BMC Medicine

RESEARCH

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COVID- 19 vaccination reduces new-onset fibromyalgia risk in survivors

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Abstract

Background Numerous studies have demonstrated that COVID-19 is associated with an increased risk of new-onset fibromyalgia (FM), which not only significantly impacts patients' quality of life but also places a substantial burden on healthcare systems. However, no studies have yet investigated whether COVID-19 vaccination may mitigate the risk of developing new-onset FM in individuals who have survived COVID-19. This study aimed to assess the potential effect of COVID-19 vaccination in reducing the risk of new-onset FM among COVID-19 survivors.

Methods We utilized the data resources from the TriNetX platform to compare 90,508 COVID-19 survivors who received the COVID-19 vaccine with 90,508 unvaccinated survivors. The Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and its corresponding 95% confidence interval (CI). The incidence was calculated using the Kaplan–Meier survival analysis method. Furthermore, we conducted detailed subgroup analyses and sensitivity analyses.

Results The cohort analysis of the present study revealed a significant reduction in the risk of new-onset FM among COVID-19 survivors who received the COVID-19 vaccine, compared to the unvaccinated group (HR 0.84; 95% CI 0.71–0.99). Notably, the results of the subgroup analysis indicated that the COVID-19 vaccine exerted a protective effect against the development of new-onset FM in males, individuals with a body mass index (BMI) < 30, and those with comorbid depression and anxiety.

Conclusions Our findings suggest that COVID-19 vaccination may play a protective role in reducing the risk of new-onset FM among COVID-19 survivors. The findings may indicate the importance of targeting vaccination to specific subgroups, such as males, individuals with lower BMIs, and those with mental health conditions, including depression and anxiety. This approach may enhance the protective effects of the vaccine and further reduce the incidence of long-term health complications associated with COVID-19. Further research is needed to validate these observations.

Keywords COVID- 19, Fibromyalgia, COVID- 19 vaccination, TriNetX, Risk, Protective effect

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Background

Fibromyalgia (FM) is a complex chronic pain syndrome clinically characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive impairments [1]. According to research statistics, the prevalence of FM worldwide is approximately 2–4%, making it the third most common musculoskeletal disorder after osteoarthritis and rheumatoid arthritis [2, 3]. Furthermore, it is associated with a high rate of suicide [4] and considerable healthcare utilization [5]. Its pathophysiological mechanisms primarily involve functional changes in the neural pathways related to pain perception within the nervous system, leading to the emergence of hyperalgesia [6]. Moreover, the etiology of FM may be associated with a variety of potential factors, including psychosocial stress and environmental exposure factors [2]. Notably, certain viral infections, such as human immunodeficiency virus infection and hepatitis C virus infection, are associated with the prevalence of FM [7]. Although the exact pathogenesis of FM remains unclear, existing research has suggested that direct virus invasion or an abnormal immune response of the host may be closely related to FM [8]. Moreover, physical and psychological stress associated with infection has been identified as a known factor that exacerbates the symptoms of FM [2]. These findings provide important clues for a deeper understanding of the complex pathological processes of FM.

Recent studies have suggested that FM may represent a form of post-viral fatigue syndrome [9]. As a global pandemic, COVID- 19 has been implicated in triggering the development of FM [2]. Notably, at least one-third of COVID- 19 patients have reported clinical features resembling those of FM following infection, including musculoskeletal pain, fatigue, and sleep disturbances [10, 11]. An online survey of 616 COVID- 19 patients revealed that 30.7% met the diagnostic criteria for FM as established by the American College of Rheumatology [12, 13]. FM is increasingly recognized as a significant long-term consequence of COVID- 19, resulting in considerable impairments in both quality of life and functional status [12]. From an etiological perspective, COVID- 19-induced inflammation appears to be closely linked to the pathogenesis of FM. COVID- 19 infection can trigger a cytokine storm, leading to heightened excitability in both the peripheral and central nervous systems [11, 14]. This immune response is also common in FM patients and plays a key role in mediating FM symptoms [15]. Additionally, research has shown that both COVID-19 and FM patients exhibit immune dysregulation, characterized by elevated serum levels of pro-inflammatory cytokines such as TNF-α, IL- 6, and IL- 8 [16]. Oxidative stress has also been identified as a critical factor in the pathogenesis of both COVID- 19 [17] and FM [18]. Elevated malondialdehyde levels have been observed in both patient groups [19, 20], and studies have demonstrated that antioxidant treatments can effectively ameliorate severe symptoms in COVID- 19 patients [21] as well as improve FM symptoms [22]. In the context of the COVID- 19 pandemic, exploring strategies to mitigate the incidence of FM in individuals suffering from long-term sequelae of COVID- 19 holds significant clinical and public health value.

