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Characterizing Persistent Post-COVID-19 Vaccination Symptoms Using MedDRA System Organ Class and Preferred Term Classifications

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Abstract

Post-COVID-19 Vaccination Syndrome (PCVS) refers to persistent, multisystemic symptoms developing after SARS-CoV-2 immunization. We established a nationwide registry across 14 Japanese outpatient clinics and analyzed 179 “clinically definitive” cases from 279 enrollees (December 2020–August 2023). All adverse events (AEs) were coded using MedDRA/J Preferred Terms and System Organ Classes; severity followed NCI-CTCAE V5.0. The cohort (66.5% female; mean age 59 years) experienced 493 AEs (median 2 per patient, range 1–29). Three System Organ Classes—General Disorders (29.2%), Nervous System Disorders (22.3%), and Musculoskeletal Disorders (10.1%)—accounted for 61.7% of events; fatigue, brain fog, dizziness, and extremity pain predominated. While 69.4% of AEs arose within 90 days post-vaccination, 12.4% appeared ≥360 days later. Severe AEs (≥Grade 3) occurred in 14.6% of patients; overall improvement was 65.1%, leaving 29.4% unresolved. A provisional phenotype classification combining symptom patterns, onset timing, and severity identified high-risk subgroups with >60% non-recovery rates. These findings underscore the need for enhanced post-vaccination surveillance systems and comprehensive care frameworks specifically tailored to address the protean manifestations and persistent nature of PCVS.

Keywords:

COVID-19 Vaccines/adverse effects; Pharmacovigilance; Adverse Drug Reaction Reporting Systems; Post-Acute COVID-19 Syndrome; Fatigue Syndrome, Chronic; Nervous System Diseases/etiology;

Introduction

The emergence of coronavirus disease 2019 (COVID-19) in late 2019 precipitated an unprecedented global race in vaccine development and deployment, resulting in substantial reductions in severe disease and mortality worldwide [1–3]. However, post-authorization surveillance has demonstrated that continuous pharmacovigilance remains essential [4–7]. Novel vaccine platforms—particularly mRNA-based vaccines—raise the possibility of adverse events that may elude detection in pre-approval clinical trials, highlighting the need for robust surveillance systems capable of monitoring long-term safety outcomes [8–11].

Large-scale epidemiological surveillance has already revealed this complexity. The Global Vaccine Data Network, analyzing 99 million individuals across multiple countries, has identified rare but clinically significant safety signals—including transverse myelitis and acute disseminated encephalomyelitis—while confirming previously recognized risks such as myocarditis and pericarditis [12]. Complementary evidence from a Belgian prospective cohort showed that moderate-to-severe booster-related reactions occurred in only 11% of recipients, but clustered among individuals with prior adverse events and female participants [13]. Collectively, these findings indicate that while absolute risk remains low, adverse events exhibit heterogeneous distribution patterns, underscoring the need for refined, symptom-level classification within precision medicine frameworks.

Recently, a constellation of persistent, multisystemic symptoms—including fatigue, exercise intolerance, and cognitive impairment ("brain fog")—has been recognized as Post-COVID-19 Vaccination Syndrome (PCVS). Immunological profiling conducted at Yale University revealed a distinct PCVS immunophenotype characterized by circulating spike protein and aberrant cytokine signatures, offering a foothold for future biomarkers [14–16]. Nevertheless, taxonomic definitions, case criteria, and prevalence estimates remain inconsistent across studies [17], thereby impeding cross-study comparability and meta-analytical synthesis.

The clinical and societal implications are substantial. PCVS may result in occupational disability and restricted healthcare access, yet compensation schemes and clinical guidelines remain underdeveloped [18]. Therefore, a longitudinal surveillance system employing internationally standardized nomenclature—such as the Medical Dictionary for Regulatory Activities (MedDRA)—is urgently required. Such a framework would simultaneously support affected individuals and inform evidence-based vaccination policy development.

In this study, we synthesize the current evidence on PCVS pathophysiology, emphasize its heterogeneity and delayed onset, and propose a research roadmap aimed at establishing diagnostic criteria and guiding clinical interventions. By doing so, we seek to address the outstanding challenges in post-vaccination care and lay the groundwork for next-generation pharmacovigilance.

Methods

Study Design and Participants

This study was a non-controlled, open-label, non-interventional observational registry study investigating persistent symptoms following COVID-19 vaccination, commonly referred to as PCVS. It was conducted based on spontaneous reports submitted by patients or their families. Eligible participants were individuals who received clinical care for adverse events at one of 14 collaborating medical institutions across Japan between December 2020 and August 31, 2023. Symptoms were subsequently assessed by study investigators and classified as ‘clinically definitive’ or ‘clinically probable’ in association with COVID-19 vaccination. Written informed consent was obtained from patients whenever possible. In cases where the outcome was death, consent for study participation and data use was obtained from legally authorized family members, in accordance with institutional review board approval. A total of 279 patients were registered in the study registry.

The study protocol received approval from the Research Ethics Committee of the Faculty of Life Sciences and Medicine, Hamamatsu University School of Medicine, on November 29, 2023 (Approval No. #23-

222), with study initiation on December 1, 2023. The planned study completion date was October 31, 2024, with enrollment continuing until February 29, 2024, at each participating site following institutional approval. The 14 participating institutions consisted predominantly of private outpatient clinics. The number of enrolled cases per facility and the geographic distribution of participating sites are presented in Figure 1.

Data Collection

Data collection encompassed informed consent documentation (date and identity of consenting individual), baseline demographic and clinical characteristics (date of birth, sex, medical history, comorbidities), and comprehensive COVID-19 vaccination history (vaccine type, number of doses, vaccination dates). Additionally, information regarding prior SARS-CoV-2 infections (number of episodes, diagnostic methods, onset dates) was recorded. History of prior COVID-19 infection was ascertained based on patient self-report and, when available, review of medical records documenting laboratory-confirmed infection.

Regarding adverse events (AEs), the registry captured data on date of onset, symptom name, severity assessment, and investigator-determined causal relationship with vaccination. Treatment details (treatment modality and response), laboratory and imaging results (test names, dates, outcomes), and biobank-related data (specimen type, collection date, storage methodology, volume) were also obtained. The feasibility of biospecimen collection was documented for each case. These data elements were considered essential for a comprehensive COVID-19 vaccine safety assessment and clinical characterization of the syndrome.

Criteria for Causality Assessment with COVID-19 Vaccination

Causality assessment between symptoms and COVID-19 vaccination was performed by study investigators based on clinical and epidemiological evidence derived from accumulated case data, employing two classification categories: “clinically definitive” or “clinically probable.”

The “clinically definitive” designation was applied to patients who were asymptomatic or in stable clinical condition (not requiring medical intervention for pre-existing conditions) prior to vaccination but subsequently experienced health deterioration sufficient to necessitate medical care post-vaccination. Eligibility criteria required: (1) symptom persistence following vaccination; (2) classification of symptom onset into three temporal categories: within 1 month (early onset), 1–6 months (intermediate onset), and more than 6 months (late onset). These time frames were defined for individual-level causality assessment and were not used as variables in the statistical analysis; and (3) exclusion of alternative etiologies through comprehensive clinical evaluation. Furthermore, cases with no abnormal findings on health examinations conducted within one year prior to vaccination, or cases demonstrating vaccine-derived spike protein in biospecimens, were classified as "clinically definitive."

Conversely, patients with pre-existing medical conditions that remained stable for at least one month prior to COVID-19 vaccination but subsequently developed unexpected symptom exacerbation were classified as "clinically probable," provided their symptoms fulfilled the aforementioned three criteria and could not be attributed to progression of the underlying disease process.

Definition and Grading of Adverse Events

Severity of AEs was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), utilizing a five-point scale from Grade 1 to Grade 5. In instances where CTCAE terminology was not applicable, severity assessment was based on impact on activities of daily living (ADLs). Grade 1 indicated mild symptoms or asymptomatic abnormalities not requiring therapeutic intervention. Grade 2 encompassed moderate symptoms interfering with some ADLs but manageable with non-invasive treatment. Grade 3 denoted severe conditions requiring hospitalization or prolonged absence from work. Grade 4 represented life-threatening conditions, and Grade 5 indicated death attributable to the AE. Serious AEs were defined as those resulting in death, life-threatening events, hospitalization or prolongation thereof, disability, congenital anomalies, or other medically significant events. Regarding the temporal aspect, AEs were further classified as persistent, intermittent, or other patterns.

Outcome Measures

The primary outcome measure was the clinical profile and incidence of AEs deemed "clinically definitive" in their causal association with COVID-19 vaccination. Secondary outcome measures included the presence of severe AEs (Grade ≥3), the presence of vaccine-related AEs that could not be excluded, and the latency period from vaccination to symptom onset.

AEs were systematically coded using the most recent Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J), applying Preferred Term (PT) classification. When patients experienced multiple episodes of the same PT during the vaccination series, only the initial occurrence was counted as a single event. Onset date was defined as the date of first clinical presentation, severity was recorded as the highest observed grade during follow-up, and clinical outcome was determined as of the most recent follow-up assessment.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Between-group comparisons for continuous variables were conducted using the Wilcoxon rank-sum test, and categorical variables were compared using the chi-square test or Fisher's exact test, as statistically appropriate.

Adverse events were systematically classified by PT and System Organ Class (SOC) using the most recent MedDRA/J version. In event-based analyses, each unique PT was counted as an individual event, even when multiple PTs were recorded for a single patient. For case-based analyses, repeated recordings of the same PT were counted once per patient. The maximum severity grade per patient was used, with Grade ≥3 defined as severe.

