	53.0 (11.8)	MS	mix	719	459		90
Jenna A	US	observational study	292	50.4 (12.4)	MS	mix				28
Fioravante Capone	Italy	Prospective, observational study	140	43.5 (12.7)	MS	mRNA vaccine	140	140		60
Ethel Ciampi	Chile	Multicentric, prospective, observational study	178	39.7 (11.2)	MS	mix	178			210
John R. Ciotti	US	prospective, observational, study	201		MS	mRNA vaccine	201			240
Massimiliano Di Filippo	Italy	Multicentric, prospective, observational study	324	42.7(10.8)	MS	mRNA vaccine	324	322		60
Alessandro Dinoto	Italy	Multicentric, Retrospective, observational study	26		MS	mRNA vaccine	26	26		
Alon Doron	Israel	observational study	150	57.2 (18)	NMOSD	mRNA vaccine	150	147	133	42
Sapir Dreyer-Alster	Israel	prospective, observational, study	211		MG	mRNA vaccine			211	66
Masoud Etemadifar	Iran	Retrospective, observational study	517	37.81 (8.74)	MS	inactivated vaccines	517	417		
Antonio Farina	Italy	observational study	104		MS	mRNA vaccine	104	98	63	60
Josep Gamez MD	Spain	prospective, observational, study	91		MG	mRNA vaccine	91	89		225
Maria Pia Giannoccaro	Italy	longitudinal observational	291		MS/ MG	mRNA vaccine	300	300		

		study									
Vanja Jovicevic	Serbia	observational study	9	54.3(10.3)	NMOSD	mix		9			
Trinchillo, A.	Italy	Retrospective, observational study	113	58.4(15.5)	MG	mRNA vaccine			113	360	
Stastna, D.	USA	Retrospective, observational study	1678		MS/ NMOSD	mix	166 1			90	
Reyes-Leiva, D.	USA	Retrospective, observational study	100	55.85 (15.48)	MG	mRNA vaccine	100	100		90	
Rauber, S.	Germany	Retrospective, observational study	59		MS	mix		59		28	
Pincheira, A. U.	Australia	Retrospective observational study	200	64.3 (13.9)	MG	mix		200		14	
Peric, S.	Serbia	cross-sectional study	125	61.7(16.9)	MG	mix	87			365	
Mariottini, A.	Italy	monocentric retrospective observational study	120		MS	mix				≥30	
Maniscalco, G.T	Italy	Retrospective, observational study	310		MS	mRNA vaccine	310	288		180	
Lotan, I.	Italy	Retrospective, observational study	55		MG	mRNA vaccine	55	51		168	
Li, H. Y	China	Retrospective, observational study	107	45.68 (1.49)	MG	inactivated vaccines	107	97	35	28	
Kong, L.	China	Retrospective, observational study	187		MS/ NMOSD					90	
Kavosh, A	Iran	cross-sectional study	1538	40.45(9.7 4)	MS	inactivated vaccines	153 8	153 8			