COVID- 19 vaccines play a crucial role in controlling the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2). Numerous studies have demonstrated that vaccination against COVID- 19 could effectively reduce the severity of infectious symptoms and significantly lower hospitalization rates and mortality associated with COVID- 19 [23, 24]. Research has indicated that among individuals with COVID- 19, those who have been vaccinated generally exhibit lower concentrations of cytokines and chemokines compared to their unvaccinated counterparts [25]. Additionally, vaccinated patients show a reduction in the percentage of Fc gamma receptor I (CD64)-positive neutrophils as well as the expression of CD64 on the surface of neutrophils [26]. As a result, COVID- 19 vaccines help to limit inflammatory responses and immune reactions, which are closely correlated with a lower severity of COVID- 19 symptoms. However, no studies have assessed the impact of COVID- 19 vaccination on the incidence of subsequent FM in infected individuals.

This study aims to investigate the impact of COVID- 19 vaccination on the incidence of new-onset FM in individuals recovering from COVID- 19. Using data from a COVID- 19 cohort of adult patients aged 18 years and older, we utilized the TriNetX database to compare the risk of subsequent FM between individuals vaccinated and unvaccinated prior to infection, with subgroup analysis conducted. In the context of the ongoing global response to COVID- 19 and its complex aftermath, this study is both timely and of practical significance. Furthermore, this study can provide a basis for optimizing vaccination strategies, mitigate the long-term health burden of COVID- 19, and provide valuable insights into public health crises.

Methods

Data sources

This retrospective cohort study utilized the TriNetX analytics platform, a web-based database containing deidentified electronic health records (EHRs) from over 100 million patients across multiple countries. The dataset includes basic demographics, diagnoses (using the International Statistical Classification of Diseases,

Tenth Revision, Clinical Modification [ICD- 10-CM] codes), procedures (using the Current Procedural Terminology codes), and medications (using the RxNorm codes). TriNetX, LLC adheres to the Health Insurance Portability and Accountability Act (HIPAA), a US federal law aimed at protecting the privacy and security of healthcare information, as well as other relevant data privacy regulations enforced by participating healthcare organizations. The platform is certified under ISO 27001:2013 and operates an Information Security Management System (ISMS) to uphold the security of healthcare data and comply with HIPAA's Security Rule. Healthcare data is then processed into a proprietary data schema through a rigorous quality assurance process, which includes comprehensive data cleaning [27]. Data extraction and analysis were performed in July 2023 using the US collaborative network subnet TriNetX, which encompasses 66 health care organizations (HCOs). This study was approved by the Institutional Review Board for Ethics of Chung Shan Medical University Hospital (IRB number: CS2 - 21,176) and was performed in accordance with the Declaration of Helsinki.

Study population and exposure

This retrospective cohort study utilized data from the US Collaborative Network spanning from January 1, 2021, to December 31, 2023. The study population consisted of adult patients aged 18 years and older who were diagnosed with SARS-CoV- 2 infection, defined by codes including positive laboratory results for SARS coronavirus 2 (TriNetX code: 9088), COVID- 19 (ICD-10-CM: U07.1), unspecified coronavirus infection (ICD- 10-CM: B34.2), pneumonia due to SARS-associated coronavirus disease 2019 (ICD- 10-CM: J12.82), and other coronavirus-related diseases (ICD- 10-CM: B97.29) (Additional file 1: Tables 1 and 2). The variable of interest was the receipt of the COVID- 19 vaccine, comparing patients with breakthrough infections post-vaccination and unvaccinated individuals with infections. The vaccinated cohort (N= 524,586) included those who received the COVID- 19 vaccine at least 2 weeks before infection. The unvaccinated group (N= 316,112) consisted of individuals who had not received the COVID- 19 vaccine but had received the influenza vaccine. This approach accounted for vaccine hesitancy, ensuring the control group included individuals who accepted vaccination in general but not for COVID- 19 vaccine. The exclusion criteria for both groups included a history of cancer before the index date, FM or pain not elsewhere classified before the index date, and death before the index date.

Outcome and covariates

The primary outcome of this study was the incidence of FM (ICD- 10-CM: M79.7). The diagnostic criteria for fibromyalgia require symptoms to persist for at least 3 months. Accordingly, a 90-day washout period was applied. Patients were then followed for 1 year, until the occurrence of fibromyalgia, or until the last documented entry within the patient's medical record during the study period, whichever came first. Second, to address competing risks and survivorship bias, we combined each outcome with death in a composite measure [28].