The time interval between vaccination and AE onset was calculated and stratified into three categories: <90 days, 90–359 days, and ≥360 days. These time-period categories were used exclusively for statistical analysis to describe the temporal distribution of adverse event onset across the study population. AE incidence rates were calculated by dividing the number of cases with each specific AE by the total number of eligible patients; however, because information on the total vaccinated population served by participating sites was unavailable, these values represent registry-based proportions rather than true population-level incidence estimates.

Symptom phenotypes were classified into four types based on combinations of three SOCs: “General Disorders and Administration Site Conditions,” “Nervous System Disorders,” and “Musculoskeletal and Connective Tissue Disorders.” The four phenotype classifications were:

Type 1 – involvement of all three SOCs;

Type 2 – General + Nervous;

Type 3 – General + Musculoskeletal;

Type 4 – Nervous + Musculoskeletal.

Clinical outcomes (complete recovery, partial remission, persistent symptoms, deterioration, or death) were compared across these phenotypic categories.

Recovery proportions and time to recovery were analyzed by individual PT. Among patients presenting with a given PT, the proportion achieving recovery or remission was calculated, and time to recovery was reported as median and interquartile range (IQR).

For visualization of symptom clustering patterns, a binary matrix (0/1) was constructed to represent the presence or absence of each symptom, and a heatmap was generated to explore overall distributional trends. No statistical clustering algorithms or distance metrics were applied; the analysis was purely descriptive, focusing on frequency distributions and co-occurrence patterns.

All statistical tests were two-tailed, with statistical significance defined as p-value <0.05. Missing data were not imputed and were analyzed as missing values. Given the exploratory nature of this analysis, no correction for multiple comparisons was applied. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics and Trial Registration

This study was conducted in accordance with all relevant ethical guidelines and regulatory requirements, having received approval from the Research Ethics Committee of Hamamatsu University School of Medicine. The study protocol was approved on November 29, 2023, and subsequently registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry on February 9, 2024 (Registration ID: UMIN000053578).

Results

Study Cohort Characteristics

A total of 279 cases were enrolled in this study. Of these, 179 patients were included in the primary analysis based on the determination that their symptoms were "clinically definitive" in relation to COVID-19 vaccination. Within this analytical cohort, 119 participants were female and 60 were male, yielding a female predominance of 66.5% (Figure 2a). Participant ages ranged from 14 to 91 years, with a mean age at consent of 59.3 years. The age distribution is shown in Figure 2b.

COVID-19 Vaccination History and Infection Status

As illustrated in Figure 2c, the most frequently reported number of vaccine doses was three (n = 76, 42.4%), followed by two doses (n = 37, 20.7%), four doses (n = 24, 13.4%), and one dose (n = 17, 9.5%). A total of 25 individuals (14.0%) received five or more doses.

Regarding infection history, 47 patients (26%) reported at least one confirmed episode of COVID-19, of whom two experienced infections within one month preceding symptom onset. Only one individual (0.5%) reported a history of two infections, while 131 cases (73%) did not report any confirmed COVID-19 infection. This substantial proportion of patients without reported COVID-19 infection may reflect the registry's specific focus on individuals seeking medical care for vaccination-related symptoms or potential underreporting of asymptomatic infections.

Temporal Characteristics of Adverse Event Onset

Figure 3 depicts the time interval between index COVID-19 vaccination and onset of AEs judged to be definitively associated with the vaccination. Among 493 total AEs, 325 (69.4%) occurred within 90 days of vaccination, while 58 events (12.4%) manifested more than 360 days post-vaccination, indicating a notable subset of delayed-onset presentations. Among the 58 adverse events that occurred ≥360 days after vaccination, the most frequently observed preferred terms were cognitive disorder (brain fog) and gait disturbance (each n=3). Depression, pyrexia, polymyalgia rheumatica, headache, pruritus, hypoesthesia, alopecia, fatigue, herpes zoster, and pain in extremity were each observed twice. With respect to severity, 47 events were classified as Grade 1–2 and 11 as Grade ≥3. At the last available follow-up, 28 events showed partial improvement and 10 had recovered, while 17 events remained persistent, including one fatal case. A detailed summary by preferred term is provided in Supplementary Table S1.

Frequency and Classification of Adverse Events by MedDRA System Organ Class

The frequency distribution of AEs by System Organ Class (SOC), based on MedDRA classification, is presented in Figure 4a. The most prevalent SOC was "General Disorders and Administration Site Conditions" (n = 144, 29.2%), followed by "Nervous System Disorders" (n = 110, 22.3%) and "Musculoskeletal and Connective Tissue Disorders" (n = 50, 10.1%). These top three SOCs collectively accounted for 61.7% of all documented AEs (n = 493).

The detailed breakdown of PTs within these three major SOCs is illustrated in Figures 3b-d. Within "General Disorders," seven specific

PTs—fatigue, chronic fatigue syndrome, pyrexia, gait disturbance, exhaustion, pain, and chest pain—constituted 87.5% of cases In “Nervous System Disorders,” the PTs of floating dizziness, headache, brain fog, hypoesthesia, and dysgeusia comprised 76.4% of events. Within “Musculoskeletal Disorders,” extremity pain, arthralgia, muscle weakness, fibromyalgia, polymyalgia rheumatica, and back pain represented 74.0% of the category. Despite considerable clinical heterogeneity, symptoms demonstrated a tendency to cluster within well-defined PT groupings.

Clinical Outcomes and Recovery Patterns

The clinical outcomes of all AEs deemed definitively associated with vaccination are illustrated in Figure 5a. Complete recovery was observed in 133 events (27.0%), while partial remission to a tolerable level occurred in 188 events (38.1%), resulting in an overall improvement rate of 65.1%. In contrast, 145 events (29.4%) remained unresolved, 5 events (1.0%) worsened over time, and 6 events (1.2%) resulted in death. When classified by SOC, “General Disorders and Administration Site Conditions” (Figure 5b) and “Nervous System Disorders” (Figure 5c) demonstrated the overall improvement (complete recovery + partial remission to a tolerable level) rates of 60.7% and 68.2%, respectively, whereas “Musculoskeletal Disorders” exhibited the lowest improvement rate at 48.0% (Figure 5d).

Symptom Pattern Analysis and Phenotypic Classification

A comprehensive heatmap illustrating individual symptom profiles for each case with definitively vaccine-related AEs is provided in Figure 6. Among the 179 patients, 59 (33.0%) presented with only a single symptom, whereas the remaining 120 individuals exhibited multiple concurrent symptoms, with the most complex case demonstrating 29 distinct symptoms.

Figure 7a presents clinical outcomes of all definitively associated AEs across the entire analytical cohort. Phenotypic classification based on combinations of the three predominant SOCs yielded four distinct subtypes: Type 1 (General + Nervous + Musculoskeletal): n = 12; Type 2

(General + Nervous): n = 42; Type 3 (General + Musculoskeletal): n = 15; Type 4 (Nervous + Musculoskeletal): n = 4. As demonstrated in Figure 7b, more than half of the cases in each phenotypic subtype showed no clinical improvement ("no recovery event").

Symptom-Specific Recovery Rates and Recovery Duration

Figure 8 presents the PT-specific recovery rates and durations, with durations evaluated among recovered AEs. For 20 key PTs—including fatigue, exhaustion, chest pain, pain, chronic fatigue syndrome, gait disturbance, headache, brain fog, floating dizziness, hypoesthesia, dysgeusia, tremor, arthralgia, polymyalgia rheumatica, back pain, alopecia, pruritus, dyspnea, asthma, nausea, and palpitations—the recovery rate was below 50%. The median time to recovery for these symptoms ranged from 150 to 300 days, indicating a prolonged clinical course.

Discussion

Principal Findings and Clinical Significance

In this comprehensive registry-based study, we analyzed 179 cases identified as Post-COVID-19 Vaccination Syndrome (PCVS) from a cohort of 279 individuals and present a detailed characterization of their clinical features using standardized MedDRA terminology. Our principal findings demonstrate that: (i) 61.7% of all adverse events concentrated within three major MedDRA System Organ Classes "General Disorders," "Nervous System Disorders," and "Musculoskeletal and Connective Tissue Disorders"; (ii) approximately 12% of adverse events exhibited delayed onset, occurring more than 360 days after vaccination; and (iii) among patients with Type 1 symptomatology (involving all three major SOCs), 63% remained without clinical improvement. These findings align with prior reports from large-scale international cohorts that identified rare but clinically significant AEs [12], as well as studies demonstrating clustering of moderate-to-severe reactions within specific demographic subpopulations following booster vaccination [13]. Moreover, our results are consistent with recent immunological evidence characterizing PCVS as a syndrome with distinct patterns of immune dysregulation [14–16]. Collectively, our data reinforce an evolving safety profile in which the absolute risk remains low, but a subset of individuals may experience multisystemic and protracted symptomatology, thereby underscoring the need for stratified post-vaccination care and surveillance. These results are also consistent with prior observations suggesting that PCVS symptoms may follow a biphasic or delayed-onset pattern, particularly after booster vaccination [19].

Methodological Rationale for MedDRA-Based Classification

Adverse events associated with PCVS were analyzed exclusively among the 179 cases determined to be “clinically definitive,” and were systematically coded using the most recent Japanese version of MedDRA at both SOC and PT levels. MedDRA, established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), represents the globally recognized standardized terminology for adverse event classification in pharmacovigilance. Its implementation ensures terminological precision and consistency in case reporting, thereby facilitating valid comparisons across institutions and studies [20–22]. Given that our registry predominantly comprised community-based practitioners capturing a broad spectrum of undifferentiated symptoms often preceding definitive diagnosis, the implementation of standardized MedDRA coding played a crucial role in minimizing ambiguity inherent in free-text clinical descriptions and reducing analytical bias. Notably, MedDRA has recently undergone systematic updates to expand its vaccine-related lexicon—incorporating terms such as “Post-vaccination syndrome”—thereby enhancing compatibility with international pharmacovigilance databases and enabling cross-platform analyses [23] Taken together, the adoption of MedDRA was indispensable in ensuring the methodological rigor, interpretability, and external validity of this study’s findings.

Clinical Heterogeneity and Pathophysiological Considerations

Among cases deemed "clinically definitive" in their association with COVID-19 vaccination, we observed a remarkably broad and heterogeneous spectrum of clinical manifestations. More than two-thirds of patients (67%) presented with multiple symptoms either concurrently or sequentially, with individual cases exhibiting up to 29 distinct clinical manifestations (Figure 8).

Mechanistic Framework and Biological Plausibility

To provide biological context for the symptom patterns observed in this study, we summarize below several mechanistic hypotheses that have been proposed in the literature. COVID-19 vaccines utilizing the mRNA-lipid nanoparticle (mRNA-LNP) platform represent the first implementation of this technology at population scale [24,25]. Emerging evidence suggests that LNPs can undergo systemic biodistribution and may cross the blood-brain barrier [26,27], while the expressed spike protein has been implicated in various biological effects including vascular injury, inflammatory pathway activation, and neurotoxicity [28-31]. Recent human tissue analysis has provided direct evidence for central nervous system involvement, demonstrating prolonged presence of SARS-CoV-2 spike protein in cerebral arteries up to 17 months post-mRNA vaccination, with spike protein positivity observed exclusively in female patients and associated with inflammatory cell infiltration [32]. Additionally, LNPs themselves possess demonstrated pro-inflammatory properties, and the mechanism by which mRNA-LNP vaccines instruct host cells to produce foreign proteins has raised concerns regarding potential induction of autoimmune phenomena [33-37].

Consistent with these mechanistic considerations, our study documented a substantial frequency of neurological adverse events, including headache and brain fog (Figure 4b), aligning with prior epidemiological reports of increased neurological symptoms following mRNA-LNP vaccination [38]. The term "spikeopathy" has been proposed to describe the pleiotropic toxicities potentially mediated by spike protein [26]. While definitive causality cannot be established through observational data, the concordance between these experimental findings and our registry-based clinical observations highlights the importance of investigating inflammatory and autoimmune mechanisms in PCVS pathogenesis.

Sex-Based Vulnerability and Potential Hormonal Modulation

The observed predominance of PCVS in female participants (Figure 2a) raises the possibility that spike protein interaction with estrogen receptors may contribute to sex-specific vulnerability patterns [39]. Although the precise mechanisms remain to be elucidated, this hypothesis is consistent with established literature on vaccine-associated adverse events and the recognized female predominance in immune-mediated disorders. Future research incorporating comprehensive hormonal and immunological profiling may help clarify the biological underpinnings of this observed sex-based disparity.

Delayed-Onset Symptoms and Long-Term Surveillance Implications

Approximately 70% of definitively associated adverse events in our study occurred within 90 days of the most recent vaccination. However, a clinically significant subset—12.4%—presented with symptom onset beyond 360 days post-vaccination. This delayed onset pattern raises important questions regarding the long-term persistence of immunological triggers. Recent studies have reported prolonged presence of spike protein in host tissues following vaccination [14,32,40], which provides biological context for the late-emerging symptom patterns observed in this registry, rather than evidence of a causal relationship. While these findings remain preliminary, they underscore the critical need for extended clinical surveillance in PCVS cases and highlight significant limitations of short-term safety assessments in current post-vaccine pharmacovigilance protocols. Accordingly, adverse events with onset ≥360 days after vaccination are described here as observational patterns that warrant further investigation, rather than as evidence of a causal association with vaccination.

Clinical Utility of Provisional Phenotypic Classification

The provisional classification matrix developed in this study—incorporating symptom cluster types (Types 1–4), onset timing (early, intermediate, delayed), and severity grading (defined as CTCAE Grade ≥3)—may serve as a valuable framework for clinical risk stratification in patients presenting with PCVS. For instance, the subgroup characterized as Type 1 + delayed onset + Grade ≥3 demonstrated a non-recovery rate exceeding 60%, indicating substantial need for long-term monitoring and proactive therapeutic intervention, such as vitamin D supplementation [41]. Conversely, individuals categorized as Type 4 + early onset achieved symptom remission within six months in over 80% of cases, suggesting that expectant management with periodic clinical observation may be appropriate for this subgroup. This three-dimensional classification system supports previously proposed PACS/PVS symptom cluster frameworks [42] with empirical data from Japanese patients and may serve as a provisional diagnostic framework bridging clinical decision-making and compensation assessment processes in the current absence of established diagnostic codes. Future research should prioritize validation of this classification system in external cohorts and enhancement of its precision through incorporation of biological markers such as persistent spike antigen or disease-specific autoantibodies.

Related Syndromes and Pathophysiological Overlap

PCVS shares substantial clinical and immunological features with established post-viral syndromes, particularly myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Post-Acute Sequelae of SARS-CoV-2 infection (PASC or Long COVID). In the present registry, 24 cases received formal diagnosis of ME/CFS, though this likely underrepresents the true prevalence given potential diagnostic conservatism. Even among patients who did not fulfill complete diagnostic criteria, a substantial proportion exhibited core ME/CFS symptoms including persistent fatigue, post-exertional malaise, cognitive dysfunction, unrefreshing sleep, and widespread pain [43,44].

The clinical overlap extends beyond symptomatology to potential shared pathophysiological mechanisms. Recent literature has documented increasing numbers of ME/CFS-like cases following mRNA vaccination, with preliminary evidence suggesting therapeutic benefit from vitamin D supplementation in affected individuals [41]. The concept of “spikeopathy,” referring to spike protein-induced endothelial injury and mitochondrial dysfunction [26], has been proposed as a unifying mechanism linking PCVS, ME/CFS, and Long COVID. Within this conceptual framework, systematic reviews have demonstrated clinical and mechanistic overlaps between ME/CFS and Long COVID, suggesting these conditions may represent different manifestations along a pathobiological spectrum [45].

The core symptoms observed in PCVS—including chronic fatigue, brain fog, musculoskeletal pain, and orthostatic intolerance—closely parallel those described in PASC literature, with both syndromes sharing common immunopathological features including prolonged circulation of spike protein, cytokine imbalances, and autoantibody production [14,16,26].

Clinical Observations Supporting Continuity

Clinically, we have observed multiple cases in which patients previously diagnosed with and stabilized from PCVS experienced sudden relapses or exacerbations following subsequent SARS-CoV-2 infection. These observations suggest that viral infection may act as a trigger that reactivates or amplifies the underlying PCVS pathology. Such clinical patterns provide strong support for the hypothesis that PCVS and PASC constitute a pathophysiological continuum—representing different manifestations of a “spike protein-dependent post-acute syndrome spectrum” [17].

Diagnostic Implications and Future Directions

Given that over 80% of the Japanese population has received COVID-19 vaccination, it is highly probable that a significant proportion of patients currently diagnosed with PASC may be experiencing a PCVS-based mixed phenotype or post-infectious exacerbation of underlying PCVS ("PCVS-exacerbated PASC") pathology. The conventional binary classification based solely on presence or absence of prior infection may obscure the true nature of these disease processes. Moving forward, it is essential to adopt an integrative diagnostic framework incorporating immunological biomarkers, symptom chronology, clinical patterns, and comprehensive patient history. The clinical features and trajectories of PCVS elucidated in this study, along with its symptomatic overlap with PASC, highlight the urgent need to reconceptualize these conditions as a unified disease spectrum and to establish comprehensive care and compensation systems accordingly.

Current Institutional Landscape and Public Health Implications

As of July 25, 2025, 2,294 deaths related to COVID-19 vaccination have been reported to the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan [46]. Applications submitted to the national Health Damage Relief System for vaccination-related injuries have reached 13,975, of which only 9,260 were approved, including 1,031 fatalities (as of July 29, 2025) [47]. These statistics indicate the existence of a substantial number of unrecognized or unresolved claims.

Although the Ministry of Health, Labour and Welfare has instructed local governments to actively collect suspected adverse event reports [48] and has established consultation hotlines for individuals experiencing prolonged symptoms [49], the current infrastructure for medical referrals and compensation procedures remains insufficient. As a result, a growing population of so-called "medically marginalized patients" has become apparent—individuals whose symptoms persist but remain clinically and administratively unacknowledged.

Significance and Limitations of This Study

This study addresses this critical gap by establishing a domestic registry targeting PCVS patients with limited access to healthcare, utilizing standardized MedDRA-based terminology to systematically characterize the clinical manifestations of this syndrome. By leveraging a network predominantly composed of community-based private practitioners, the study successfully captured nuanced clinical details of PCVS cases. However, the inherent dependence on spontaneous reports renders the findings susceptible to underreporting and information gaps, thereby necessitating cautious interpretation regarding external validity. Despite these limitations, the registry serves as a foundational resource for visualizing the lived experiences of affected individuals and provides crucial empirical evidence to support future enhancements in both compensation frameworks and clinical care systems.

Implications for Clinical Practice and Public Health

PCVS currently lacks both diagnostic coding and inclusion in national compensation frameworks, thereby creating a cohort of medically marginalized patients who fall outside conventional healthcare systems [12]. The systematic categorization of symptom spectra using internationally standardized terminology, combined with longitudinal follow-up via real-time epidemiological platforms, represents an urgent public health priority [14,15,16].

The Yale group's identification of persistent spike protein circulation and cytokine dysregulation [14], combined with preliminary evidence of therapeutic benefit from vitamin D supplementation in affected individuals [41], offers promising avenues for establishing objective diagnostic criteria and individualized treatment strategies. Furthermore, given the substantial clinical overlap between PCVS, myalgic encephalomyelitis/chronic fatigue syndrome, and Long COVID [45], there exists a pressing need for harmonized nosological frameworks and development of transdisciplinary care models capable of addressing these interconnected syndromes.