Covariates were assessed within 1 year before the index date and included age, sex, ethnicity, and race. Medical utilization covariates included office or other outpatient services, hospital inpatient services, and emergency department services. Socioeconomic and psychosocial circumstances were considered. Lifestyle factors such as tobacco use (ICD- 10-CM: Z72.0), nicotine dependence (ICD- 10-CM: F17), and alcohol-related disorders (ICD- 10-CM: F10) were also assessed. The comorbidities included hypertensive diseases (ICD- 10-CM: I10-I1 A), fibromyalgia mellitus (ICD- 10-CM: E08-E13), hyperlipidemia (ICD- 10-CM: E78), rheumatoid arthritis with rheumatoid factor (ICD- 10-CM: M05), other rheumatoid arthritis (ICD- 10-CM: M06), systemic lupus erythematosus (SLE) (ICD- 10-CM: M32), gout (ICD- 10-CM: M10), ankylosing spondylitis (ICD- 10-CM: M45), other and unspecified osteoarthritis (ICD- 10-CM: M19), depressive episodes (ICD- 10-CM: F32), other anxiety disorders (ICD- 10-CM: F41), delusional disorders (ICD- 10-CM: F22), sleep disorders (ICD- 10-CM: G47), chronic kidney disease (CKD) (ICD- 10-CM: N18), heart failure (ICD- 10-CM: I50), ischemic heart diseases (ICD-10-CM: I20-I25), and cerebrovascular diseases (ICD-10-CM: I60-I69) (Additional file 1: Table 3).

Statistical analysis

The TriNetX platform was used to perform all the statistical analyses. To minimize the influence of confounding factors, propensity score matching (PSM) was conducted using greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations between the two groups. Matching was based on age at index, gender, race, ethnicity, medical utilization, socioeconomic status, lifestyle, and all comorbidities outlined in the covariate Sect. [29]. The standardized mean difference (SMD) was utilized to assess the balance of baseline characteristics in the propensity score-matched groups, with SMD values less than 0.10 serving as indicators of balance within the studied population [30].

The hazard ratio (HR) alongside its confidence intervals (CIs) and the test for proportionality were computed

through R's survival package (version 3.2–3). A log-rank test and the associated Kaplan–Meier method were also used to evaluate the incidence of FM. R software, version 4.0.2 (Free Software Foundation Inc) was used for analyses in this study. Statistical significance was defined as a 2-sided p value < 0.05.

We performed subgroup analyses stratified by sex (females, males), age (18–44, 45–64, 65 years and older), body mass index (BMI) (less than 30, 30–39, 40 and above), and comorbidities. Studies have shown that more than one-third of patients with rheumatoid arthritis (RA) develop secondary FM [31, 32]. Anxiety disorders and depression are significant predisposing factors for FM. Notably, the onset of anxiety and depression typically precedes the development of FM symptoms by an average of 1 year [33], suggesting that psychological factors may play a critical role in the onset and progression of FM. Additionally, sleep disorders have been implicated in the development of new-onset FM. Research has demonstrated that sleep spindles, which result from the rhythmic discharge of thalamic relay neurons, are closely linked to the onset and persistence of non-restorative sleep [34]. Given these associations, we conducted an analysis of a subgroup of COVID- 19 patients with comorbid RA, depressive episodes, anxiety disorders, and sleep disturbances, in order to examine the impact of these conditions on the development of new-onset FM.

Further sensitivity analyses included the following: (1) redefining the unvaccinated group as those who had not received the COVID- 19 vaccine; (2) validating our primary results across the global collaborative network with a larger population, encompassing regions such as the USA, EMEA, APAC, Latin America, and other international networks; (3) restricting the analysis to individuals who had at least one inpatient or outpatient visit within 0–6 months before the index date and at least one visit within 7–12 months before the index date to exclude the possibility that patients with new-onset FM were undiagnosed before the index date due to lack of medical attention; and (4) restricting the analysis to severe COVID- 19 cases, defined as those with hospital inpatient services, critical care services, and mechanical ventilation codes in their EHRs.

Results

Baseline characteristics of the study population

Following the application of propensity score matching (PSM), we identified 90,508 patients in both the vaccinated and unvaccinated groups (Fig. 1). The mean age at the index date was 49.6 ± 18.4 years in the vaccinated group and 45.9 ± 18.8 years in the unvaccinated group. After matching, the mean ages were closely aligned at 46.5 ± 18.3 years and 46.6 ± 18.8 years, respectively, with an SMD of 0.0014.

The sex distribution was similar after matching: 59.2% of patients were female in the vaccinated group, and 59.1% of the patients were female in the unvaccinated group (SMD = 0.0019). Ethnicity was classified into three categories: Hispanic or Latino, not Hispanic or Latino, and unknown. Before matching, there was a notable difference in the proportion of individuals who were not Hispanic or Latino (SMD = 0.1259), which was similar after matching (77.0% vs. 76.4%; SMD = 0.0144). Significant variations in race distribution were observed before matching, particularly for Asians (9.3% in the vaccinated group vs. 3.5% in the unvaccinated group; SMD = 0.2396). These differences were substantially reduced after matching.