Study Limitations

This investigation has several inherent methodological limitations that warrant consideration. First, as a registry initiated through spontaneous patient and family reports, the study is unavoidably subject to selection bias arising from underreporting, reporting delays, and incomplete information capture [18]. Second, the absence of a control group precludes comparative estimation of excess risk relative to background incidence rates in the general population. Third, interpretation of very late-onset adverse events (≥360 days after vaccination) is subject to substantial uncertainty within the current study design. Fourth, symptom assessment relied solely on clinical judgment regarding causality and lacked systematic implementation of objective biomarker measurements or advanced diagnostic imaging protocols. The study as a whole was not designed to establish overall causal relationships between vaccination and adverse events, and this limitation should be considered when interpreting the findings. Fifth, the study was geographically limited to 14 domestic institutions, predominantly in outpatient settings, which may constrain the generalizability of findings and necessitates cautious interpretation [17]. Finally, this study did not quantify socioeconomic consequences, including quality-of-life impairment or occupational disability measures, suggesting potential underestimation of the true societal burden associated with PCVS [18].

Conclusion

Although COVID-19 vaccination has been extensively promoted for its demonstrable public health benefits, this study highlights three critical dimensions of Post-Vaccination Syndrome that merit careful consideration in current risk-benefit assessments: (1) its protean and multisystemic clinical manifestations, (2) its potential for delayed onset presentation, and (3) the persistence of unresolved cases over extended follow-up periods. Collectively, these findings underscore the urgent need for a comprehensive, multifaceted response strategy encompassing: (i) establishment of standardized symptom definitions and objective biomarker criteria, (ii) long-term risk estimation through large-scale prospective cohort studies with extended follow-up, and (iii) development of personalized therapeutic strategies and institutional frameworks for medical and social support specifically tailored to the pathophysiology of PCVS. The empirical data presented in this investigation contribute foundational knowledge essential for advancing next-generation pharmacovigilance systems and therapeutic innovation in post-vaccination care.

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Data and materials availability

All requests for materials and raw data should be addressed to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Author Contributions Statement

AF, EN, and MF designed the study. AK, EO, MM, and YH performed the formal statistical analysis. AF, SK, NK, JU, EN, and MF interpreted the data. AF wrote the first draft of the manuscript. All authors contributed to the critical revision of the manuscript. All the authors have read and approved the final version of the manuscript.

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Figure Legends

Figure 1. Participating medical facilities and geographic distribution

Registry enrollment by participating medical institutions showing facility names, case contributions, and geographic distribution across Japan. The 14 facilities were predominantly private outpatient clinics distributed across multiple prefectures, with the highest concentrations in Hokkaido (northern Japan) and Osaka/Kansai region (central Japan). Honbetsu Cardiovascular Medicine Clinic and Kodama Hospital contributed the majority of cases (66 and 50 cases respectively), while Osaka Proctology Medical Clinic provided 51 cases. The remaining facilities contributed 1-22 cases each. Geographic distribution shows representation from northern (Hokkaido), central (Tokyo, Osaka), and other regional areas, providing a multi-regional perspective on post-COVID-19 vaccination syndrome presentations across Japan's healthcare system.

Figure 2. Baseline characteristics of patients with clinically definitive adverse events

Patient demographics and vaccination history for 179 cases classified as having clinically definitive vaccine-related adverse events. (a) Sex distribution showing female predominance (66.5%, n=119) compared to males (33.5%, n=60). (b) Age distribution by decade showing peak frequencies in the 50-59 and 60-69 year age groups, with female predominance maintained across most age categories. (c) Distribution of COVID-19 vaccine doses received, with three doses being most common (n=76), followed by two doses (n=37), four doses (n=24), and smaller numbers receiving 1, 5, 6, or 7 doses.

Figure 3. Temporal relationship between vaccination and adverse event onset

Time intervals from most recent COVID-19 vaccination to onset of clinically definitive adverse events. The distribution shows that approximately 325 events occurred within 0-89 days post-vaccination, with smaller numbers in subsequent time periods: 90-179 days (~50 events), 180-269 days (~20 events), 270-359 days (~10 events), and 360+ days (~50 events), demonstrating that while most adverse events occur early, a notable subset exhibits delayed onset beyond one year.

Figure 4. MedDRA classification of adverse events by System Organ Class and Preferred Terms

Distribution of 493 clinically definitive adverse events using MedDRA terminology. (a) System Organ Class frequency showing predominance of General Disorders and Administration Site Conditions (144 events), Nervous System Disorders (110 events), and Musculoskeletal and Connective Tissue Disorders (50 events), with smaller contributions from multiple other organ systems. (b) Preferred Terms within General Disorders showing chronic fatigue syndrome (24), malaise (51), pyrexia (13), gait disturbance (11), and fatigue (11) as leading manifestations. (c) Preferred Terms within Nervous System Disorders led by dizziness (24), headache (24), brain fog (17), and hypoesthesia (14). (d) Preferred Terms within Musculoskeletal Disorders showing arthralgia (8), pain in extremity (8), muscular weakness (7), fibromyalgia (6), and polymyalgia rheumatica (5) as predominant symptoms.

Figure 5. Clinical outcomes of adverse events by MedDRA System Organ Class

Recovery outcomes for clinically definitive adverse events showing complete recovery, partial improvement, and persistent symptoms. (a) Overall outcomes for all 493 events with 133 complete recoveries, 188 improved to tolerable level, 145 unresolved, 5 worsened, 6 deaths, and 14 unknown outcomes. (b) Outcomes for General Disorders and Administration Site Conditions showing 35 complete recoveries, 52 improved to tolerable level, and 50 unresolved. (c) Outcomes for Nervous System Disorders with 29 complete recoveries, 46 improved to tolerable level, and 29 unresolved. (d) Outcomes for Musculoskeletal and Connective Tissue Disorders showing 7 complete recoveries, 17 improved to tolerable level, 25 unresolved, and 1 death.

Figure 6. Individual patient symptom profiles using System Organ Class heatmap

Comprehensive visualization of symptom patterns for 179 patients with clinically definitive adverse events arranged by System Organ Class. Each row represents one patient, with columns indicating presence (dark blue) or absence (white) of symptoms within each MedDRA System Organ Class category. The heatmap reveals complex multi-system presentations across patients, with symptoms spanning General Disorders, Nervous System Disorders, Musculoskeletal Disorders, and multiple other organ systems, demonstrating the heterogeneous nature of post-vaccination syndrome manifestations.

Figure 7. Clinical outcomes across phenotypic subtypes based on major System Organ Classes

Recovery patterns for patients categorized by involvement of the three major SOCs. (a) Overall outcomes for all patients showing 36 with all event recovery, 34 with partial event recovery, and 109 with no event recovery. (b) Outcomes by phenotypic subtype based on SOC combinations: Type 1 (General + Nervous + Musculoskeletal), Type 2 (General + Nervous), Type 3 (General + Musculoskeletal), and Type 4 (Nervous + Musculoskeletal), with stacked bars showing proportions of complete recovery (light blue), partial recovery (medium blue), and no recovery (dark blue) for each subtype.

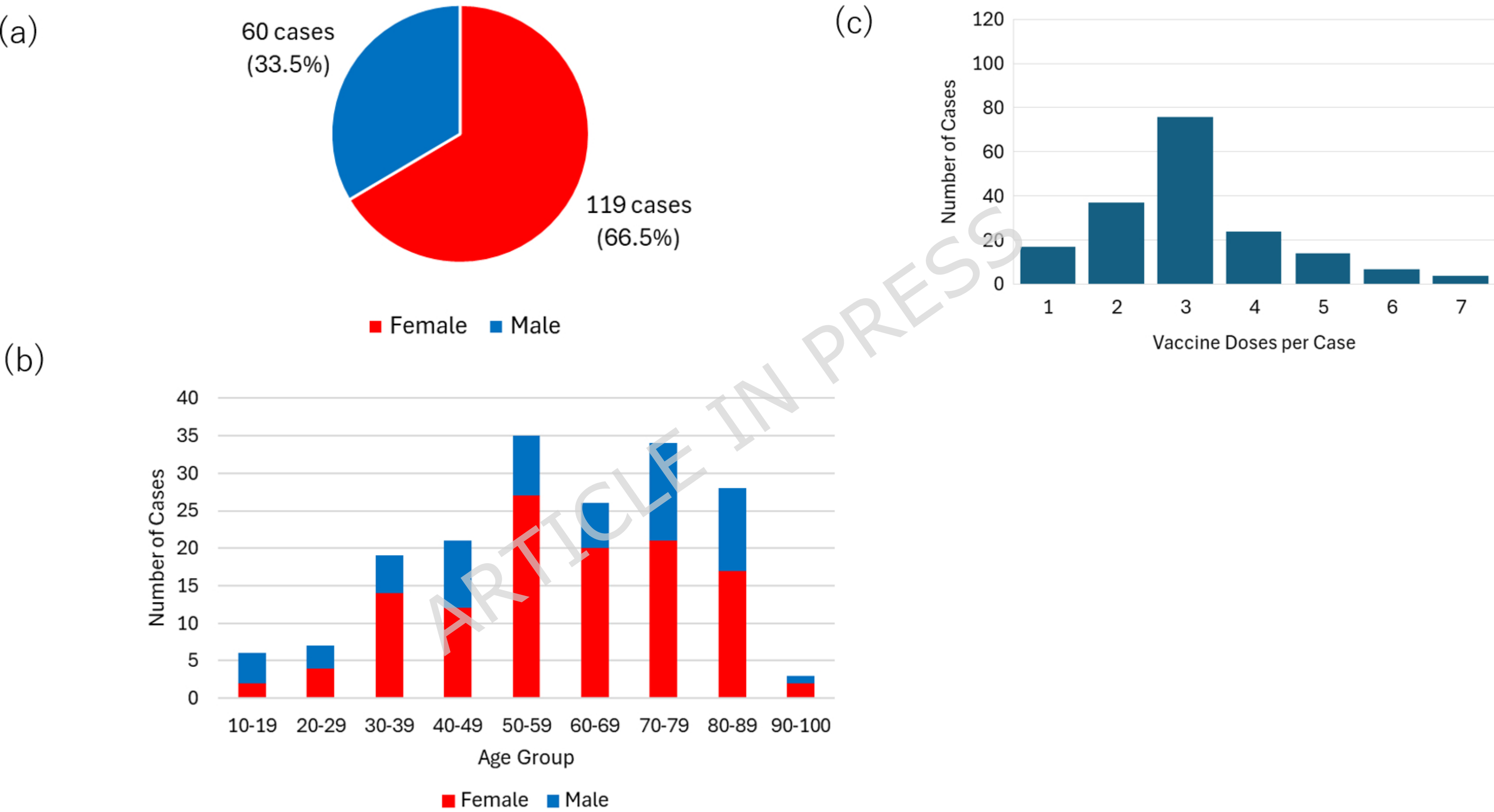
Figure 8. Recovery rates and time to recovery by individual Preferred Terms