Medical utilization indicators, such as office or other outpatient services and emergency department services, were higher in the unvaccinated group before matching but became comparable after matching. Comorbidities such as hypertensive diseases, FM mellitus, hyperlipidemia, depressive episodes, anxiety disorders, sleep disorders, and chronic kidney disease were balanced after matching, ensuring comparable groups for subsequent analyses (Additional file 1: Table 4).

Lower FM risk in vaccinated individuals

In the vaccinated group, 242 patients developed FM, whereas 289 patients in the unvaccinated group did. The hazard ratio for FM in the vaccinated group was 0.843 (95% CI: 0.710, 0.999), indicating a reduced risk compared to the unvaccinated group. When considering composite endpoints of FM or death, 785 patients in the vaccinated group experienced these outcomes, whereas 963 patients in the unvaccinated group experienced them. The hazard ratio for the composite endpoint was 0.820 (95% CI: 0.746, 0.901), further demonstrating a lower risk for the vaccinated group (Table 1). These hazard ratios were calculated after propensity score matching to ensure comparable groups, providing robust evidence of the protective effect of vaccination against FM and related outcomes. Figure 2 illustrates that the Kaplan–Meier curves revealed a lower incidence of FM in the vaccinated group than in the unvaccinated group (log-rank $p = 0.049$).

Subgroup analyses

The subgroup analyses of the cohort revealed several key findings. Both female- and male-vaccinated patients were analyzed, with males showing a significantly reduced risk of FM (HR: 0.520, 95% CI: 0.342–0.792). The BMI analysis demonstrated a significantly reduced risk in patients with a BMI < 30 (HR: 0.564,

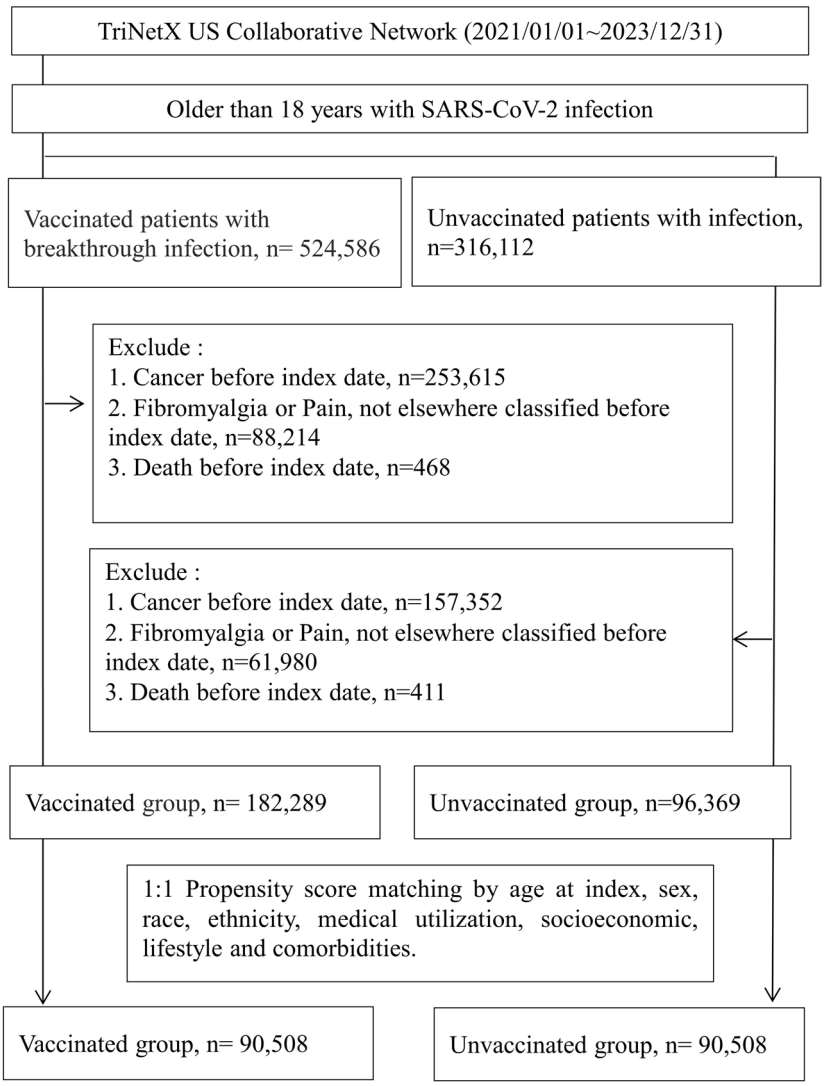

Fig. 1 Study flowchart

Table 1 Hazard ratio and 95% CIs for the risk of fibromyalgia (*N* = 90,508)

	Patients in cohort	Patients with outcome	Hazard ratio (95% CI)
Fibromyalgia			
Vaccinated	90,508	242	0.843 (0.710, 0.999)
Unvaccinated	90,508	289	Reference
Composite end points—fibromyalgia or death			
Vaccinated	90,508	785	0.820 (0.746, 0.901)
Unvaccinated	90,508	963	Reference

Note: Hazard ratio for outcomes among vaccinated group compared to unvaccinated group subjects (after propensity score matching). *95% CI*, 95% confidence interval

95% CI: 0.347–0.918). Additionally, patients with comorbidities such as depressive episodes (HR: 0.552, 95% CI: 0.365–0.835) and other anxiety disorders (HR: 0.598, 95% CI: 0.425–0.841) also demonstrated significantly reduced risks of FM (Fig. 3 and Additional file 1: Table 5).

Sensitivity analyses

To ensure the reliability of our results, we conducted four sensitivity analyses to validate our findings (Additional file 1: Table 6).

Redefining the unvaccinated group

We redefined the unvaccinated group as those who had not received the COVID- 19 vaccine. In this redefined

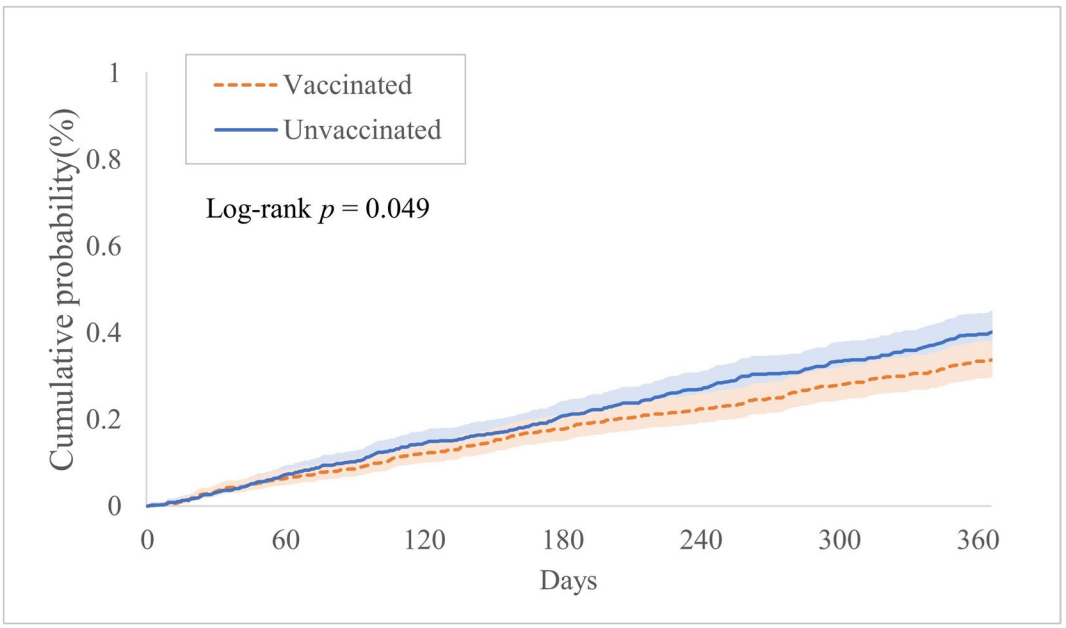

Fig. 2 Kaplan–Meier curves of cumulative probability (%) of fibromyalgia comparing vaccinated and unvaccinated groups

Subgroup	No. of Event / N		HR (95% CI)
	Vaccinated	Unvaccinated	
Sex			
Female	188/54049	188/54049	1.00 (0.82 — 1.23)
Male	33/34621	64/34621	0.52 (0.34 — 0.79)
Age			
18-44	84/41789	112/41789	0.78 (0.58 — 1.03)
45-64	94/26378	106/26378	0.89 (0.67 — 1.17)
>=65	47/22274	64/22274	0.70 (0.48 — 1.02)
BMI			
<30	25/13739	46/13739	0.56 (0.35 — 0.92)
30.0~39.9	36/12655	50/12655	0.73 (0.48 — 1.12)
>=40.0	132/40627	162/40627	0.80 (0.63 — 1.00)
Comorbidities			
Rheumatoid arthritis	10/893	10/893	0.66 (0.25 — 1.73)
Depressive episode	35/9649	63/9649	0.55 (0.36 — 0.83)
Other anxiety disorders	53/15535	88/15535	0.60 (0.42 — 0.84)
Sleep disorders	37/9092	51/9092	0.71 (0.47 — 1.09)