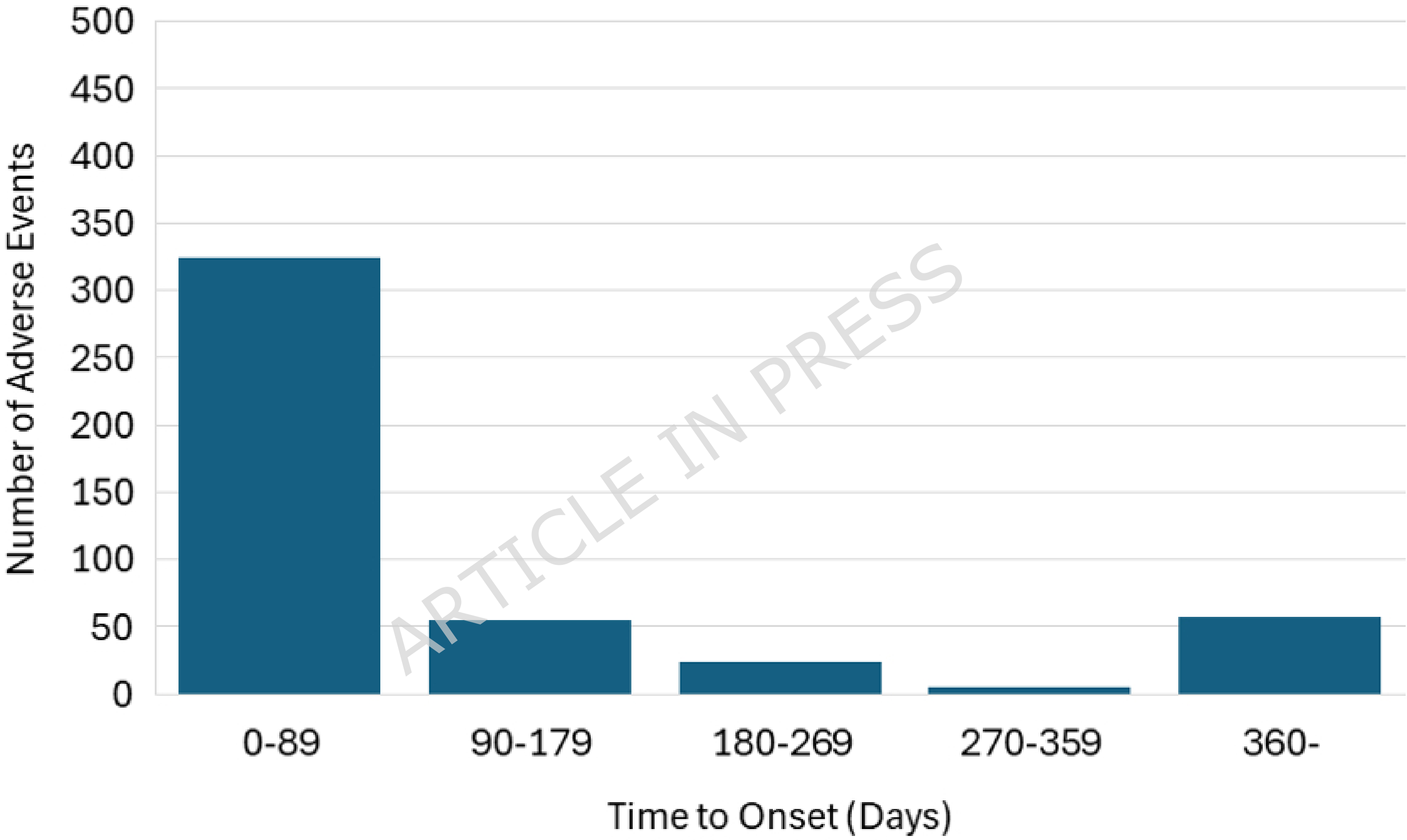
Symptom-specific recovery outcomes for individual MedDRA Preferred Terms showing the number of patients with each symptom (PT), number achieving recovery, recovery rate percentage, and median days to recovery. The comprehensive table demonstrates varying recovery patterns across different symptoms, with many neurological, general, and musculoskeletal symptoms showing prolonged recovery times exceeding 200-400 days, indicating the chronic nature of many post-vaccination syndrome manifestations.

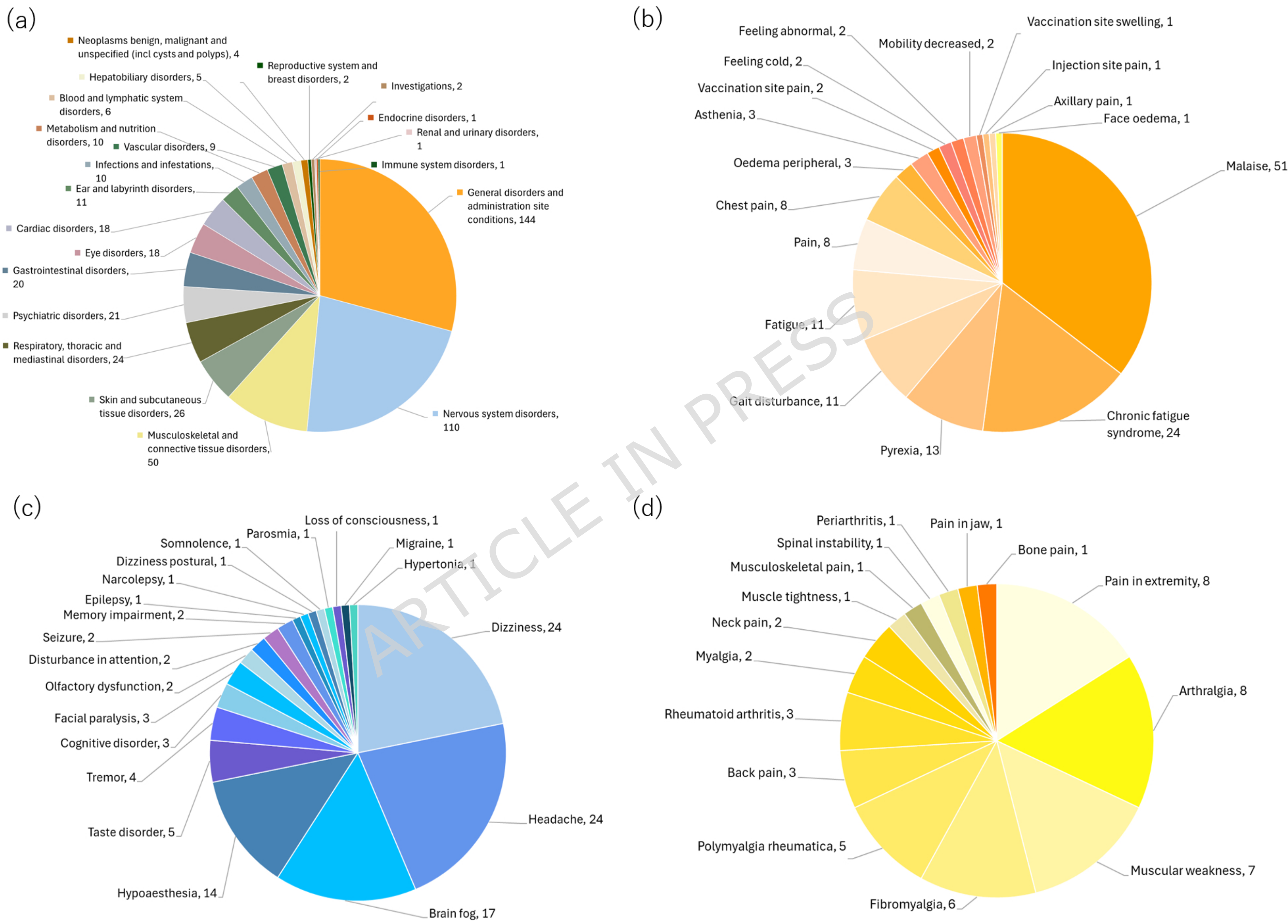
(a)