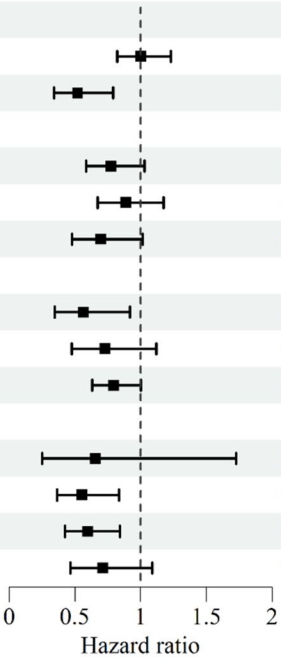

Fig. 3 Subgroup analysis

group, vaccinated individuals had a hazard ratio of 0.872 (95% CI: 0.766–0.992) for FM compared to their unvaccinated counterparts. For the composite endpoint of FM or death, the hazard ratio for the vaccinated group was 0.816 (95% CI: 0.764–0.871) relative to that of the unvaccinated group (Additional file 1: Table 6–1).

Validation within the global collaborative network

To validate our primary results within a broader population, we analyzed data from the global collaborative network. For the risk of FM, vaccinated individuals had a hazard ratio of 0.826 (95% CI: 0.701–0.972) compared to their unvaccinated counterparts. For the composite endpoint of FM or death, the hazard ratio for the vaccinated group was 0.794 (95% CI: 0.725–0.869) relative to that of the unvaccinated group (Additional file 1: Table 6–2).

Restricting analysis to individuals with prior medical visits

We restricted the analysis to individuals who had at least one inpatient or outpatient visit within 0–6 months before the index date and at least one visit within 7–12 months before the index date. This approach was used to exclude the possibility that patients with new-onset FM were undiagnosed before the index date due to a lack of medical attention. For the risk of FM, vaccinated individuals had a hazard ratio of 0.767 (95% CI: 0.634–0.928) compared to their unvaccinated counterparts. For the composite endpoint of FM or death, the hazard ratio for the vaccinated group was 0.809 (95% CI: 0.730–0.897) relative to that of the unvaccinated group (Additional file 1: Table 6–3).

Restricting analysis to severe COVID- 19 cases

We restricted the analysis to only include severe COVID-19 cases, defined as those with hospital inpatient services, critical care services, and mechanical ventilation codes in their EHRs. For the risk of FM among patients with severe COVID- 19, vaccinated individuals had a hazard ratio of 0.747 (95% CI: 0.332–1.682) compared to their unvaccinated counterparts. Regarding the composite endpoint of FM or death, the hazard ratio for the vaccinated group was 1.053 (95% CI: 0.878–1.262) relative to that of the unvaccinated group (Additional file 1: Table 6–4).

Discussion

In this large-scale cohort study, we compared the risk of new-onset FM in 90,508 COVID- 19 survivors who received the COVID- 19 vaccine and 90,508 unvaccinated individuals. The results indicated that the risk of new-onset FM in vaccinated COVID- 19 survivors was 84.3% (HR: 0.843, 95% CI: 0.710, 0.999) of that in the unvaccinated control group, reflecting a 15.7% reduction in risk. These findings suggest that COVID- 19 vaccination may offer a protective effect in reducing the likelihood of new-onset FM among COVID- 19 survivors.

Immune dysfunction has been identified as a potential pathological mechanism in fibromyalgia (FM) patients [15]. COVID- 19 can exacerbate immune and inflammatory responses [35] and significantly increase the incidence of FM [12, 36]. In a prospective study by Zhu et al. [25] evaluating dynamic inflammatory responses in 882 COVID- 19 survivors, vaccinated COVID- 19 survivors exhibited lower levels of inflammatory markers, such as interleukin- 7 (IL- 7) and tumor necrosis factor-α, in the short and long term after infection. Specifically, 90 days after infection, the concentrations of IL- 7, IL- 8, and vascular endothelial growth factor A in fully vaccinated COVID- 19 survivors were approximately 20% lower than those in unvaccinated individuals. In addition, Huapaya et al. [26] compared the peripheral blood cellular immune responses of 118 COVID- 19 survivors who had received and not received the COVID- 19 vaccine, and finding that the immune response of vaccinated individuals was more moderate. These findings suggest that the COVID- 19 vaccine may reduce the risk of new-onset FM by regulating the immune response and reducing the level of inflammatory mediators.