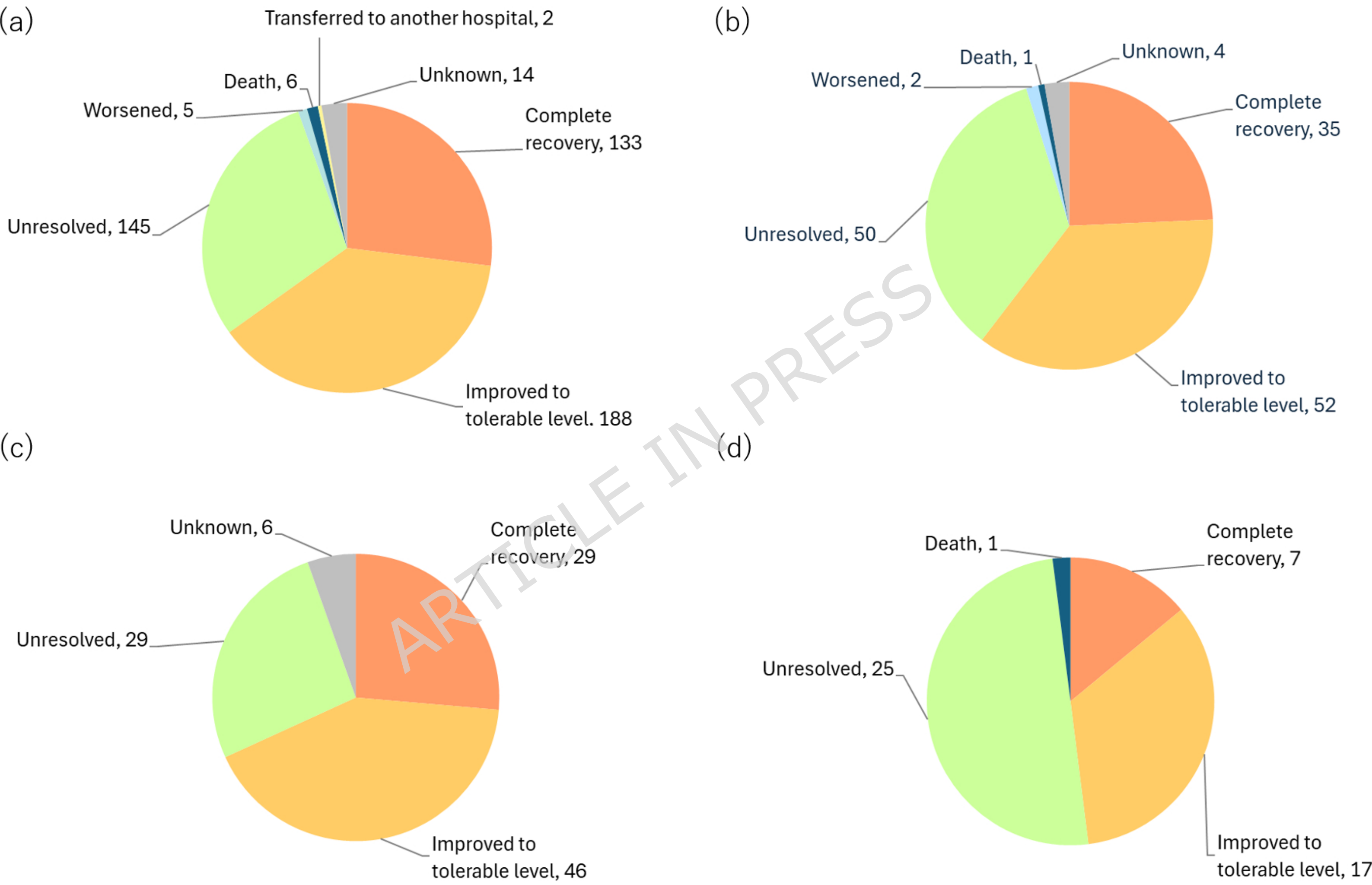
No	Name of facility	Number of registered cases
1	Honbetsu Cardiovascular Medicine Clinic	66
2	Kodama Hospital & Kodama Medical Office	50
3	Ikezawa Women's Health Clinic	6
4	Kamata Yoshino Medical Clinic	22
5	Koide Clinic	19
6	Osaka Proctology Medical Clinic	51
7	Koseido Medical Corporation, Suda Clinic	21
8	Kamihata ENT Clinic	8
9	Koshio Orthopedics Clinic	7
10	Kidasanyakudo Medical Clinic	6
11	Kobayashi Clinic	19
12	Fushimi Keimei Orthopedic & Osteoporosis Clinic of Sapporo	2
13	Otofuke ENT (Ear, Nose, and Throat) Clinic	1
14	Tokachi Mutsumino Medical Clinic	1

(b)


(a)
60 cases
(33.5%)
119 cases
(66.5%)
Female
Male
(b)
Number of Cases
40
35
30
25
20
15
10
5
0
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-100
Age Group
Female
Male
(c)
Number of Cases
120
100
80
60
40
20
0
1
2
3
4
5
6
7
Vaccine Doses per Case


500
450
400
350
300
250
200
150
100
50
0
Number of Adverse Events
0-89
90-179
180-269
270-359
360-
Time to Onset (Days)


(a)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), 4
Reproductive system and breast disorders, 2
Hepatobiliary disorders, 5
Investigations, 2
Blood and lymphatic system disorders, 6
Endocrine disorders, 1
Metabolism and nutrition disorders, 10
Renal and urinary disorders, 1
Vascular disorders, 9
Infections and infestations, 10
Immune system disorders, 1
Ear and labyrinth disorders, 11
General disorders and administration site conditions, 144
Cardiac disorders, 18
Eye disorders, 18
Gastrointestinal disorders, 20
Psychiatric disorders, 21
Respiratory, thoracic and mediastinal disorders, 24
Skin and subcutaneous tissue disorders, 26
Nervous system disorders, 110
Musculoskeletal and connective tissue disorders, 50
(b)
Vaccination site swelling, 1
Feeling abnormal, 2
Mobility decreased, 2
Feeling cold, 2
Injection site pain, 1
Vaccination site pain, 2
Axillary pain, 1
Asthenia, 3
Face oedema, 1
Malaise, 51
Oedema peripheral, 3
Chest pain, 8
Pain, 8
Fatigue, 11
Gait disturbance, 11
Chronic fatigue syndrome, 24
Pyrexia, 13
(c)
Loss of consciousness, 1
Somnolence, 1
Parosmia, 1
Migraine, 1
Dizziness postural, 1
Hypertonia, 1
Narcolepsy, 1
Epilepsy, 1
Memory impairment, 2
Seizure, 2
Dizziness, 24
Disturbance in attention, 2
Olfactory dysfunction, 2
Facial paralysis, 3
Cognitive disorder, 3
Tremor, 4
Taste disorder, 5
Headache, 24
Hypoaesthesia, 14
Brain fog, 17
(d)
Periarthritis, 1
Pain in jaw, 1
Spinal instability, 1
Bone pain, 1
Musculoskeletal pain, 1
Pain in extremity, 8
Muscle tightness, 1
Neck pain, 2
Myalgia, 2
Arthralgia, 8
Rheumatoid arthritis, 3
Back pain, 3
Polymyalgia rheumatica, 5
Muscular weakness, 7
Fibromyalgia, 6


(a)
Transferred to another hospital, 2
Death, 6
Unknown, 14
Worsened, 5
Complete recovery, 133
Unresolved, 145
Improved to tolerable level. 188
(b)
Death, 1
Unknown, 4
Worsened, 2
Complete recovery, 35
Unresolved, 50
Improved to tolerable level, 52
(c)
Unknown, 6
Complete recovery, 29
Unresolved, 29
Improved to tolerable level, 46
(d)
Death, 1
Complete recovery, 7
Unresolved, 25
Improved to tolerable level, 17

SUBJID \ SOC	Total Number of AEs per Case	General disorders and administration site conditions	Nervous sy... d...	Musculoskeletal ...	Skin and ...	Respiratory, ...	[illegible]	[illegible]	[illegible]	[illegible]	Ear and ...	[illegible]	Metabolism ...	[illegible]	Blood and ...	[illegible]	Neoplasms benign, ... polyps)	Reproductive ...	[illegible]	Renal and ...	[illegible]	Immune ...	[illegible]	All event recovery: 1 / ...covery: 2 / ...ery: 3	Sex	Age	No. of Vaccine Doses	History of COVID-19 Infection
007-0004	29	4	5	4	1	1	3	2	4	1	1	1		1			1						13	2	Female	55	2	Yes
007-0017	8	1	2	1	2	1			1														6	2	Female	34	3	Yes
002-0036	5	1	1	1	1						1												5	3	Female	46	1	Unknown
002-0020	11	1	4	1		2	1	1		1													7	3	Male	36	3	Unknown
002-0009	6	1	1	2		1				1													5	3	Female	35	1	Unknown
002-0026	6	2	1	1			2																4	3	Male	49	3	Unknown
014-0001	6	3	1	1					1														4	1	Male	39	3	No
003-0002	4	1	2	1																			3	2	Female	41	3	Yes
002-0027	4	1	1	1									1										4	3	Female	37	3	Yes
002-0011	4	1	2	1																			3	3	Female	36	2	Unknown
013-0003	3	1	1	1																			3	1	Female	60	3	No
001-0008	3	1	1	1																			3	3	Female	57	2	Yes
001-0018	6	2	3		1																		3	2	Female	64	3	No
002-0033	4	2	1		1																		3	3	Female	48	2	Unknown
010-0007	7	1	2			1	1			1	1												6	1	Male	52	2	No
002-0043	5	1	2			1			1														4	3	Female	65	4	Unknown
001-0022	6	2	3			1																	3	2	Female	55	3	Yes
013-0015	4	1	1			1							1										4	2	Female	83	3	No
001-0015	4	1	1			1							1										4	2	Female	55	1	Yes
013-0001	3	1	1			1																	3	3	Female	69	2	Yes
002-0005	9	4	1				1			2				1									5	3	Male	69	5	Yes
013-0019	8	4	3				1																3	3	Female	45	1	No
013-0008	5	1	1				1						1						1				5	2	Male	48	3	No
007-0017	5	2	2				1																3	3	Female	71	2	Unknown
013-0016	5	2	1					1			1												4	3	Male	45	3	No
002-0032	5	1	1					1				1						1					5	2	Female	80	3	Yes
002-0007	5	1	3					1															3	3	Male	14	2	Unknown
014-0002	3	1	1					1															3	1	Female	18	4	No
013-0005	7	2	3						1				1										4	2	Male	37	2	Yes
013-0006	8	2	2						2						1					1			5	2	Female	72	3	Yes
013-0002	4	1	2						1														3	3	Male	82	3	No
001-0061	6	3	2							1													3	3	Female	68	5	No
002-0034	3	1	1							1													3	3	Female	79	4	Unknown
002-0006	7	1	4								1											1	4	3	Female	84	6	Unknown
010-0002	4	2	1								1												3	3	Female	37	3	No
002-0024	3	1	1									1											3	2	Male	71	2	Yes
013-0012	4	1	2												1								3	2	Female	58	3	No
011-0003	3	2	1																				2	3	Female	81	3	Unknown
008-0001	3	1	2																				2	1	Female	51	2	No
002-0041	3	2	1																				2	3	Female	25	3	Unknown
002-0039	3	1	2																				2	3	Male	47	4	Yes
002-0031	3	1	1													1							3	3	Male	28	2	Unknown
001-0024	3	2	1																				2	3	Male	50	3	No
011-0006	2	1	1																				2	3	Female	79	5	Yes
011-0001	2	1	1																				2	3	Female	47	2	Yes
008-0018	2	1	1																				2	3	Female	55	4	No
006-0013	2	1	1																				2	3	Female	57	2	Unknown
006-0011	2	1	1																				2	3	Female	52	3	Yes
006-0002	2	1	1																				2	3	Female	72	4	No
002-0045	2	1	1																				2	3	Male	83	6	Unknown
002-0021	2	1	1																				2	3	Female	20	3	Unknown
002-0002	2	1	1																				2	3	Female	81	3	No
001-0037	2	1	1																				2	2	Female	87	3	No
001-0019	2	1	1																				2	3	Female	86	3	Yes
002-0046	4	2		1			1																3	3	Male	77	4	Unknown
001-0032	4	1		2			1																3	3	Female	71	4	No
006-0003	5	1		1					1		2												4	2	Female	58	3	No
011-0004	3	1		1										1									3	1	Female	87	4	Unknown
006-0012	3	1		2																			2	3	Female	41	5	Unknown
006-0007	3	1		2																			2	3	Female	56	1	Unknown
002-0048	3	1		2																			2	3	Female	71	6	Yes
006-0018	2	1		1																			2	3	Male	83	4	Unknown
006-0016	2	1		1																			2	3	Male	82	4	Unknown
006-0014	2	1		1																			2	3	Female	54	3	Unknown
006-0006	2	1		1																			2	3	Female	39	3	Unknown
006-0005	2	1		1																			2	3	Female	24	3	Unknown
002-0022	2	1		1																			2	3	Male	49	3	Yes
002-0010	2	1		1																			2	3	Female	36	1	Yes
001-0004	2	1		1																			2	2	Female	77	2	No
002-0019	4		2	1	1																		3	3	Female	64	3	Unknown
002-0028	3		2	1																			2	3	Female	34	3	Unknown
008-0009	2		1	1																			2	3	Female	59	4	No
001-0040	2		1	1																			2	1	Female	81	2	No
007-0002	6	1			1			1		1	1			1									6	2	Female	80	3	No
001-0050	3	1			1					1													3	2	Female	70	2	Yes
002-0042	3	1			1								1										3	2	Female	36	4	Unknown
013-0018	5	2			1											1			1				4	1	Male	29	3	No
002-0008	2	1			1																		2	3	Male	76	5	No
001-0021	2	1			1																		2	3	Female	81	3	No
001-0044	3	1				1				1													3	3	Male	82	4	No
007-0018	3	1				1										1							3	2	Male	24	2	Unknown
013-0014	2	1				1																	2	1	Male	84	3	No
001-0053	2	1				1																	2	2	Male	74	6	No
001-0062	4	1						1					1			1							4	2	Female	68	2	No
013-0013	4	1						1							1		1						4	2	Female	56	3	No
006-0004	2	1						1															2	2	Female	56	2	Unknown
007-0009	3	2							1														2	2	Female	47	5	Yes
001-0058	3	2								1													2	2	Female	63	2	Yes
001-0035	2	1								1													2	3	Female	63	2	No
001-0013	2	1								1													2	3	Male	84	4	No
001-0005	2	1										1											2	1	Female	76	3	No
011-0007	3	3																					1	1	Female	72	3	Yes
012-0006	2	2																					1	1	Female	51	1	Unknown
002-0050	2	2																					1	3	Female	54	1	Unknown
002-0025	2	2																					1	2	Male	15	1	Yes
001-0055	2	2																					1	1	Female	72	2	Yes
015-0001	1	1																					1	3	Male	34	3	Yes
012-0004	1	1																					1	3	Male	39	1	Unknown
010-0004	1	1																					1	1	Female	42	3	Yes
010-0003	1	1																					1	1	Male	17	3	Yes
010-0001	1	1																					1	1	Male	67	3	No
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007-0049	1	1																					1	3	Male	59	3	No
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004-0008	1	1																					1	3	Male	84	1	Yes
002-0047	1	1																					1	1	Female	19	3	Unknown
007-0001	1	1																					1	3	Male	47	4	Unknown
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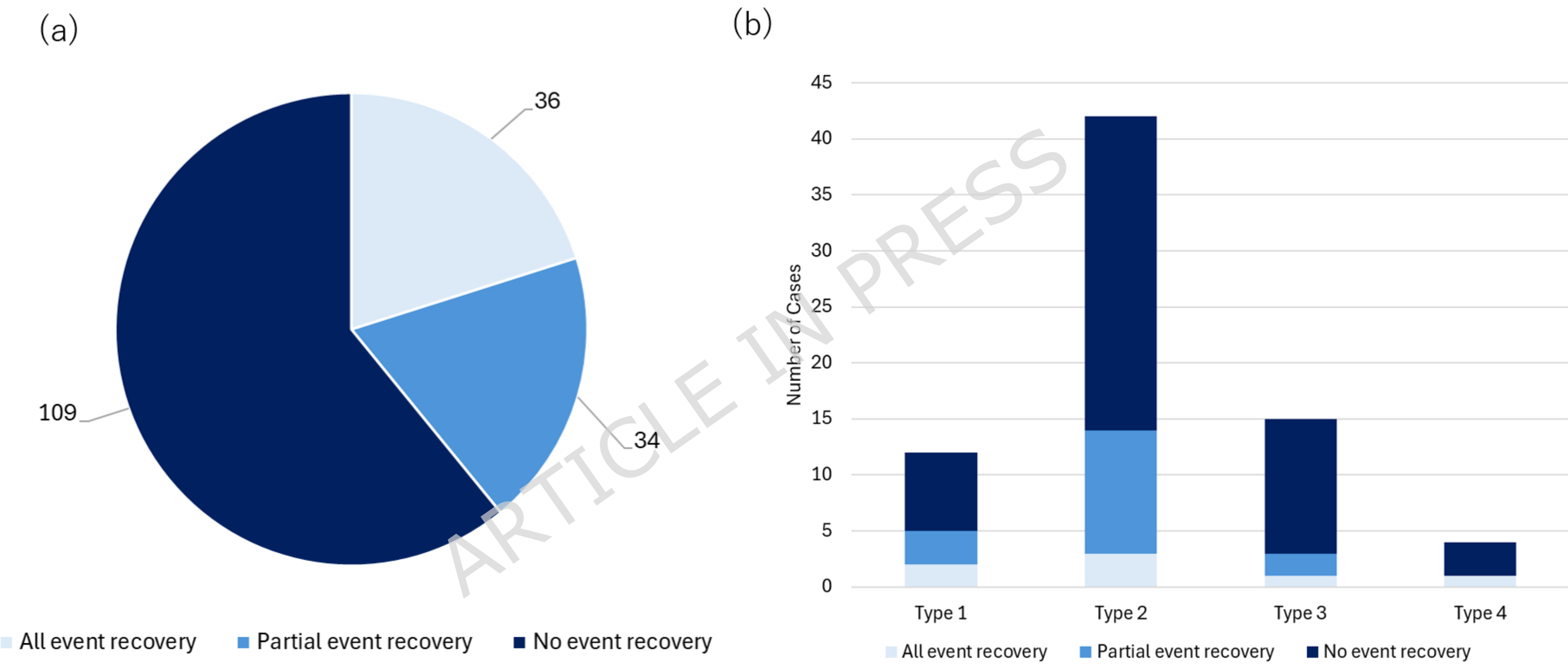
001-0020	1	1																					1	3	Female	67	5	No
002-0040	4		2		1	1																	3	3	Female	68	2	Unknown
013-0009	3		1		1		1																3	2	Female	51	2	No
002-0030	5		1				1	1				2											4	2	Male	60	3	Yes
013-0017	3		2				1																2	3	Female	74	5	Unknown
007-0022	3		1					1	1														3	3	Female	45	3	Yes
006-0015	2		1								1												2	3	Female	39	3	Unknown
001-0030	2		1									1											2	1	Male	84	3	No
007-0006	2		1											1									2	1	Female	62	3	Unknown
013-0004	1		1																				1	3	Female	75	3	No
012-0002	1		1																				1	1	Female	65	3	No
010-0006	1		1																				1	1	Female	57	3	Yes
007-0014	1		1																				1	3	Female	68	4	Yes
003-0006	1		1																				1	1	Male	17	3	No
002-0044	1		1																				1	3	Female	55	2	Yes
001-0031	1		1																				1	1	Male	68	4	Unknown
001-0026	1		1																				1	1	Male	64	3	No
002-0004	2			1			1																2	3	Female	87	5	Unknown
003-0004	2			1										1									2	2	Male	74	3	No
013-0011	2			1											1								2	2	Female	58	3	No
002-0003	2			2																			1	3	Female	75	3	Unknown
008-0002	1			1																			1	1	Male	70	4	No
002-0029	1			1																			1	3	Female	79	4	Unknown
007-0014	1			1																			1	3	Male	88	7	Yes
001-0057	1			1																			1	3	Female	54	2	No
001-0047	1			1																			1	3	Female	90	3	No
001-0036	1			1																			1	3	Male	59	3	Yes
002-0023	3				2		1																2	2	Female	84	4	Unknown
002-0013	2				1		1																2	3	Male	49	3	No
002-0035	2				1								1										2	3	Male	71	5	Unknown
007-0045	1				1																		1	3	Female	67	6	Yes
007-0038	1				1																		1	1	Female	62	6	Yes
007-0037	1				1																		1	3	Female	65	3	No
007-0003	1				1																		1	3	Female	59	3	Unknown
003-0005	1				1																		1	3	Female	43	4	No
001-0060	1				1																		1	1	Male	57	3	No
001-0052	1				1																		1	3	Female	75	2	No
001-0023	2					1						1											2	2	Male	67	3	No
001-0001	2					1									1								2	3	Female	70	3	No
001-0039	2					2																	1	3	Female	71	4	No
002-0037	1					1																	1	3	Female	83	7	Unknown
001-0048	1					1																	1	3	Male	71	3	No
001-0041	1					1																	1	3	Female	46	3	Yes
001-0025	1					1																	1	3	Female	67	2	No
002-0038	3						2							1									2	3	Male	70	5	Unknown
013-0010	2							1					1										2	1	Female	37	4	No
002-0049	3							3															1	1	Female	77	6	Unknown
013-0007	1							1															1	3	Male	50	3	No
007-0019	1							1															1	1	Female	56	3	Unknown
002-0015	1							1															1	3	Female	91	6	Unknown
007-0033	2								1		1												2	2	Female	61	3	Yes
007-0036	2								2														1	3	Female	37	1	Yes
010-0005	1								1														1	3	Female	52	4	Yes
001-0028	2									2													1	3	Male	41	3	No
012-0001	1									1													1	1	Female	63	2	No
002-0012	1									1													1	3	Male	91	5	Unknown
012-0005	1											1											1	1	Male	62	3	Unknown
008-0006	1											1											1	3	Male	79	7	Yes
001-0002	1												1										1	1	Female	85	2	Yes
006-0008	1													1									1	3	Male	72	5	Unknown
002-0016	1													1									1	3	Male	84	5	Unknown
007-0046	1														1								1	3	Female	35	2	Yes
001-0016	1															1							1	1	Male	50	2	No
012-0003	1																1						1	1	Female	82	3	No
008-0014	1																1						1	3	Male	41	3	No
003-0001	1																	1					1	1	Female	54	2	Yes
001-0007	1																				1		1	3	Male	74	3	No
Number of Clinically Definitive AEs	493	144	110	50	26	24	21	20	18	18	11	10	10	9	6	5	4	2	2	1	1	1						
Number of Cases with Clinically Definitive AEs		109	74	41	24	22	17	17	13	16	10	9	10	9	6	5	4	2	2	1	1	1						
Number of Cases with Complete PT Recovery		21	17	5	6	7	1	7	3	4	2	5	6	3	3	2	1	2	2	0	0	0						