In the context of the COVID- 19 pandemic and vaccination, the significance of gender differences in vaccine effectiveness cannot be ignored. This study demonstrated the protective effect of COVID- 19 vaccination on the risk of new-onset FM in different sex groups through detailed subgroup analysis. Notably, for male COVID-19-infected people, vaccination significantly reduced the risk of new-onset FM (HR 0.520; 95% CI 0.342–0.792). However, for females, the effect of vaccination was not significant (HR 1.003; 95% CI 0.820–1.228). The protective effect of COVID- 19 vaccination on the risk of new-onset FM was primarily observed in male survivors. Firstly, females were more susceptible to FM than males. Studies have demonstrated that the male-to-female ratio in both clinical and population-based studies ranges from 1:6 to 1:9 [1]. This gender disparity was thought to be linked to various factors, including differences in physiological structure, hormone levels, immune system characteristics, and psychosocial influences [37, 38]. While vaccination may offer a certain degree of immune protection, its efficacy may be diminished in females due to their heightened susceptibility to FM. Secondly, Ursini et al. identified male sex as an independent and strong predictor of new-onset FM following COVID- 19 infection, suggesting that the observed increase in FM prevalence among males could be attributed to a generally more aggressive disease course [12]. Males may experience a more severe clinical progression of COVID- 19. Specifically, the hospitalization rate for COVID- 19 is approximately 50% higher in males compared to females, with the rate of male patients requiring intensive care units being 2–4 times greater than that for females [39]. Therefore, the COVID- 19 vaccine may play a crucial

role in mitigating the severity of symptoms and damage caused by the virus, thus reducing the risk of new-onset FM after COVID- 19 infection.

This study found that the COVID- 19 vaccine offered some protection against new-onset FM in COVID- 19 patients with a BMI < 30. However, as BMI increased, this protective effect gradually diminished and was no longer statistically significant. This phenomenon may be attributed to immune dysfunction, reduced humoral response, and socio-behavioral factors associated with obesity. Specifically, the humoral immune response in obese individuals decreased with increasing BMI [40, 41], and the rate at which antibody titers decline was faster, resulting in a lower neutralizing capacity compared to individuals with a normal BMI [41, 42]. Moreover, during the pandemic, obese individuals were disproportionately affected by lockdown measures, which led to poorer dietary habits, decreased physical activity, and impaired weight management [43]. These factors could contribute to negative emotions, such as anxiety and depression, which, in turn, may weaken immune function and reduce vaccine efficacy. In light of these findings, future vaccination strategies should address the specific needs of the obese population, such as incorporating booster doses to sustain immunity, thereby enhancing protection against COVID- 19 and reducing the risk of new-onset FM in obese individuals.

According to the subgroup analysis of this study, the risk of new-onset FM in COVID- 19 survivors with comorbid anxiety or depressive symptoms was significantly reduced by approximately 50% after vaccination. Mental health has been shown to have a significant correlation with FM [44], and the COVID- 19 epidemic has had a profound impact on global mental health [45]. First, anxiety and depression are associated with chronic inflammation and immune system dysregulation. The COVID- 19 vaccine may mitigate the inflammatory response, thereby reducing the risk of new-onset FM [46]. Additionally, vaccination offers a sense of psychological security for COVID- 19 survivors, which may reduce psychological stress and negative emotions [47], thereby indirectly preventing new-onset FM.

Sensitivity analysis enhanced the robustness of research conclusions. Meta-analyses have confirmed that COVID-19 vaccination was effective in protecting patients with rheumatic diseases from severe illness caused by the virus and was generally considered safe [48]. Moreover, vaccinated patients with rheumatic diseases had exhibited a lower incidence of pneumonia and hospitalization compared to their unvaccinated counterparts [49]. The sensitivity analysis in our study, which redefined the unvaccinated group and validated the results within a global collaborative network, showed a reduced effect of vaccination on the risk of FM. This finding aligns with previous studies suggesting that vaccines helped reduce the risk of various diseases. Restricting the analysis to individuals with prior medical visits further mitigated the potential for missed diagnoses due to inadequate medical attention, thereby increasing the reliability of the results. Notably, a trend towards a protective effect of COVID-19 infection was observed in elderly individuals (aged over 65) within high-risk populations, although this did not reach statistical significance. Our study found that COVID- 19 vaccination may have a significant protective effect against the onset of FM in females, individuals with a BMI < 30, and those with depression and anxiety. Consequently, vaccination strategies should include mental health support and education to encourage vaccination among these vulnerable groups.

It is important to note that individuals' vaccine hesitancy and attitudes [50] may influence their acceptance and response to health information. Those who choose not to be vaccinated may exhibit skepticism towards health information [51], which could affect their awareness of symptoms and willingness to seek medical treatment, thereby increasing their susceptibility to FM. In contrast, vaccinated individuals may be more proactive in seeking healthcare services, potentially reducing the incidence of FM. Additionally, psychological factors [51], such as fear of vaccination or mistrust of the medical system, along with excessive worry and panic, may increase the risk of developing new-onset FM.

Our study had several strengths that enhanced the robustness of our results. First, the TriNetX electronic health record database, which contains the largest world COVID- 19 dataset [52] and encompasses diverse geographic locations, age groups, and racial populations, was utilized. We established a large national cohort through the TriNetX network to investigate the association between COVID- 19 vaccination and new-onset FM in COVID- 19 survivors. Second, we restricted the COVID- 19 diagnosis to individuals who tested positive by RNA or antigen tests (using antigen testing as the index event) to avoid misclassification bias. Furthermore, the validity of COVID- 19 vaccination and diagnosis within this dataset is well-established. We matched vaccinated and unvaccinated cohorts on variables such as age, race, socioeconomic factors, and comorbidities and performed subgroup and sensitivity analyses to verify the potential impact of other factors on the results.

This study has several limitations. First, it focused on cases of new-onset FM in a hospital setting following COVID- 19 recovery and potential biases, such as underdiagnosis of FM due to variations in healthcare access across demographics. As a result, individuals who did not seek medical attention and were not diagnosed with new-onset FM may have been excluded from the analysis. This

selection bias could lead to a misestimation of the true effect between new-onset FM and COVID- 19 vaccination. Second, the use of electronic health record data may be susceptible to underdiagnosis, overdiagnosis, or misdiagnosis, misclassification bias and may not account for all potential confounding factors. Finally, the database lacked detailed information on autoimmune status, B-cell function, genetic predispositions, and post-COVID- 19 and FM diagnoses, limiting our study of the biological mechanisms underlying the observed associations.

Conclusions

This cohort study suggests that the risk of new-onset FM may be lower in COVID- 19 survivors who are vaccinated, compared to those who are unvaccinated, particularly among males and individuals with anxiety or depression. These findings underscore the potential protective effect of COVID- 19 vaccination in reducing the risk of new-onset FM in COVID- 19 survivors. Future research should explore the mechanism of the effects of vaccination on new-onset FM following COVID- 19.

Abbreviations

FM	Fibromyalgia
BMI	Body mass index
COVID- 19	Global pandemic of coronavirus disease
SARS-CoV- 2	Severe acute respiratory syndrome coronavirus 2
CD64	Fc gamma receptor I
EHRs	Electronic health records
HCOs	Health care organizations
SMD	Standardized mean difference
HR	Hazard ratio
CIs	Confidence intervals
PSM	Propensity score matching
IL- 7	Interleukin-7

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04069-z.

Additional file 1: Figures 1–6. Table 1 Definition of SARS-CoV-2 infection (at least 1 outpatient/inpatient visit within 1 year before SARS-CoV-2 infection). Table 2 Codes for vaccinated and unvaccinated group definition. Table 3 Codes for definitions of covariates. Table 4 Baseline characteristics of the study population. Table 5 Subgroup analysis. Table 6 Sensitivity analysis. Table 6-1 Hazard ratio and 95% CIs for the risk of fibromyalgia. Table 6-2 Hazard ratio and 95% CIs for the risk of fibromyalgia by global collaborative network. Table 6-3 Hazard ratio and 95% CIs for the risk of fibromyalgia by at least two visits before the index date. Table 6-4 Hazard ratio and 95% CIs for the risk of fibromyalgia by severe COVID-19 cases

Acknowledgements

The authors would like to express their deep appreciation to Zhejiang Provincial People's Hospital and National Natural Science Foundation of China for their financial support. Special thanks are due to Dr. Zhenhua Ying and Dr. James Cheng-Chung Wei for their invaluable guidance and expertise throughout the study. Our gratitude extends to the participants of the study, without whom this research would not have been possible. We also thank the reviewers for their constructive comments and suggestions, which have helped to improve the manuscript significantly.

Authors' contributions

A.L. contributed to the study design and manuscript writing; P.L. contributed to the methodology and software usage;H.J. contributed to the creation of figures and the review of the manuscript;S.H. contributed to the organization of data;S.L. contributed to the refinement of statistical methods;J.W. contributed to the improvement of the overall study design and the revision of the manuscript;Z.Y. contributed to the enhancement of the study design and the supervision of the entireresearch project.

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Funding

This work was supported by the Key Laboratory of Traditional Chinese Medicine Arthritis Diagnosis and Treatment Research in Zhejiang Province (grant number A- 2023-W2008).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board for Ethics of Chung Shan Medical University Hospital (IRB number: CS2 - 21176) and was performed in accordance with the Declaration of Helsinki.

Consent for publication

All authors consent for publication.

Competing interests

The authors declare no competing interests.

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Received: 15 October 2024 Accepted: 10 April 2025
Published online: 01 May 2025

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