No AE Recovery*
≥1 AE Recovery within Same SOC (Multiple AEs Present)
Recovery

*No data cases are classified as 'No AE Recovery'.


(a)
36
34
109
All event recovery
Partial event recovery
No event recovery
(b)
45
40
35
30
25
20
15
10
5
0
Number of Cases
Type 1
Type 2
Type 3
Type 4
All event recovery
Partial event recovery
No event recovery

SOC	PT	AE Count	Recovery Count	Recovery Rate (%)	Days to Recovery
General disorders and administration site conditions	Malaise	51	11	22	43 - 908
	Pyrexia	13	10	77	3 - 987
	Fatigue	11	3	27	272 - 978
	Chest pain	8	3	38	45 - 874
	Pain	8	2	25	65 - 872
	Oedema peripheral	3	2	67	43 - 269
	Chronic fatigue syndrome	24	1	4	533 - 533
	Gait disturbance	11	1	9	81 - 81
	Vaccination site pain	2	1	50	883 - 883
	Feeling cold	2	1	50	978 - 978
Nervous system disorders	Headache	24	6	25	16 - 865
	Brain fog	17	5	29	480 - 816
	Dizziness	24	3	13	149 - 745
	Facial paralysis	3	3	100	28 - 908
	Hypoaesthesia	14	2	14	50 - 537
	Taste disorder	5	2	40	907 - 909
	Cognitive disorder	3	2	67	680 - 863
	Tremor	4	1	25	516 - 516
	Memory impairment	2	1	50	863 - 863
	Olfactory dysfunction	2	1	50	907 - 907
	Seizure	2	1	50	414 - 414
	Epilepsy	1	1	100	865 - 865
	Loss of consciousness	1	1	100	271 - 271
Musculoskeletal and connective tissue disorders	Rheumatoid arthritis	3	2	67	298 - 772
	Arthralgia	8	1	13	384 - 384
	Polymyalgia rheumatica	5	1	20	99 - 99
	Back pain	3	1	33	777 - 777
	Neck pain	2	1	50	855 - 855
	Pain in jaw	1	1	100	855 - 855
Skin and subcutaneous tissue disorders	Rash	6	3	50	26 - 523
	Alopecia	9	1	11	576 - 576
	Pruritus	4	1	25	479 - 479
	Alopecia areata	1	1	100	266 - 266
	Skin exfoliation	1	1	100	197 - 197
	Urticaria chronic	1	1	100	457 - 457
Respiratory, thoracic and mediastinal disorders	Dyspnoea	12	5	42	197 - 560
	Asthma	4	1	25	572 - 572
	Dyspnoea exertional	2	1	50	725 - 725
Psychiatric disorders	Thinking abnormal	1	1	100	863 - 863
	Anxiety	2	1	50	863 - 863
	Insomnia	3	1	33	516 - 516
Gastrointestinal disorders	Nausea	5	2	40	94 - 987
	Abdominal pain	3	2	67	17 - Unknown
	Diarrhoea	2	2	100	12 - 774
	Stomatitis	2	1	50	342 - 342
	Abdominal pain upper	2	1	50	506 - 506
	Lower gastrointestinal haemorrhage	1	1	100	5 - 5
	Gingival swelling	1	1	100	365 - 365
Eye disorders	Vision blurred	2	2	100	240 - 777
	Vogt-Koyanagi-Harada disease	1	1	100	21 - 21
Cardiac disorders	Palpitations	11	3	27	266 - 892
	Ventricular extrasystoles	1	1	100	195 - 195
Ear and labyrinth disorders	Vertigo	2	1	50	745 - 745
	Deafness	2	1	50	119 - 119
Infections and infestations	Herpes zoster	4	3	75	38 - 549
	Cystitis	2	1	50	33 - 33
	Herpes virus infection	1	1	100	138 - 138
	Herpes zoster reactivation	1	1	100	243 - 243
Metabolism and nutrition disorders	Decreased appetite	10	6	60	94 - 908
	Hypertension	1	1	100	402 - 402
	Hypotension	1	1	100	82 - 82
	Peripheral artery thrombosis	1	1	100	620 - 620
Blood and lymphatic system disorders	Lymphadenitis	2	2	100	390 - 668
	Thrombotic thrombocytopenic purpura	1	1	100	435 - 435
Hepatobiliary disorders	Hepatic function abnormal	2	1	50	49 - 49
	Hepatitis acute	1	1	100	741 - 741
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Oesophageal cancer metastatic	1	1	100	613 - 613
	Uterine haemorrhage	1	1	100	149 - 149
	Heavy menstrual bleeding	1	1	100	742 - 742
Investigations	Fibrin D dimer increased	1	1	100	117 - 117
	Weight decreased	1	1	100	533 - 533

Table 1. Participating medical facilities and geographic distribution

No	Name of facility	Number of registered cases
1	Honbetsu Cardiovascular Medicine Clinic	66
2	Kodama Hospital & Kodama Medical Office	50
3	Ikezawa Women's Health Clinic	6
4	Kamata Yoshino Medical Clinic	22
5	Koide Clinic	19
6	Osaka Proctology Medical Clinic	51
7	Koseido Medical Corporation, Suda Clinic	21
8	Kamihata ENT Clinic	8
9	Koshio Orthopedics Clinic	7
10	Kidasanyakudo Medical Clinic	6
11	Kobayashi Clinic	19
12	Fushimi Keimei Orthopedic & Osteoporosis Clinic of Sapporo	2
13	Otofuke ENT (Ear, Nose, and Throat) Clinic	1
14	Tokachi Mutsumino Medical Clinic	1

Registry enrollment by participating medical institutions showing facility names, case contributions, and geographic distribution across Japan. The 14 facilities were predominantly private outpatient clinics distributed across multiple prefectures, with the highest concentrations in Hokkaido (northern Japan) and Osaka/Kansai region (central Japan). Honbetsu Cardiovascular Medicine Clinic and Kodama Hospital contributed the majority of cases (66 and 50 cases respectively), while Osaka Proctology Medical Clinic provided 51 cases. The remaining facilities contributed 1-22 cases each. Geographic distribution shows representation from northern (Hokkaido), central (Tokyo, Osaka), and other regional areas, providing a multi-regional perspective on post-COVID-19 vaccination syndrome presentations across Japan's healthcare system.